Current prospects for and the future of Enabling Chemistry Technology

Stevan W Djuric, PhD

AbbVie

Dial-a-Molecule Annual Meeting,

Imperial College, London, UK

July 10th 2018

How Can Chemistry Technology help?

- Cycle Time
- Cost of Goods
- Improve overall PoS

$$\text{R and D Productivity} \sim \frac{\text{WIP.p (TS)}}{\text{CT}} \cdot \frac{1}{\text{C}} \cdot \text{V}$$

Paul et al (Lilly) NRDD 2010

Drug Discovery can be characterized as a race in which several firms pursue investigational drugs with similar chemical structures or with the same mechanism of action before any drug in the class obtains regulatory marketing approval

– J. A. DiMasi and L. B. Faden, NRDD, 2011, 10, p23.

Goal of AbbVie's HTC Facility

A centralized, highly automated, state-of-the-art, parallel synthesis facility that enables the discovery of more highly optimized biological tools and drug candidates

- Preparation of libraries of analogs designed to
- Rapidly generate structure activity relationships (SAR)
- Accelerate lead development and optimization

Benefits for AbbVie's Discovery Organization:

- ✓ More analogs = "more shots on goal"
- ✓ Libraries created more efficiently
- ✓ Project chemists focus on targets not amenable to parallel synthesis
- ✓ Quality and scope of SAR enhanced
- ✓ Libraries contribute to file enhancement

Overview of Library Production at AbbVie

Library Characteristics

- ✓ Solution Phase
- ✓ Individual, Pure Compounds
- ✓ Focused Chemical Space
- ✓ 48-144 Member Libraries
- ✓ 10-40 mg Scale
- ✓ Minimal Development
  ~ 2 Week Turnaround
- ✓ High Purities and Yields
- ✓ Fully Characterized Products

Enabling Tools

Mass-directed HPLC

SFC

Supported Reagents/Scavengers

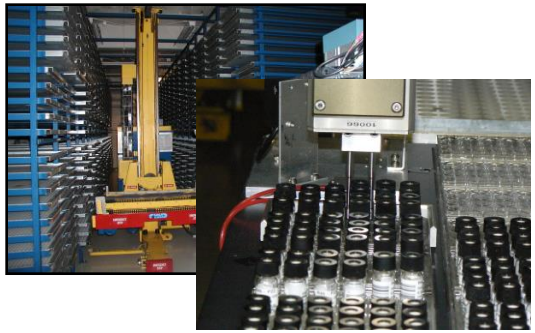
Microwave Synthesis

Standardized Chemistry Protocols

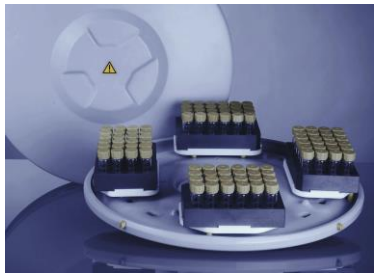
Automation

- 4,000 Compounds/Chemist/Year
- Rapid Library Synthesis
- Cost per Analog Decreased

Historic(Relatively) Optimized Process



iStore - inventory of pre-weighed monomers



Synthos parallel MW

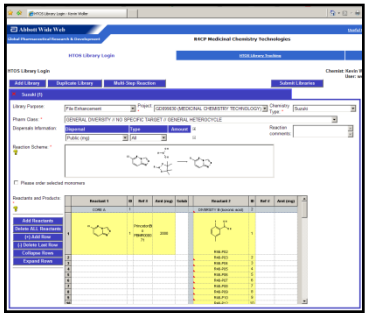
Mass triggered purification

Synthesis
2-3 days – **hours-1 day**

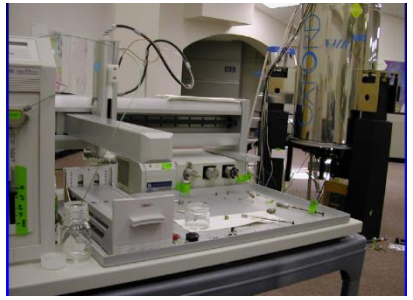
Purification & Analysis
4-5 days – **3-4 days**

Assay / SAR determination
3-4 weeks – **1-2 weeks**

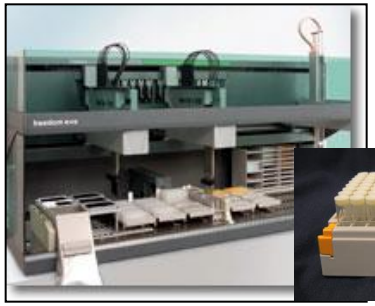
Library design & monomer selection
2-3 days – **1 day**



Web-based library log in & design tools



NMR



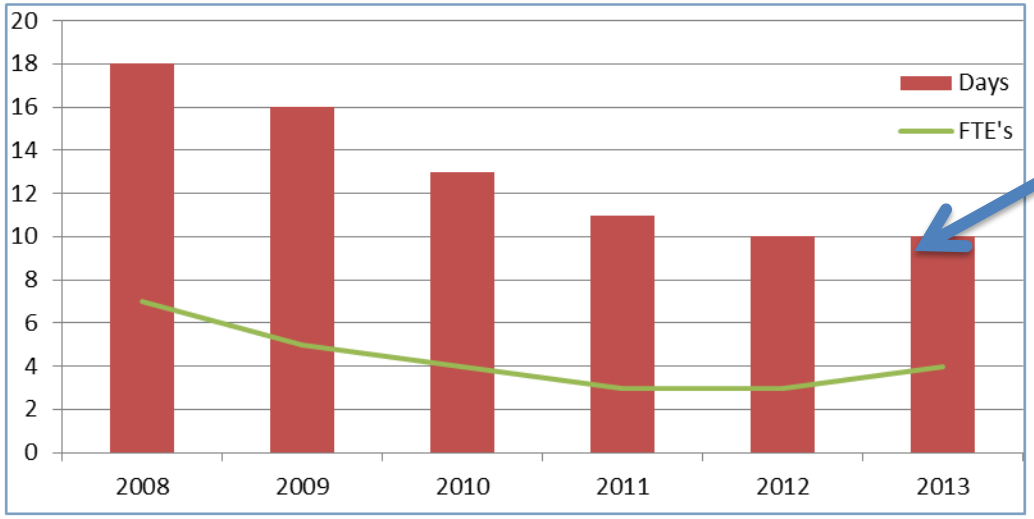
Tecan liquid handler and plate reader

Matrix 2D bar-coded tubes

Acquity UPLC

AbbVie High Throughput Chemistry Engine

Cycle Times



Batch library production cycle time

Tipping Point-
Technology Trigger
Requires transformational
technology change
in order to improve

- Operational efficiencies realized (purification and analysis)

Abbott High-Throughput Chemistry Engine

Next Steps….

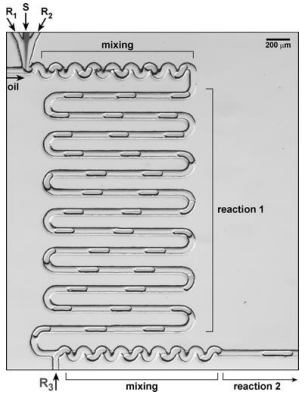
- Technology trigger – need a next generation system
  - ✓ *Needs to be transformational!*
- The next generation :

  -Flow Chemistry approaches *e.g* segmented flow

High-Throughput Measurements

A Microfluidic System for Controlling Reaction Networks in Time**

*Helen Song, Joshua D. Tice, and Rustem F. Ismagilov**



Molecules **2011**, *16*, 9161-9177; doi:10.3390/molecules16119161

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Article

Small Molecule Library Synthesis Using Segmented Flow

Christina M. Thompson [1,*], Jennifer L. Poole [2], Jeffrey L. Cross [1], Irini Akritopoulou-Zanze [1] and Stevan W. Djuric [1]

[1] Medinical Chemistry Technologies, Abbott Laboratories, Global Pharmaceutical Research and Development, 100 Abbott Park Road, Abbott Park, IL 60064, USA

[2] Department of Chemistry at KU, 1251 Wescoe hall Drive, 2010 Marlott Hall, Lawrence, KA 66045, USA

Use Flow Chemistry only when you need it!

Process Optimization

DOI: 10.1002/anie.200906095

The Flow's the Thing…Or Is It? Assessing the Merits of Homogeneous Reactions in Flask and Flow**

Fernando E. Valera, Michela Quaranta, Antonio Moran, John Blacker, Alan Armstrong,* João T. Cabral,* and Donna G. Blackmond**

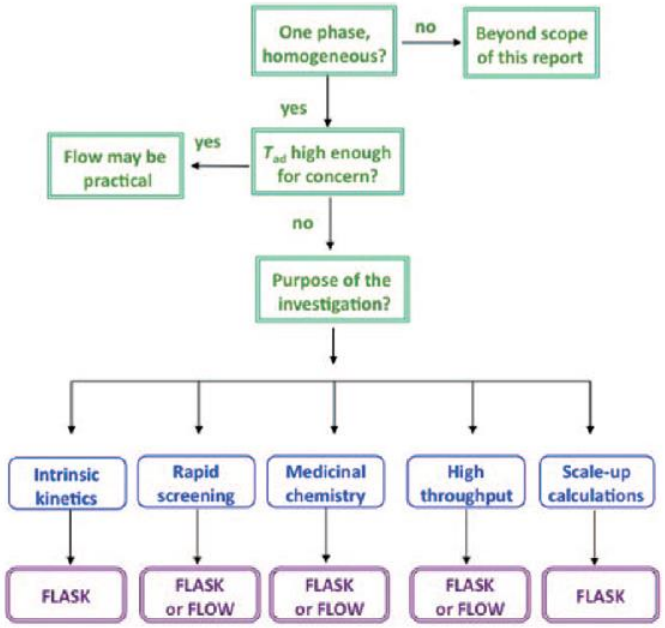


Figure 5. Road map for assessing the feasibility of carrying out a reaction in flask versus in a microflow reactor.

Reviews

K. F. Jensen et al.

Flow Chemistry

DOI: 10.1002/anie.201004637

Deciding Whether To Go with the Flow: Evaluating the Merits of Flow Reactors for Synthesis

*Ryan L. Hartman, Jonathan P. McMullen, and Klavs F. Jensen**

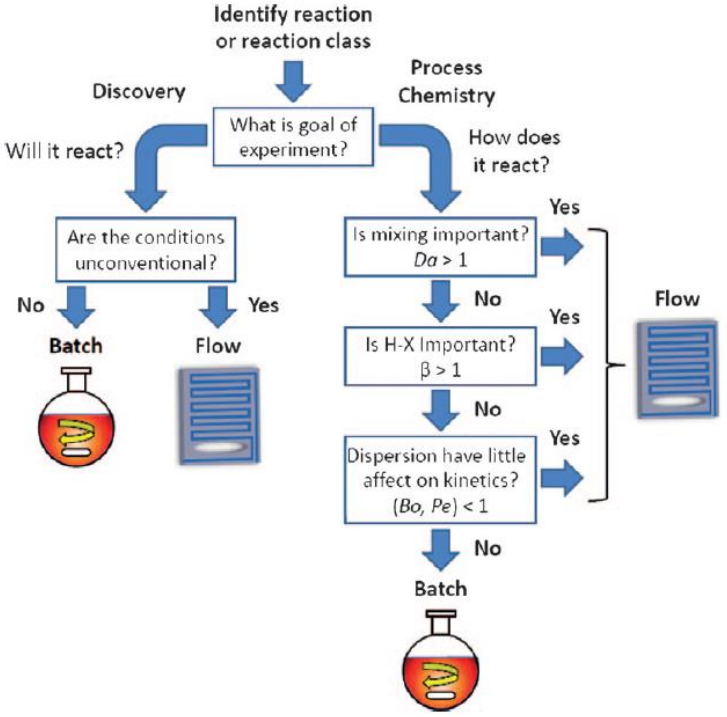
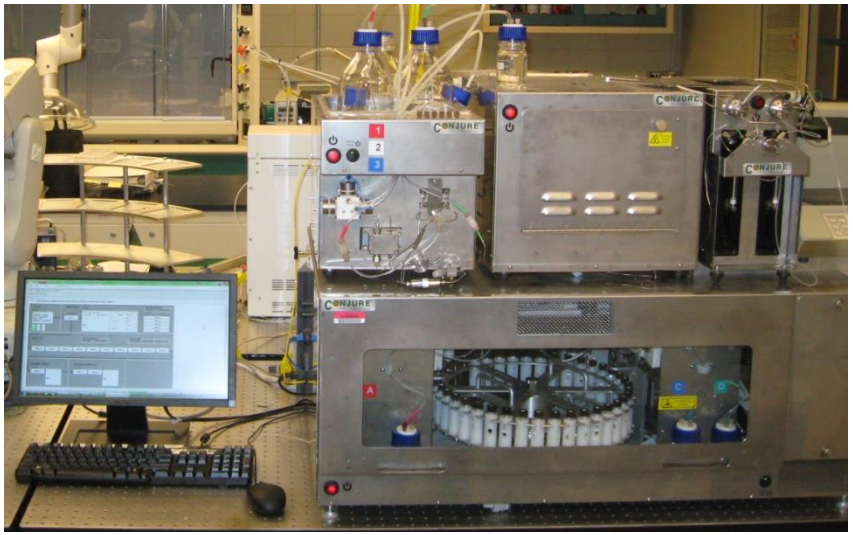
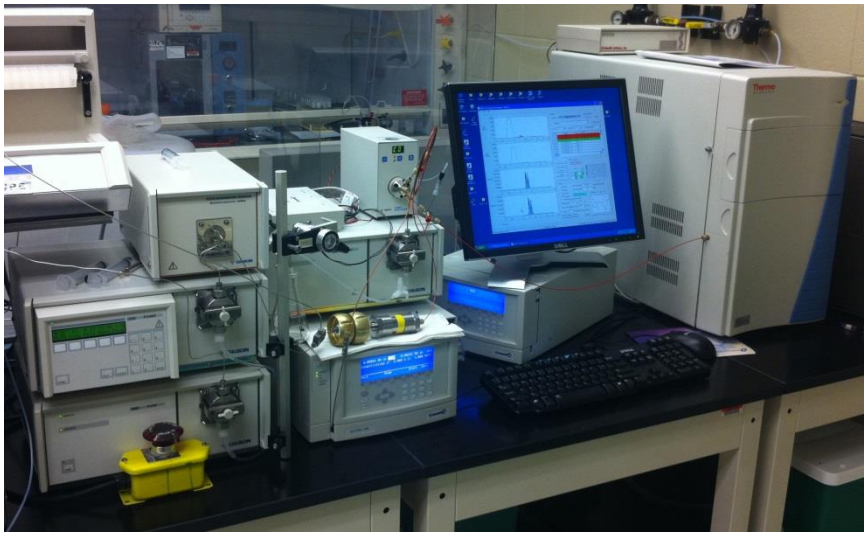


Figure 10. Decision roadmap for flow chemistry. (H-X stands for heat transfer)

Recent review : Seeberger et al Chem Rev 2017

- ***SWIFT – A first in class compound library production engine***





SWIFT – Synthesis With Integrated Flow Technology

Next generation fully integrated synthesis/purification platform

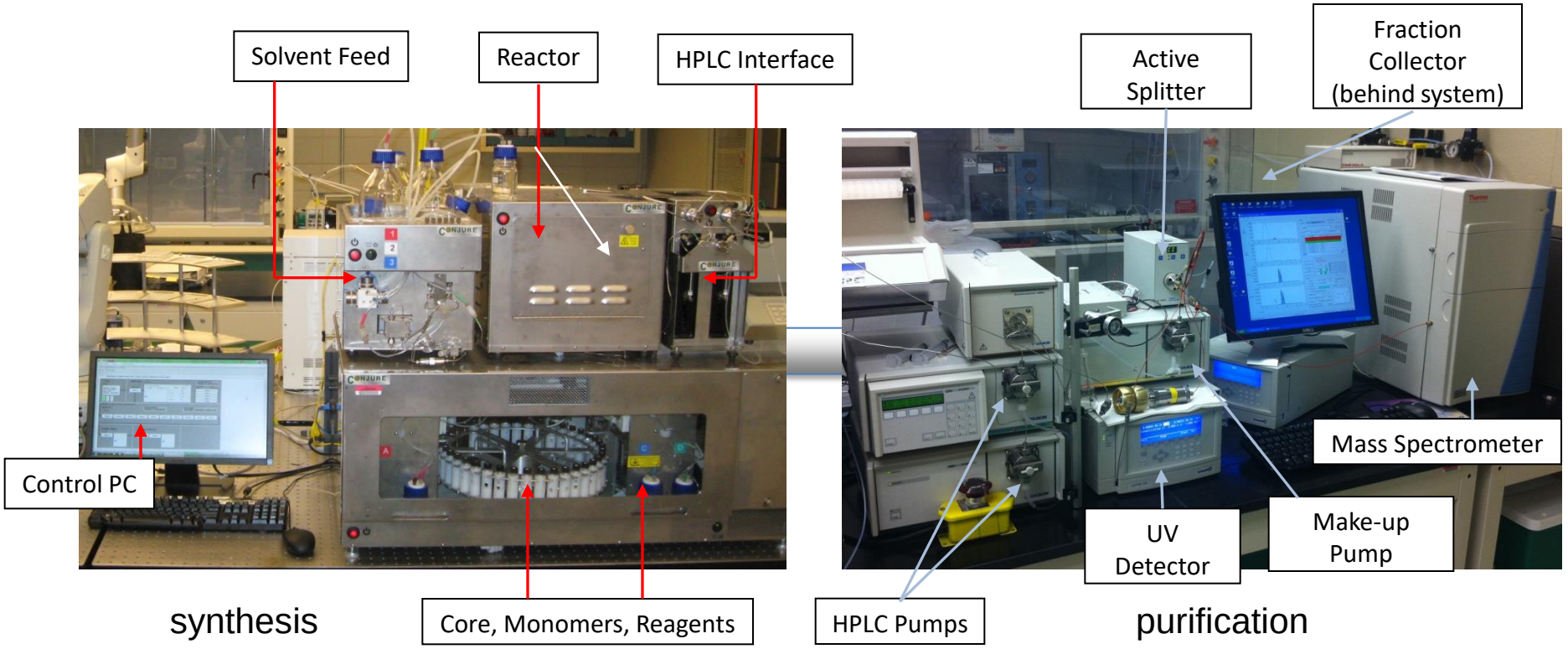
Goal: Achieve a 4 day turn-around for

- ✓ ***Method development***
- ✓ ***Synthesis***
- ✓ ***Purification***
- ✓ ***Analysis***
- ✓ ***Compounds ready for bioassay and storage***

Utilizing a segmented flow chemistry platform

SWIFT – Synthesis With Integrated Flow Technology

System Setup based on Accendo Conjure Reactor

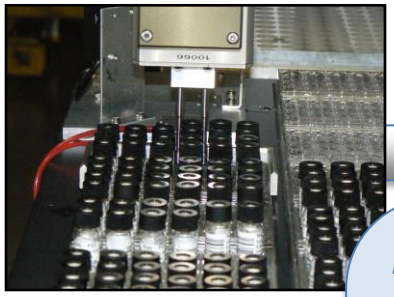


- ✓ Product is purified by HPLC-MS while next in queue is being synthesized
- ✓ Standard 10 minute LC method, 1 fraction per reaction collected by MS trigger

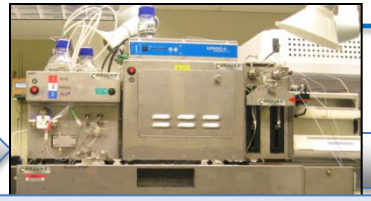
Djuric et al. J. Flow Chem. 2011, 2, 56–61

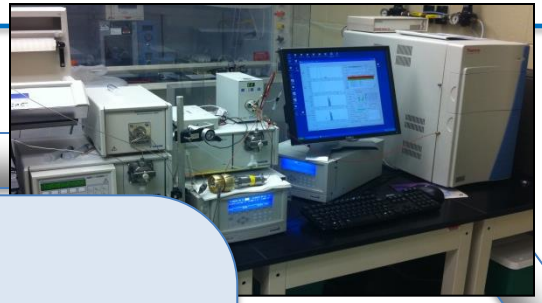
SWIFT – Synthesis With Integrated Flow Technology

Flow Library Synthesis Process



Pre-weighed monomers dissolved by liquid handle





urification, isition

Proprietary software for library setup, fraction handling and data acquisition

Automated labelling of fraction (1 fraction/prd), over night dry down

final liquid handler sample transfer for NMR analysis, dry down and weighing (Tecan)

Storage in 2D bar-coded tubes

Centralized assay plate preparation

Flow

- *Synthesis in segmented flow*
- *10-30mg scale*
- *"In line" purification*
- *Chemistries dictated by solubility (up to 2 steps)*
- *2-4 day cycle time till registration*

Reaction type

Acylation

Urea formation

Sulfonylation

Reductive amination

2-step acylation & deprotection

2-step reductive amination & deprotection

S_NAr

Various heterocycle formations

Pyrazole acylation

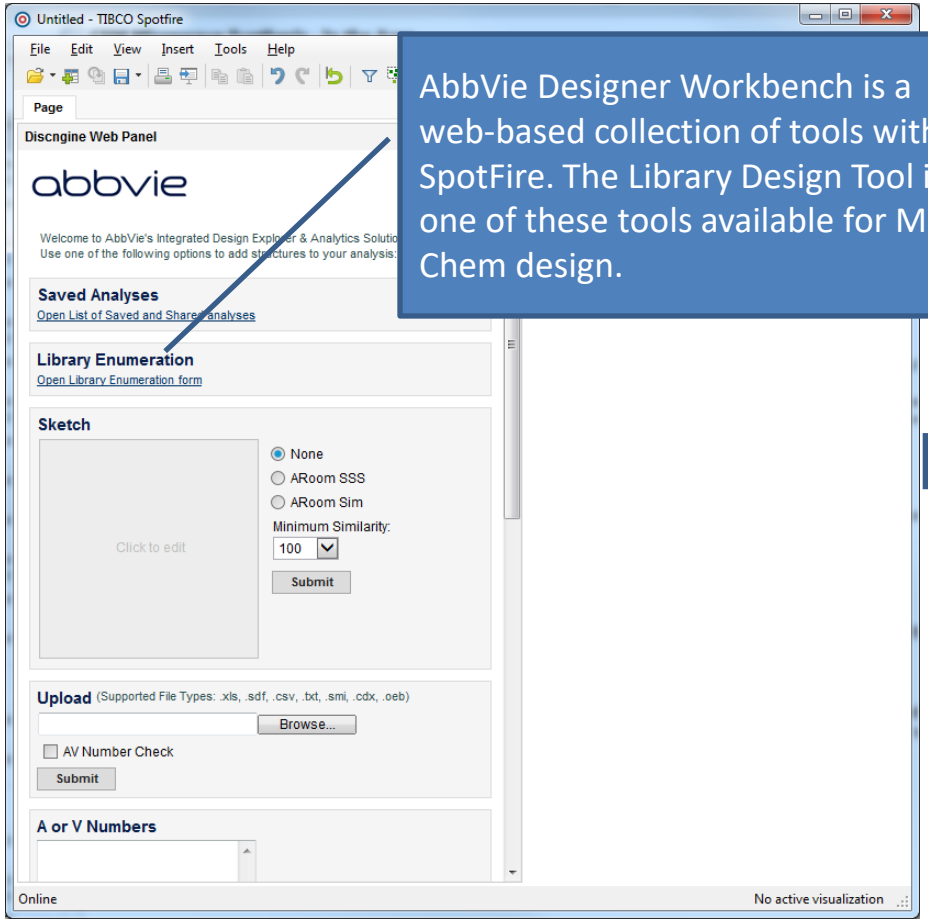
Epoxide openings

Carbamate formation

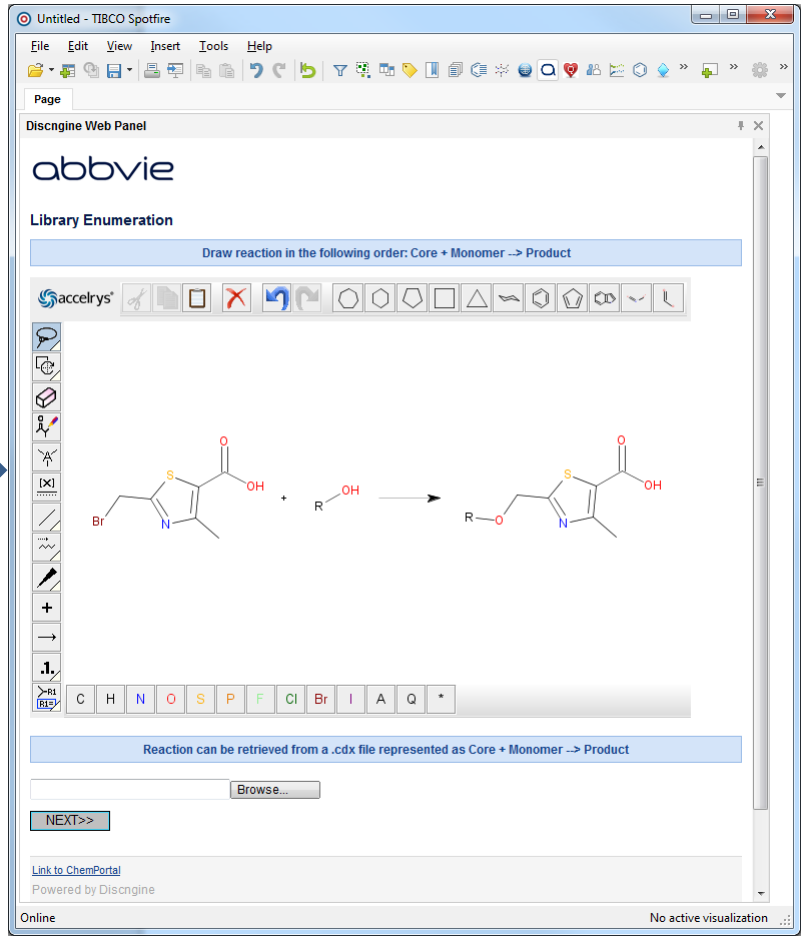
One-pot Click chemistry

2011-2015 ~9.5k compounds synthesized, ~70% average success rate

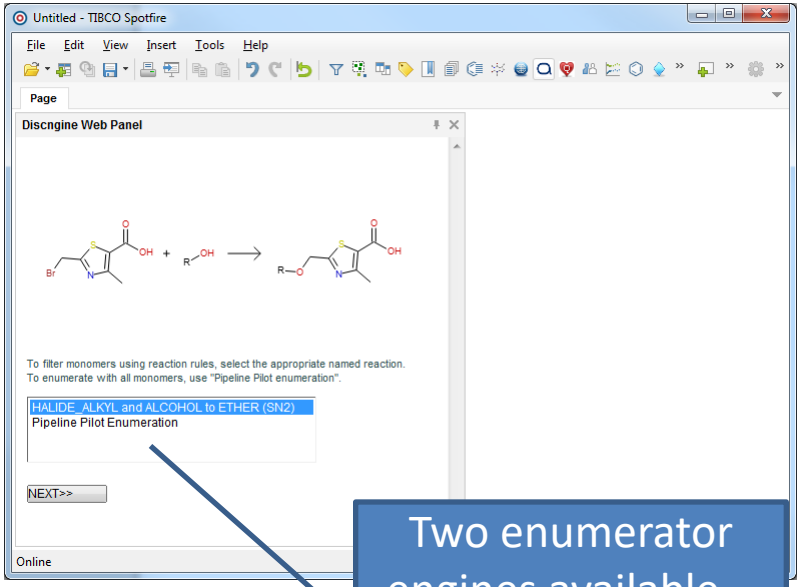
Library Design Tool – Part of the AbbVie Designer Workbench



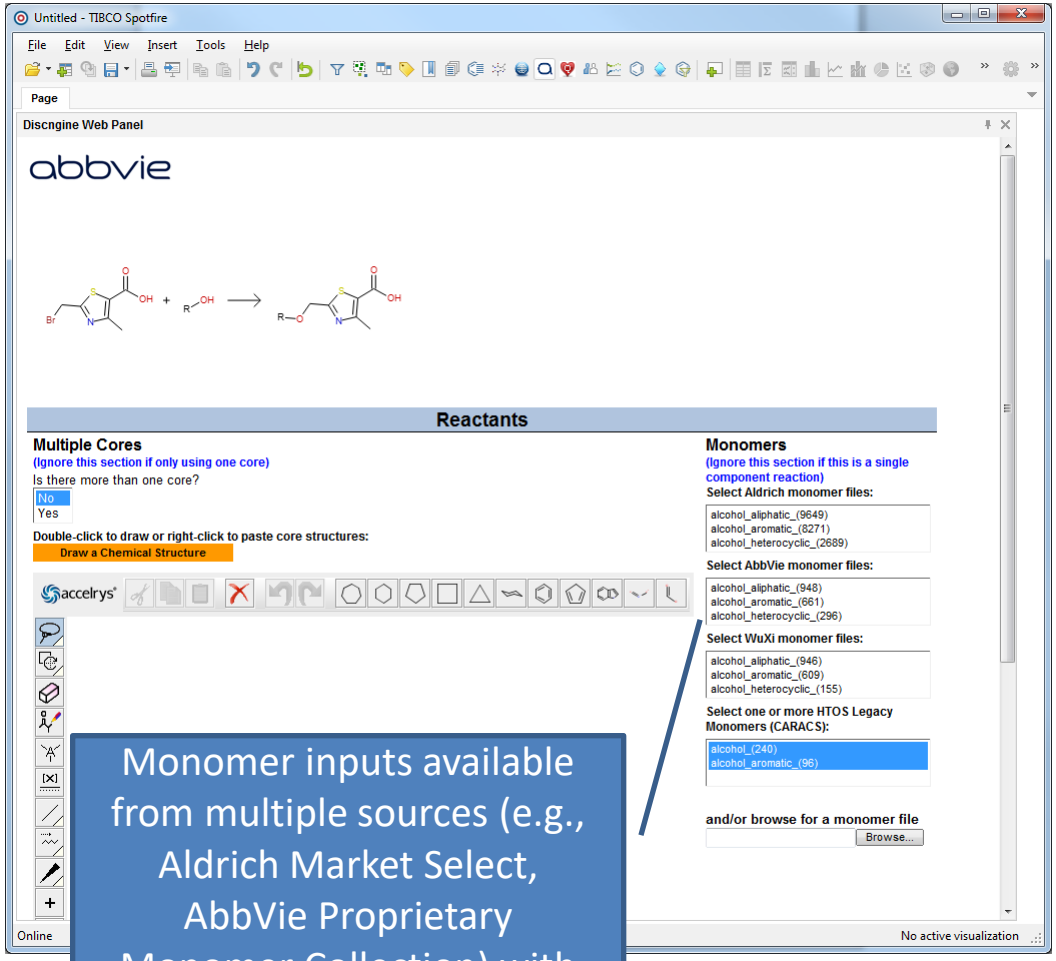
AbbVie Designer Workbench is a web-based collection of tools within SpotFire. The Library Design Tool is one of these tools available for Med Chem design.



Enumeration and Monomer Selection

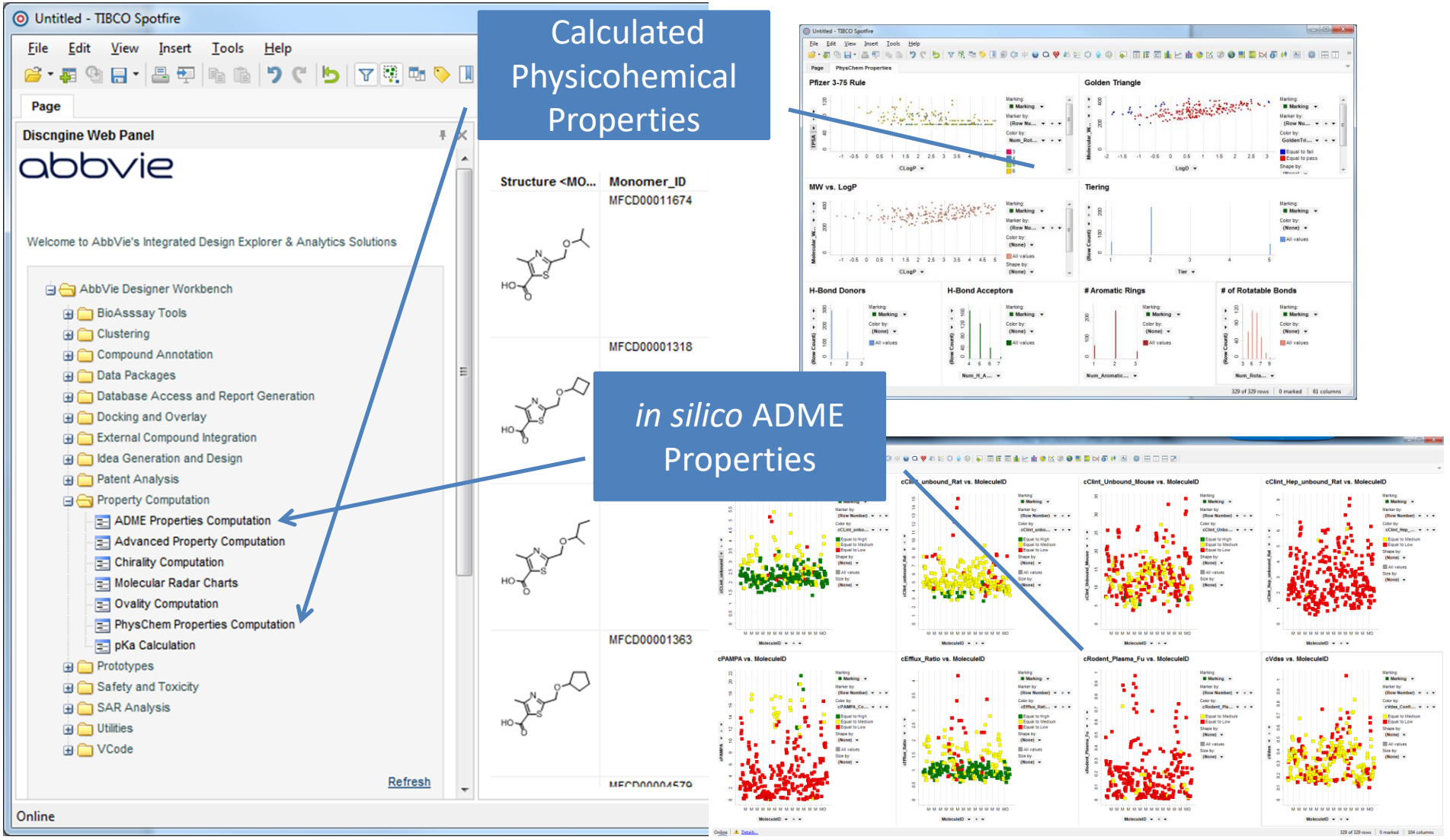


Two enumerator engines available – ChemAxon and Pipeline Pilot



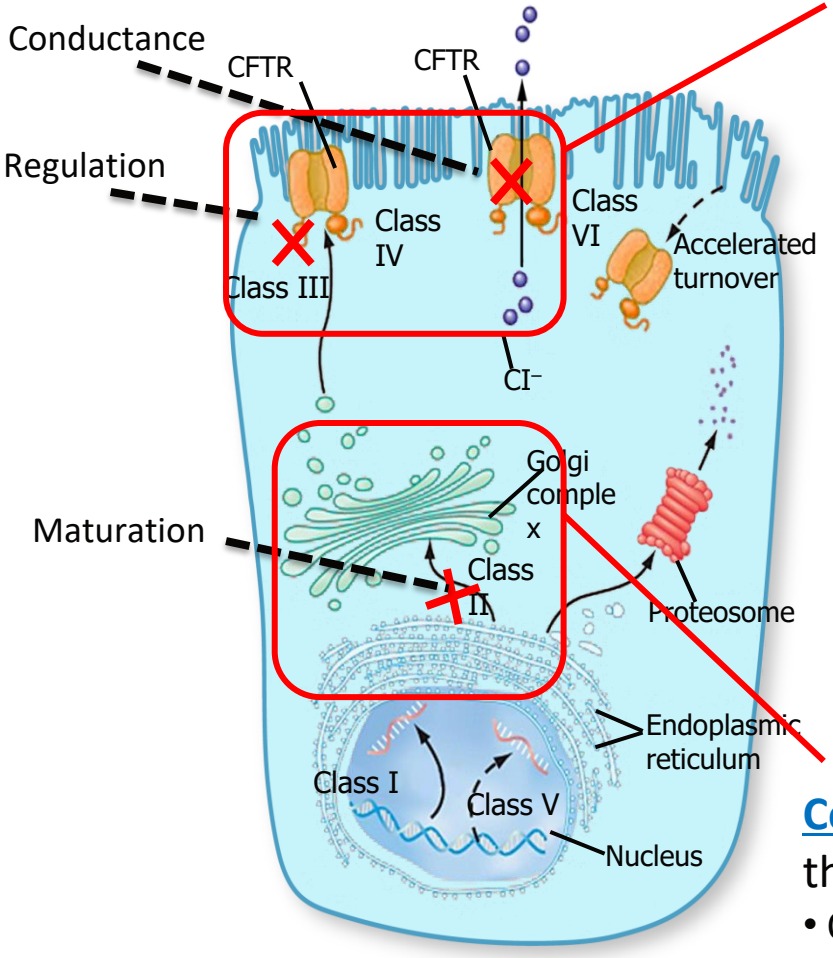
Monomer inputs available from multiple sources (e.g., Aldrich Market Select, AbbVie Proprietary Monomer Collection) with estimated delivery times

Manipulation of the Virtual Library



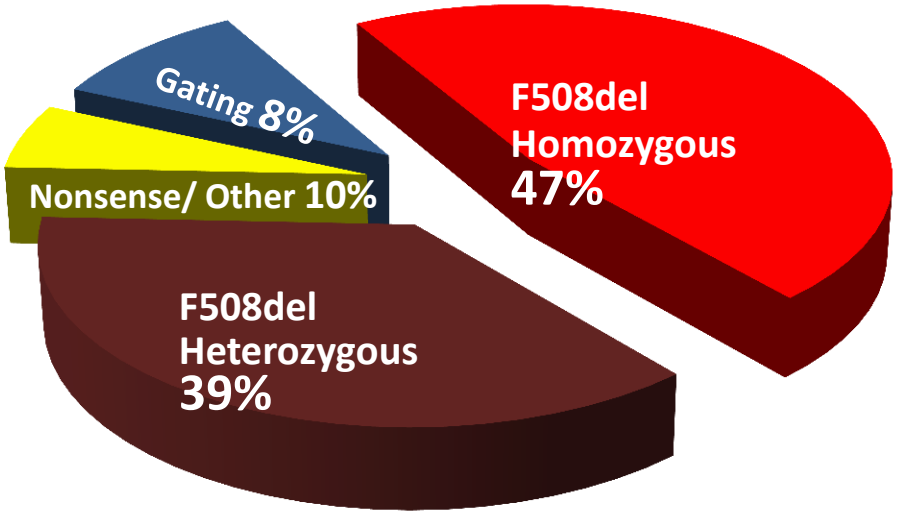
Cystic Fibrosis is Driven by Defects in CFTR

Two Main Approaches to Fix CFTR



Potentiators restore the flow of ions through activated CFTR

- Ivacaftor (VX-770) approved



Correctors restore the processing of CFTR from to the surface

- Orkambi approved (Lumacaftor (VX-809)+ Ivacaftor)
- Need of type 1 (C1) corrector and type 2 (C2) corrector for maximum channel restoration

CFTR Correctors - Assays

$$I = n.Po.\gamma$$

I = Total current
n = Number of channels
Po = Open probability
γ = Channel conductance

Functional Assays

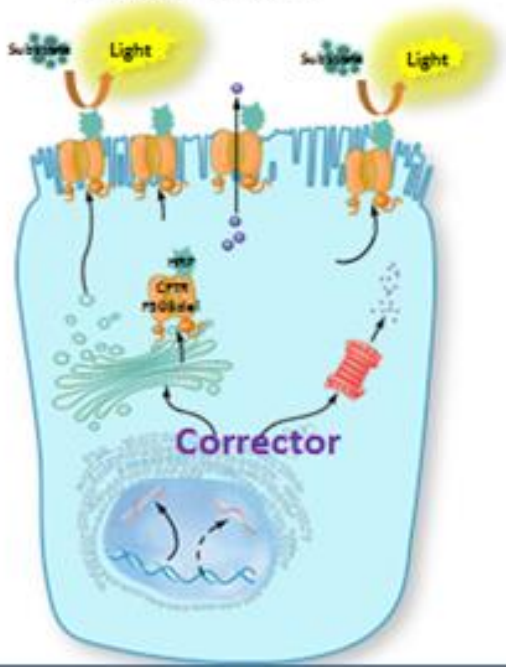
HBE-TECC (Human Bronchial Epithelial- TransEpithelial Clamp Circuit)

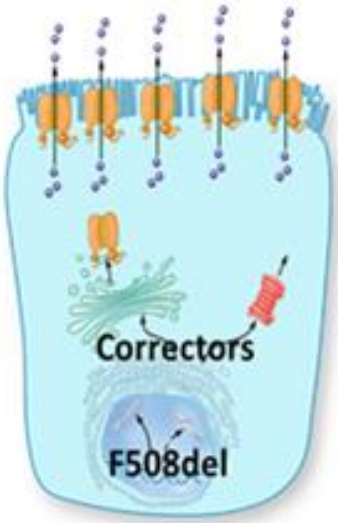
- Primary **human bronchial epithelial** cells from **CF patients**
- E-Phys measurement of ion flux
- Measure (Ieq) current changes
- Gold standard for CFTR function and clinical efficacy correlation

Localization Assays

CSE-HRP (Cell Surface Expression)

- CSE-HRP-tagged

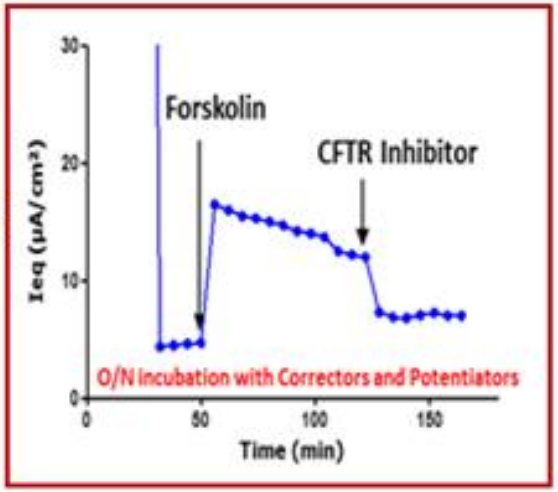




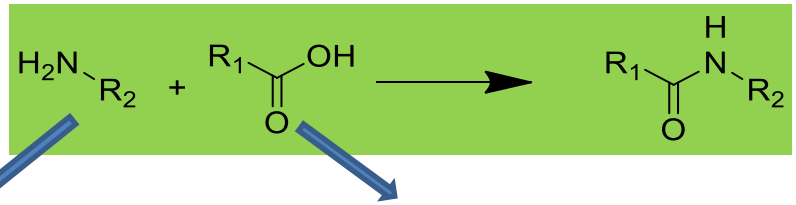
Primary Human bronchial epithelial cells

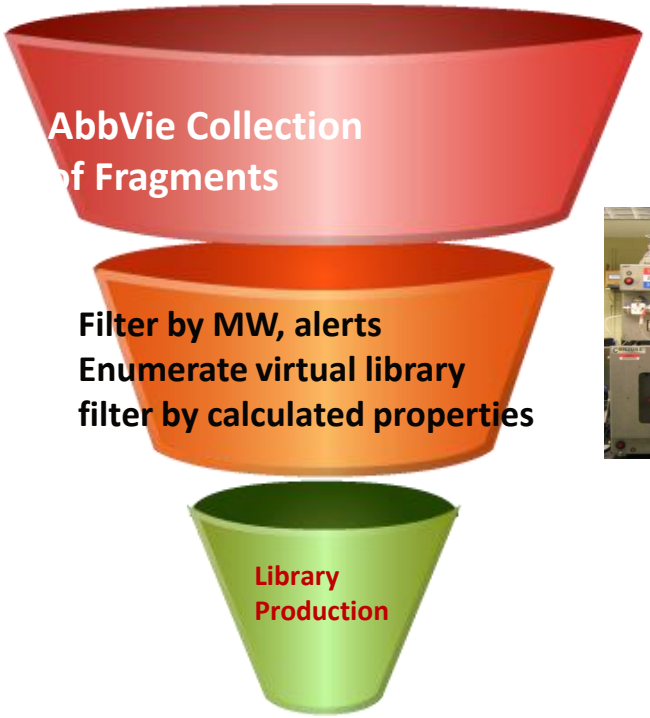
Co-incubate Correctors with Potentiator overnight

Measure Ieq in TECC after Forskolin activation of CFTR



SWIFT Platform applied to CFTR C1 corrector program

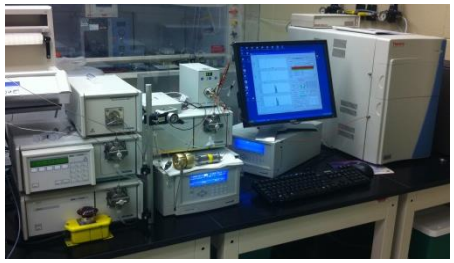


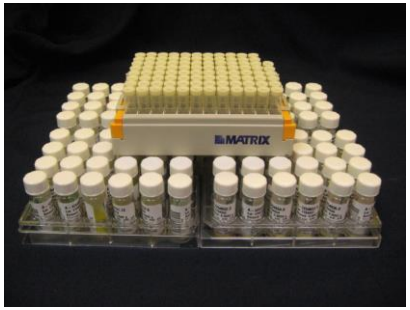


SWIFT Synthesis Platform

- Reactions run in Conjure flow reactor
- Fully integrated synthesis and purification, enabling rapid registration

Fully integrated synthesis and purification



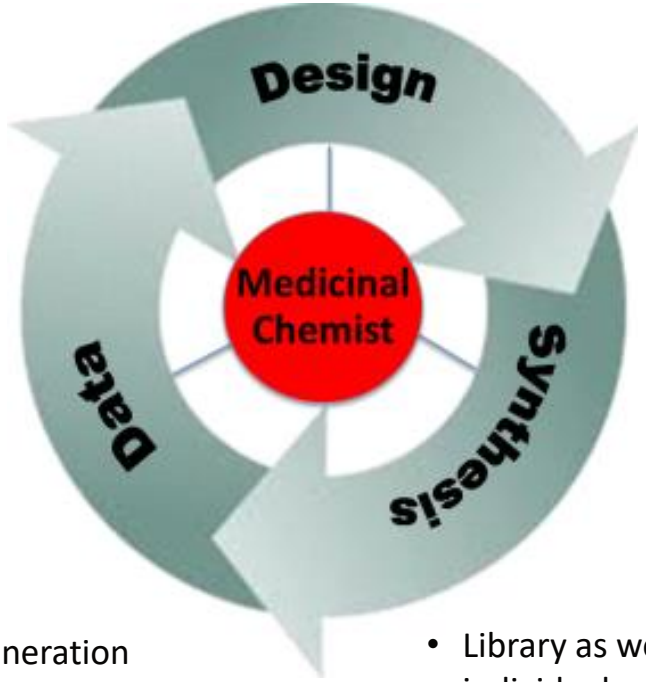


Registration and dispersal

S.W Djuric. et al. *J. Flow Chem.* **2011,** 2, 56–61.

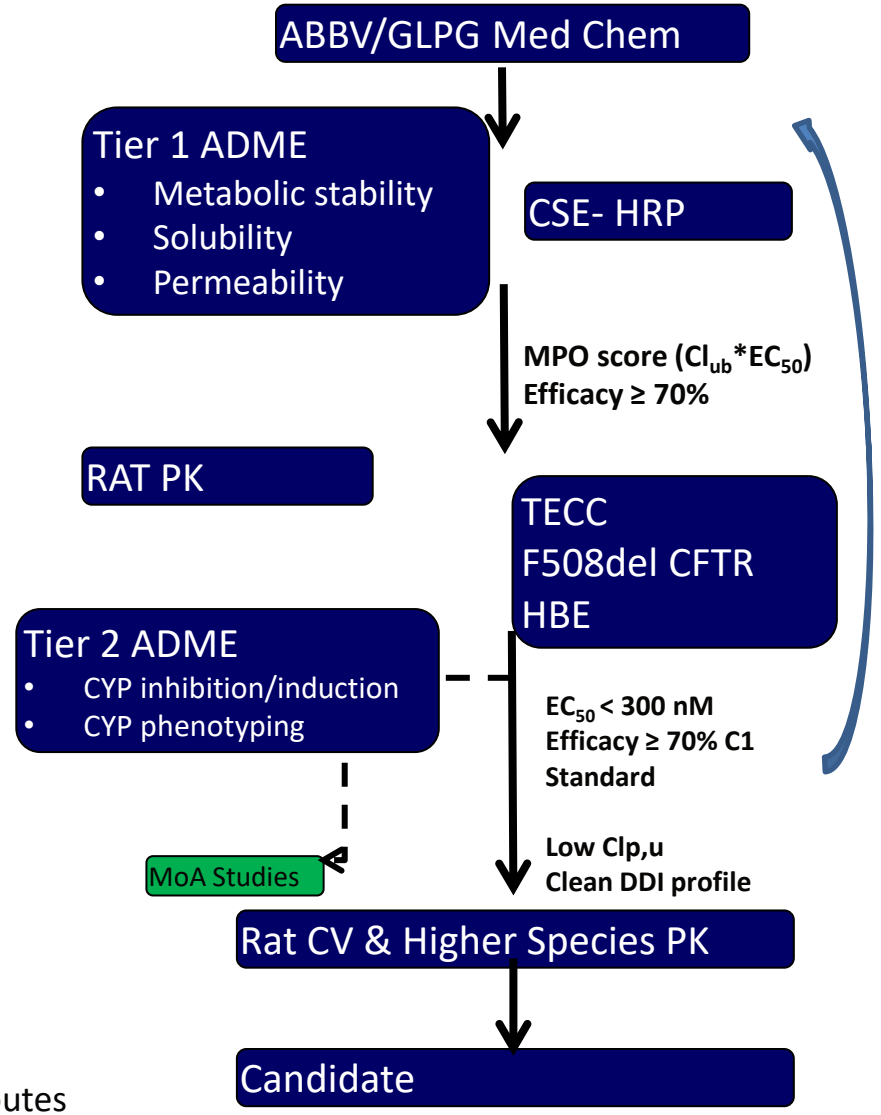
Medicinal Chemistry Approach and Assay Funnel

- Compound design based on data analysis, experience, and cheminformatic tools
- Prospective property calculation
- Prioritization based on synthetic accessibility



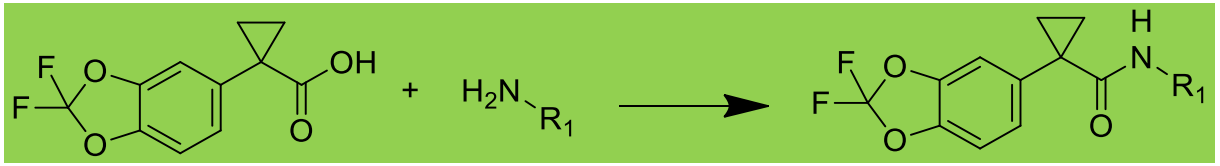
- Data generation and analysis

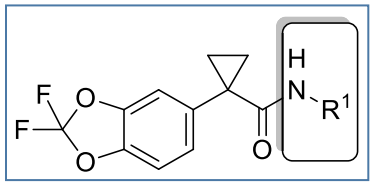
- Library as well as individual compound generation
- Specialized synthetic chemists tackle novel cores and optimize routes

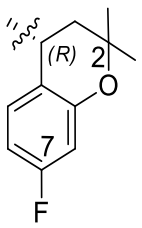


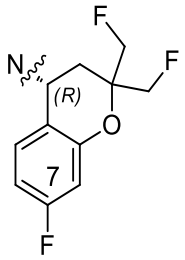
CFTR C1

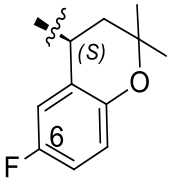
Chromane SAR Exploration via Segmented Flow Based Libraries

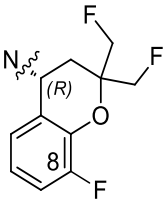


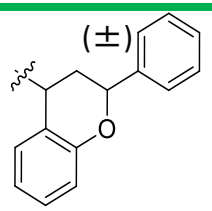










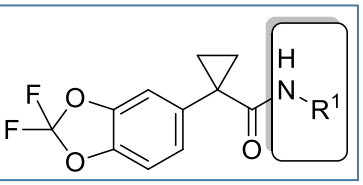


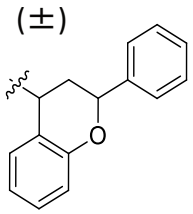
	1	2	3	4	5
CSE-HRP (EC_{50} μM, Max. Act% C1 control)	2.6, 99%	4.1,100%	>20, 8%	>10, 22%	2.7, 110%

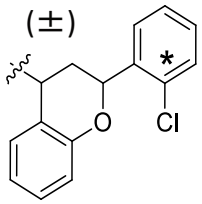
- Chromane groups demonstrated unexpected activity
  - **From proprietary amine collection**
- Difference in stereochemistry observed
- C-2 phenyl analogs followed up: high efficacy, tunable SAR

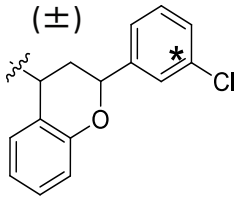
CFTR C1

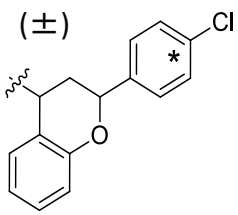
Chromane SAR Exploration-Contd

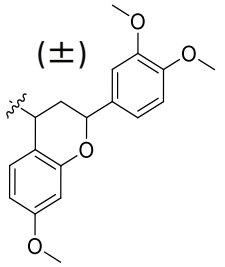










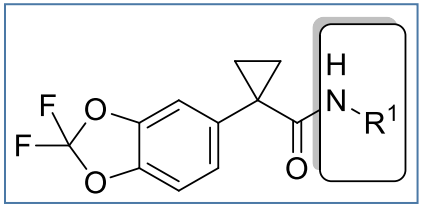


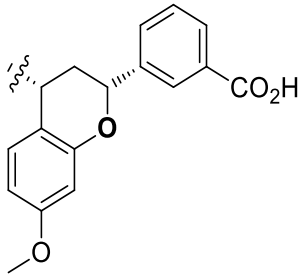
Compound		5	6	7	8	9
CSE-HRP (EC_{50} μM, Max. Act% C1 Control)		2.7, 110%	12, 33%	4.1, 77%	0.80, 92%	0.21, 119%
In Vitro ADME	Rat/Human Clint,u (L/hr/kg)- hep	470/49		580/110	460/110	230/77
	PAMPA Peff (x10-6 cm/s)	0.04	0.3	0.26	0.03	0.3

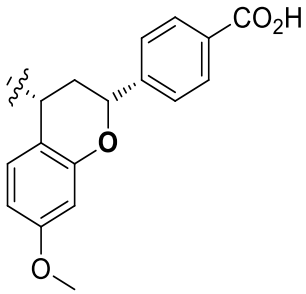
- C-2 phenyl potent/efficacious
- Substitution on distal phenyl important
- Compounds have high in vitro hepatocyte clearance (>>20L/hr/kg) and poor permeability (<1 x 10^{-6} cm/s))

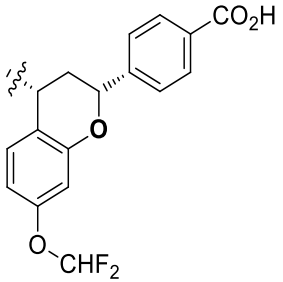
CFTR Type 1 Correctors

Chromanes - Candidate Identification









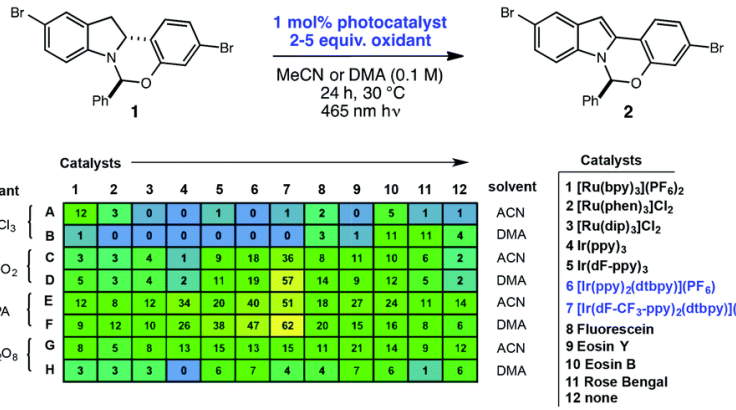
Compound		13	17	18
In-Vitro Assay	HBE TECC EC_{50} µM, Max %C1 standard	**0.238, 95%**	**0.009, 94%**	**0.005, 87%**
In Vitro ADME	Rat/Human Clint,u (L/hr/kg)- hep	25/17	15/3	7/3
	CYP 3A4 induction	Negative	Negative	Negative
In Vivo PK	Cl_p (%LBF) (rat)	< 30%	< 30%	< 30%
	$T_{1/2}$ (hr);	3.3	~3	3~5

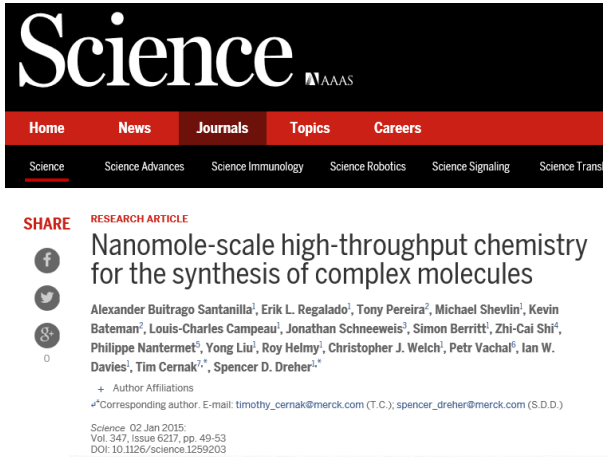
- para-substituted acid **17** unexpectedly has improved potency, and reduced clearance

➢ Compound **18** was nominated as preclinical candidate – **ABBV-2222**

High Throughput Chemistry Technology – the Future

- Integrated Synthesis-purification –bioassay platforms
- Reaction scouting – High Throughput Experimentation techniques
  - Yields for reactions such as Buchwald, Negishi , Chan-Lam etc generally low in a parallel synthesis context (~20-30%)



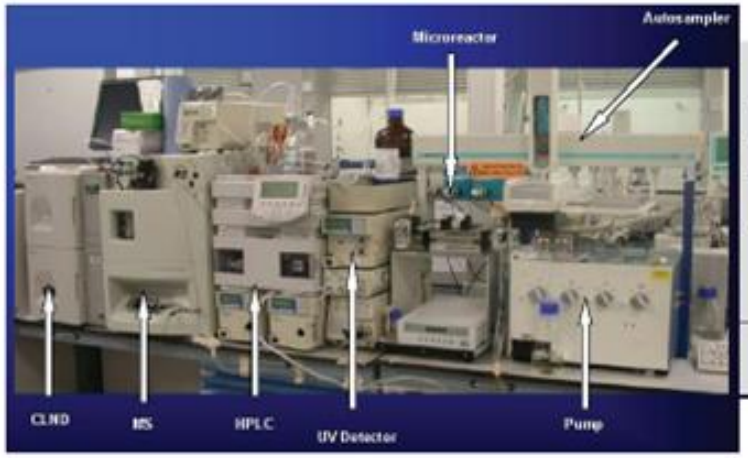


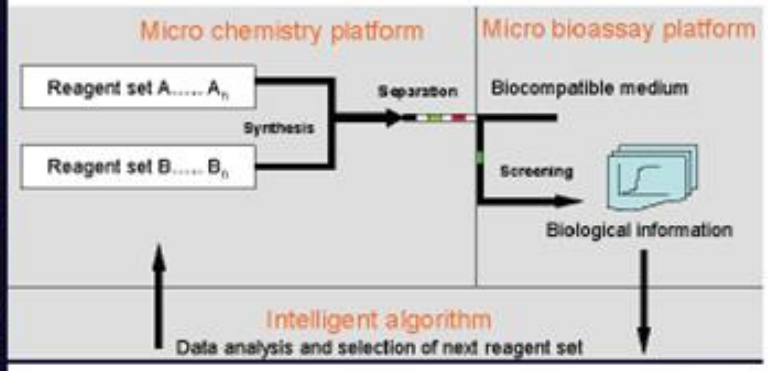
- Robochemists
- AI based interpretation/ analysis of SAR data
- Virtual Reality enabled drug design

Integrated Synthesis-Purification-Bioassay platforms

- Compound synthesis and testing takes weeks. How about

  Integrated chemistry – biology systems on chip?



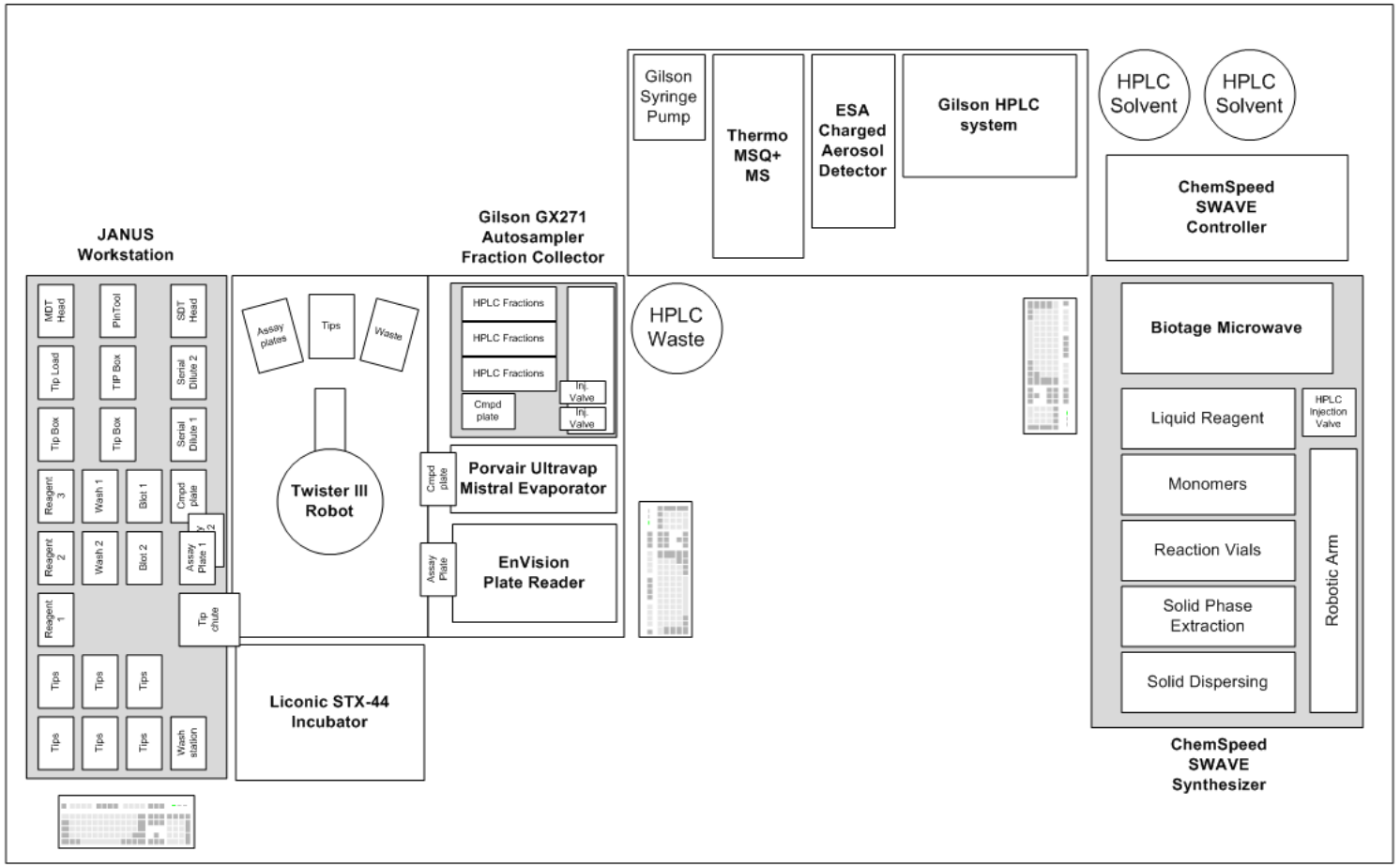


Stephanie Y. F. Wong-Hawkes, et al, GSK; 30th National Medicinal Chemistry Symposium, Washington, June 2006

- Key components – Synthesis and Purification using a microfluidic kit followed by in-line bioassay in flow.
  - New seed SAR followed by CADD of next compounds (need proprietary software)
- Subsequently, Cyclofluidic and Roche

Compound library production- Next steps

- Synthesis and purification of compounds using segmented flow technology – SWIFT Platform
- What's next?
  - Integrated Synthesis-purification-bioassay - ***BIOSIP***



BioSIP - Fully Integrated Synthesis-Purification-Bioassay System

- Process needs to be achieved in a couple of days maximum
- Compounds will be made on small scale (1-2 mgs) and assayed.
  - Compounds of interest will be re-synthesized

Decisions:

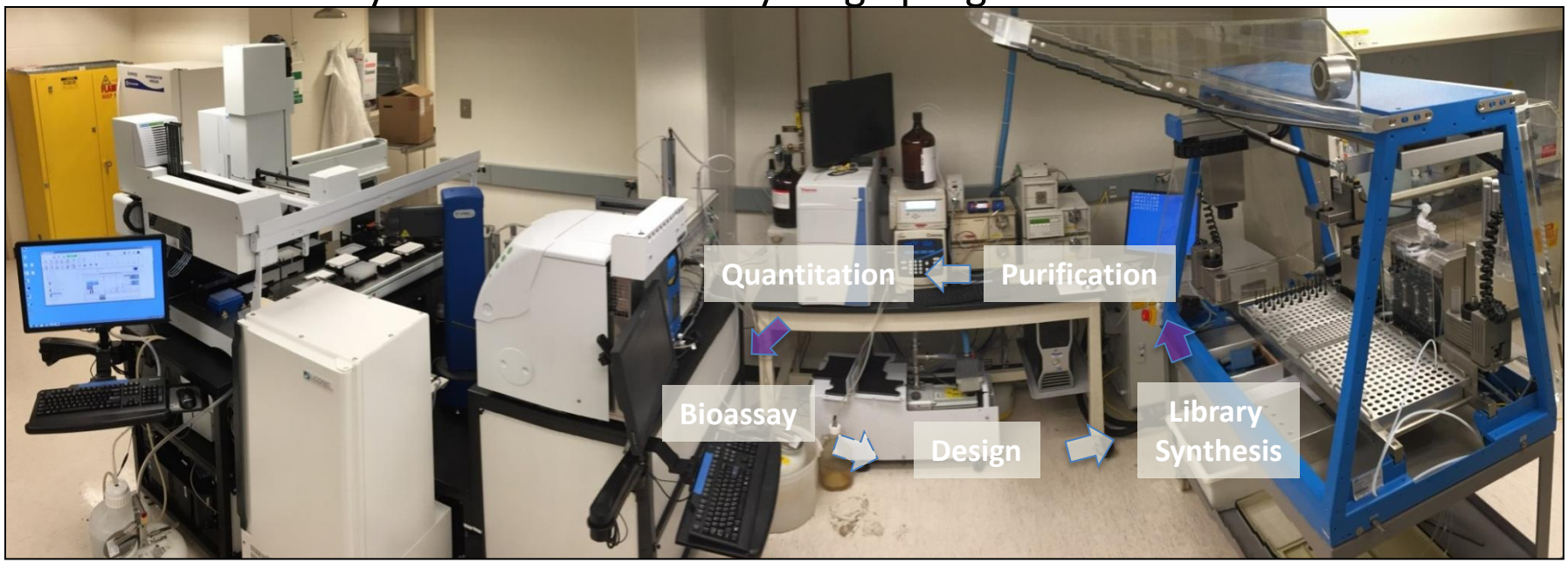
1. Choice of projects e.g HtL
2. Choice of synthesis platform
3. Choice of method of compound quantitation
4. Choice of bioassay platform
   - Assay scope?

2.5 years in development

Integrated Synthesis – Purification - Bioassay System (BioSIP)

Goal: *Deliver primary bioassay data within 36 hr of start of synthesis*

✓ Particularly well-suited for early stage programs



Status:

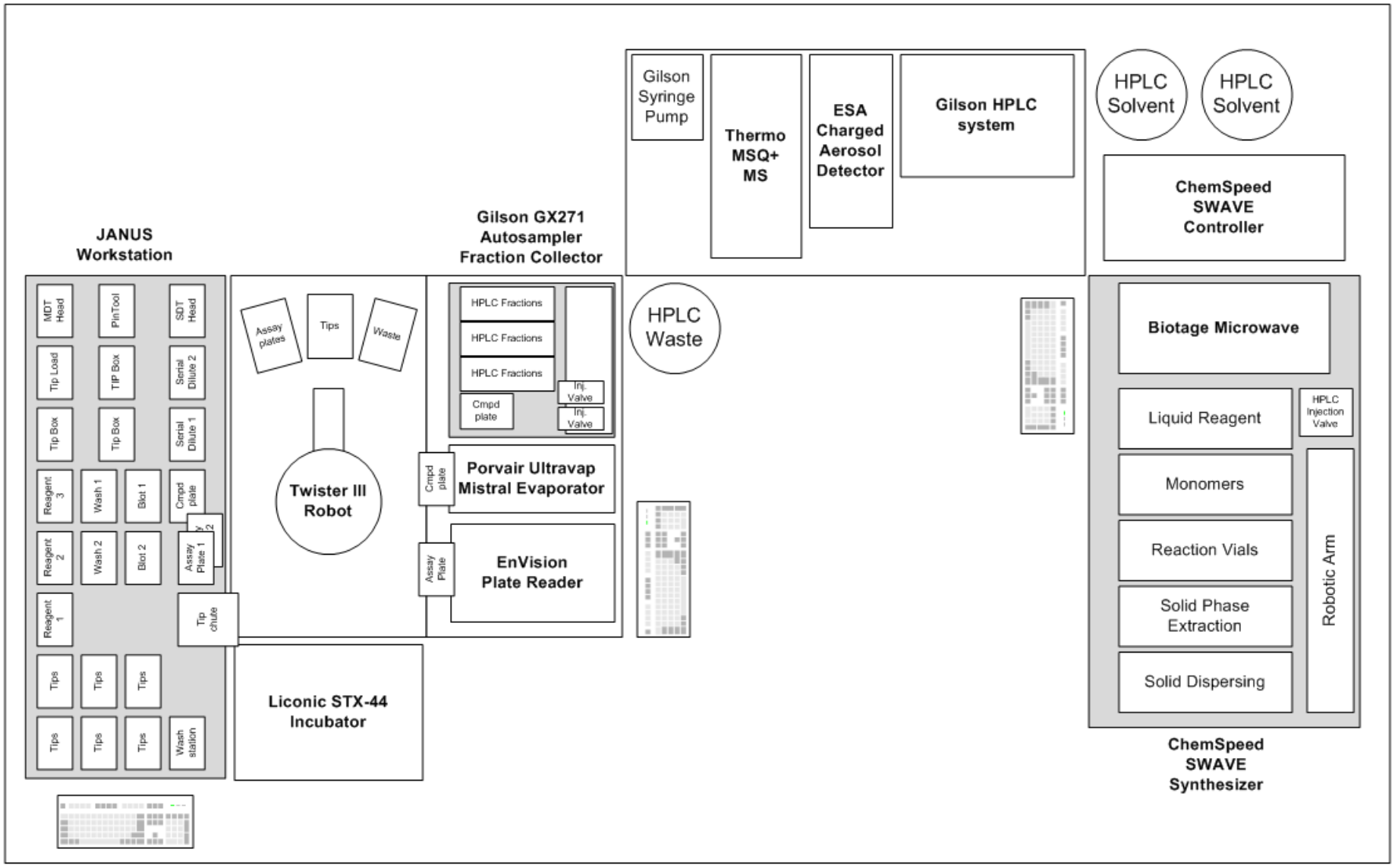
- Implemented 9 libraries for Project A, 11 libraries for Project B and 2 libraries for Project C during 2016
- Average cycle time from *start of synthesis to bioassay data* < 24 h
- 5 Reaction chemistries: Acylation, Sulfonylation, Suzuki, Nucleophilic subn, Reductive amination
- Bioassay data shows very good correlation with data from HTS

2018 – routine use for HTL programs

Integrated Synthesis – Purification - Bioassay System (BioSIP)

Integrated Synthesis-Purification-Bioassay System.
ChemSpeed Synthesizer (1); Gilson HPLC (2); Thermo MSQ-Plus MS (3); Charged Aerosol Detector (4); Autosampler/fraction collector (5); Ultravap Mistral Evaporator (6); Twister III robotic arm (7); JANUS liquid handling workstation (8); Incubator (9); EnVision plate reader (10).

BioSIP- Layout



Innovation through External Collaborations – Selected Examples

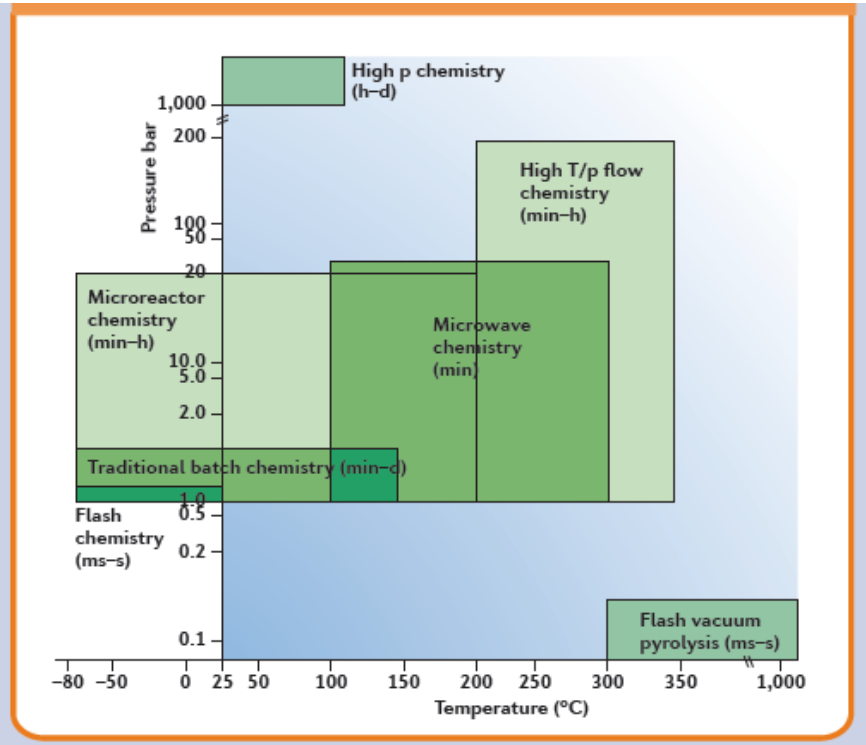
- Noel Group - Eindhoven University of Technology, Netherlands: Late stage oxygenation reactions using photocatalysis in flow
- Cooks group – Purdue University, USA: Microdroplet accelerated chemistry
- NewPath Molecular – Cambridge UK: Laboratory Robotics and Automation

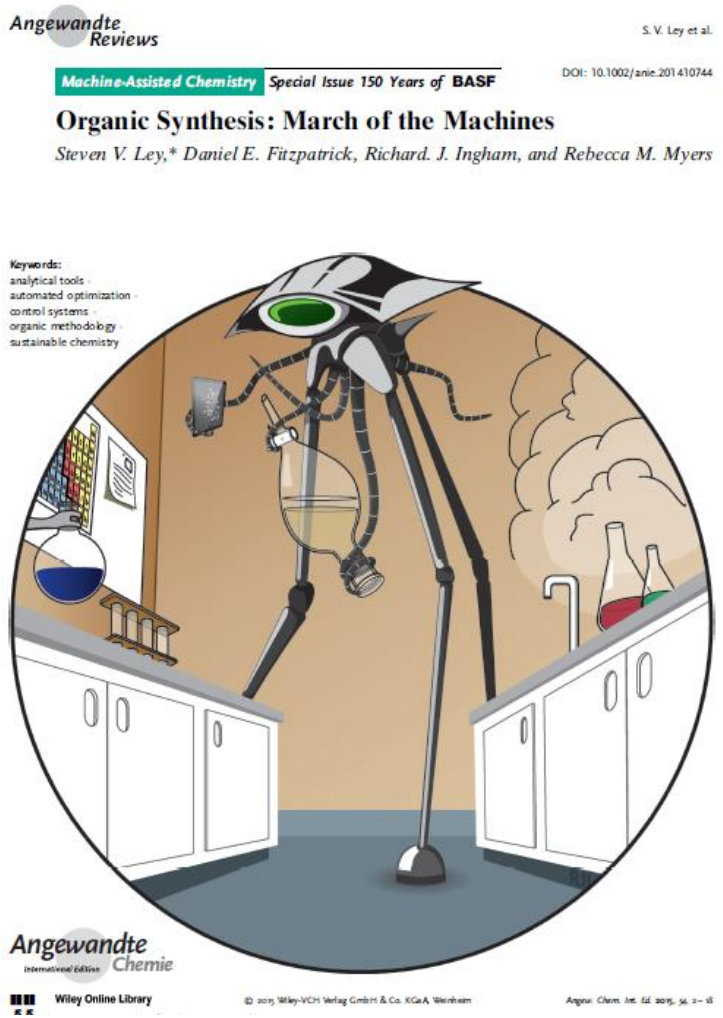
New Chemistry Technology

Problem of Anthropogenic Reaction Parameters

Welcome to the machine

- Flow Synthesis Platforms
  - Integrated Synthesis/Bioassay platforms
  - Photochemistry
  - Electrochemistry
  - High Temperature Chemistry





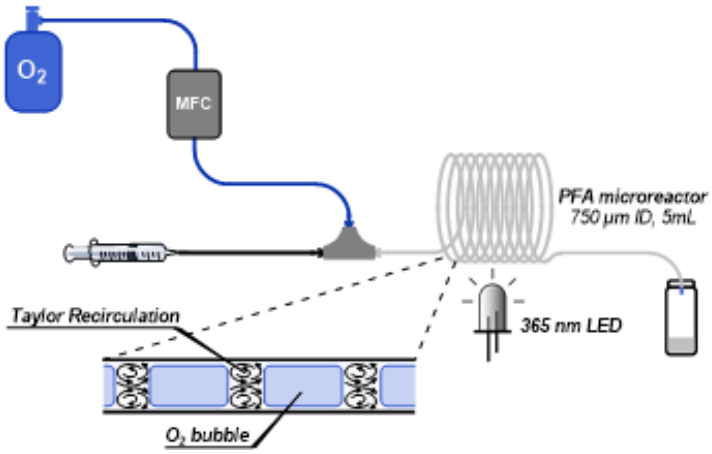
Oxidation in Flow – Photocatalytic approach
Late stage molecular functionalization.

Selective *sp*^{3} C–H Aerobic Oxidation enabled by Decatungstate Photocatalysis in Flow

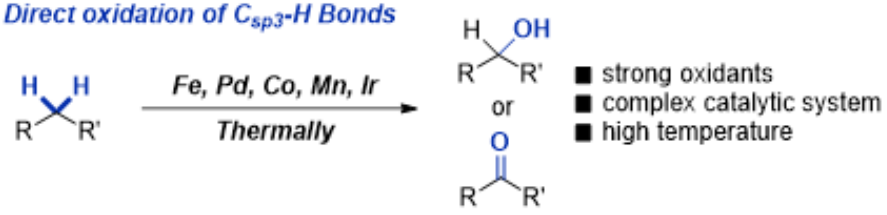
Gabriele Laudadio, Sebastian Govaerts, Ying Wang, Davide Ravelli, Hannes F. Koolman, Maurizio Fagnoni, Stevan W. Djuric, Timothy Noël*

ACIE (2018) in press

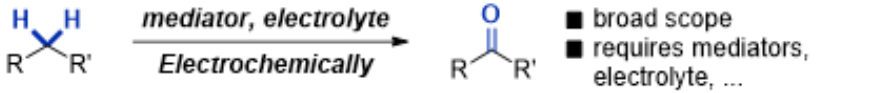
Table 2. Reaction optimization of the C_{sp3}–H oxidation enabled by decatungstate photocatalysis in flow.



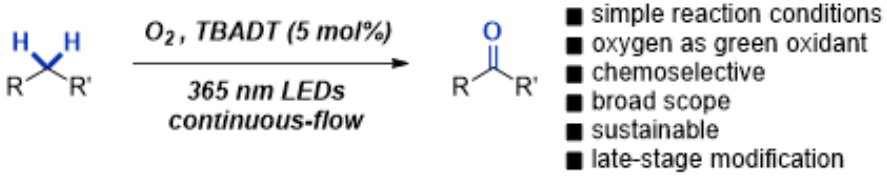
a) Direct oxidation of C_{sp3}-H Bonds



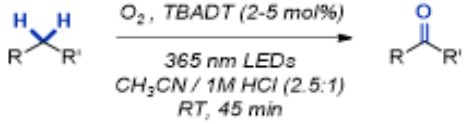
b) Electrochemical oxidation of C_{sp3}-H Bonds (Baran)



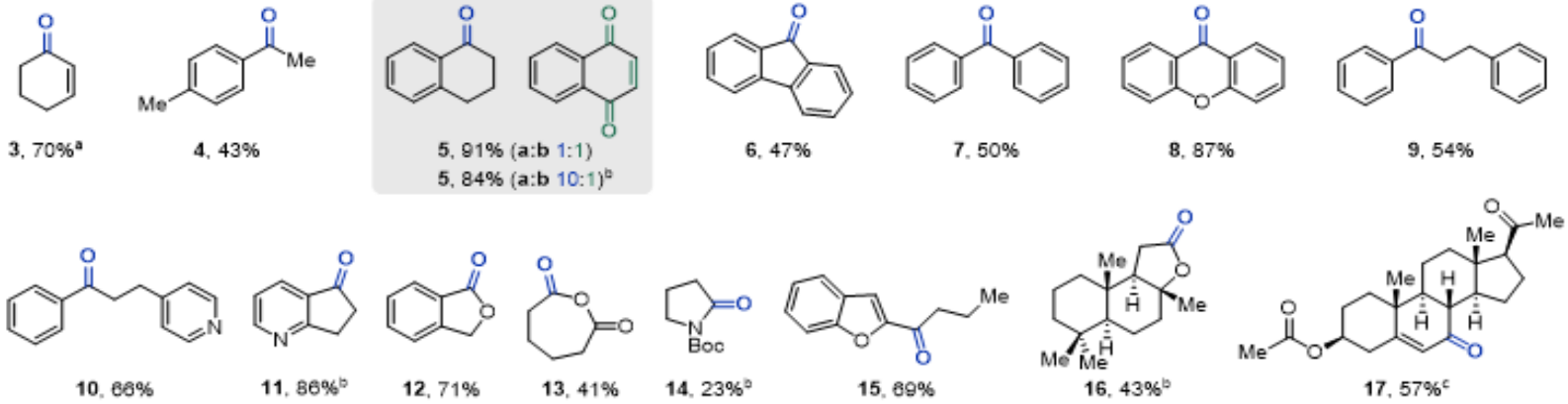
c) This Work: Photocatalytic aerobic oxidation of activated and unactivated C_{sp3}-H Bonds



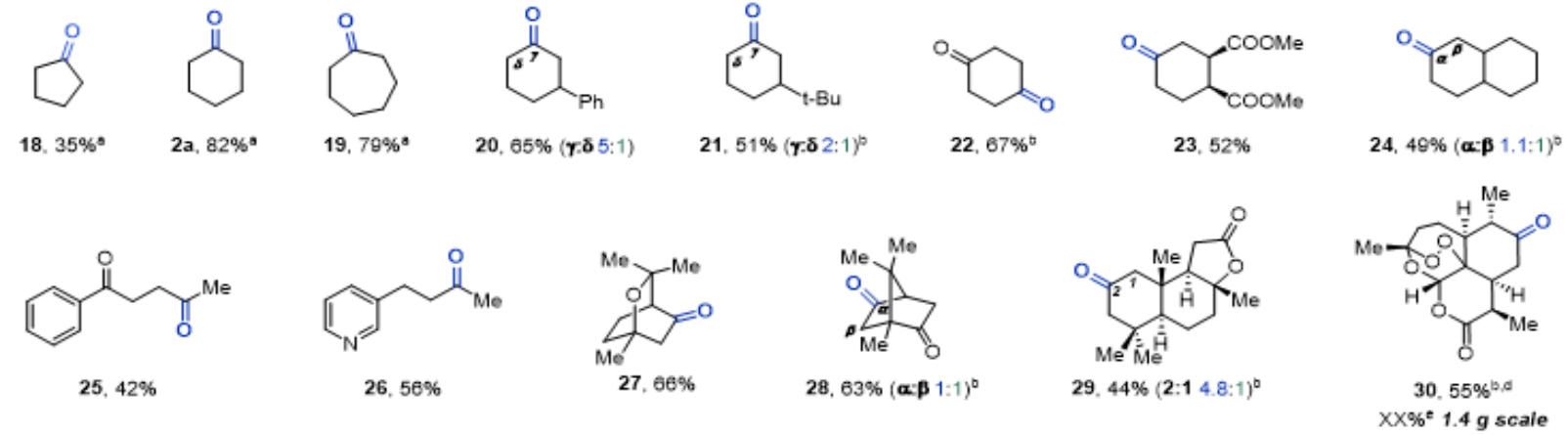
Scheme 2. Substrate scope of the Csp^3–H oxidation enabled by decatungstate photocatalysis in flow.



Activated C-H Bonds



Unactivated C-H Bonds



Exploration of "Forbidden" Chemistries:

High Temperature Chemistry

The Arrhenius Equation

$$k = Ae^{-Ea/RT}$$

where *k* is the rate constant at T

E_a is the activation energy

R is the energy gas constant

= 8.3145 J/(mol K)

T is the Kelvin temperature

A is the collision frequency factor

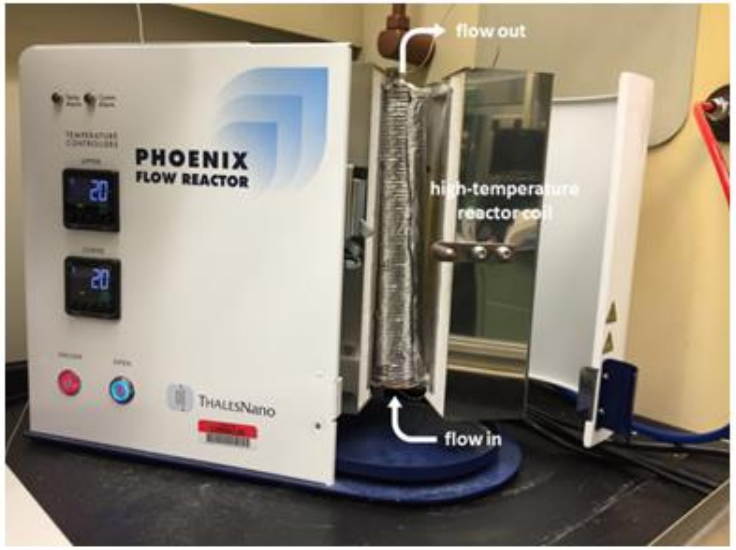
Table 3. Reaction Time Dependence on Temperature[a]

T/(°C)	times/(h/min/s)				
20	1	4	12	48	172
40	15	1	3	12	86
60	4	15	45	3	11
80	56	2	11	45	3
100	14	56	3	11	40
120	4	14	42	3	10
140	53	4	11	42	3
160	13	53	3	11	38

[a]An illustrative table for the theoretical decrease in the reaction time. Adapted from *Flow Chemistry: Fundamentals.*[98]

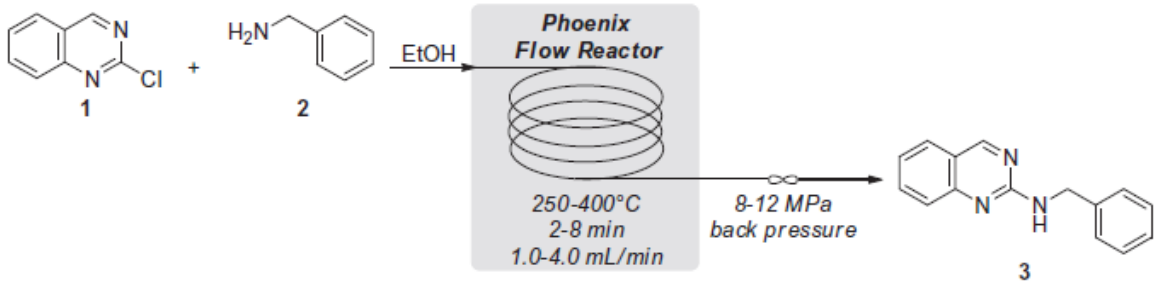
For many common chemical reactions at room temperature, the reaction rate doubles for every 10 degree Celsius increase in temperature.

- Collaboration with ThalesNano using the Phoenix reactor
- Goal: Expand current range of chemistries available esp for synthesis of novel heterocyclic building blocks



Nucleophilic Aromatic Substitution of Heterocycles using a High Temperature and High Pressure reactor

Table 1
DoE optimization of continuous-flow S_NAr between 2-chloroquinazoline and benzylamine



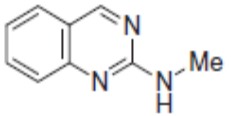
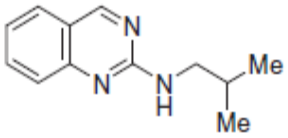
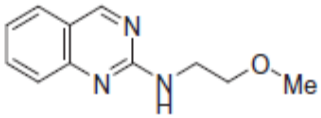
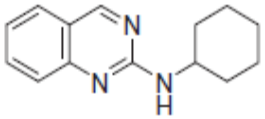
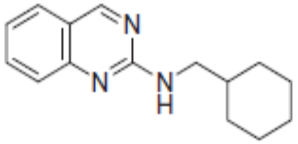
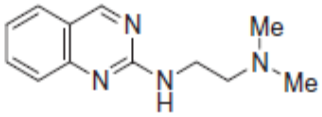
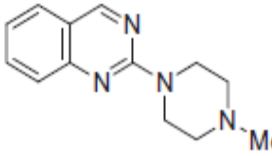
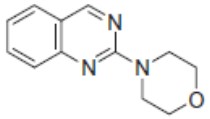
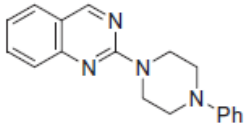
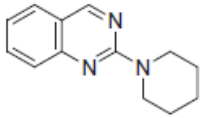
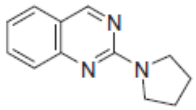
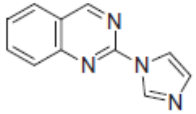
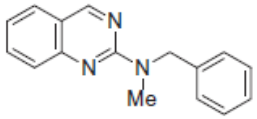
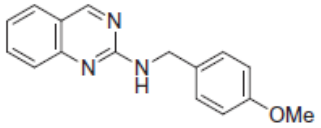
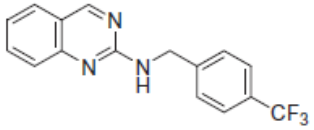
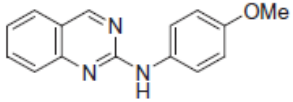
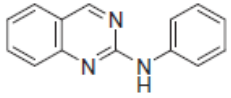
Temperature (°C)	Pressure (MPa)	Flow rate (mL/min)	Product[a] (%UV)
250	8	2.5	46
250	10	4.0	29
250	10	1.0	75
250	12	2.5	42
325	8	1.0	37
325	8	4.0	20
325	10	2.5	34[b]
325	12	1.0	62
325	12	4.0	47
400	8	2.5	25
400	10	1.0	37
400	10	4.0	27
400	12	2.5	37

[a] Percent product by analytical HPLC.
[b] Center point, average of 4 runs.

x 11.02 in

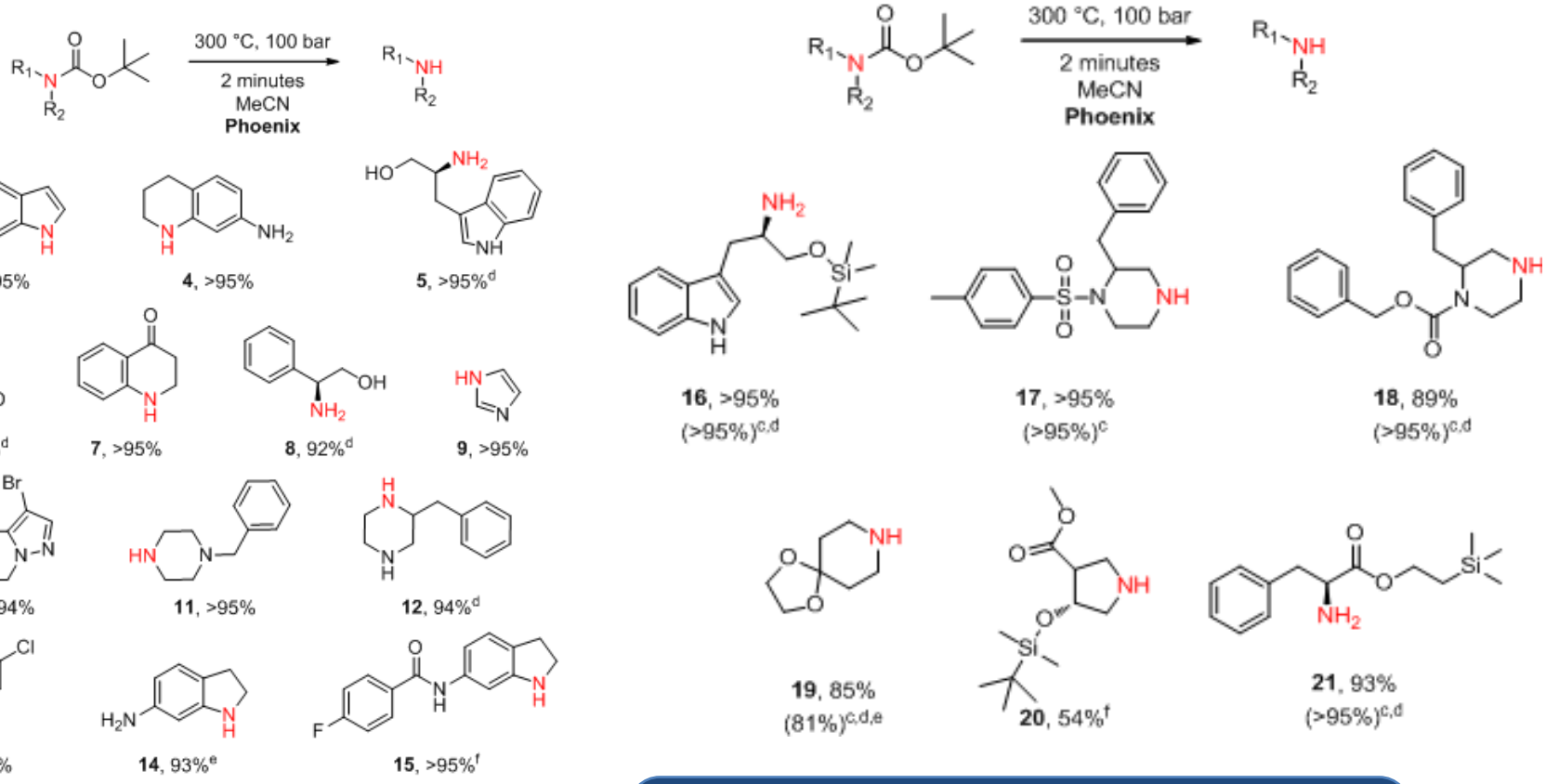
Tetrahedron Letters. 57 1035 (2016)

Table 2
Scope for the continuous-flow S_NAr of **1** with nitrogen nucleophiles[a–c]

	2-Aminoquinazoline product	Isolated yield (%)
4		73
5		92
6		92
7		82
8		90
9		38
10		71
11		79
12		66
13		64
14		73
15		50
16		68
17		66
18		60
19		63
20		39

Novel, Selective Removal of N-Boc groups:

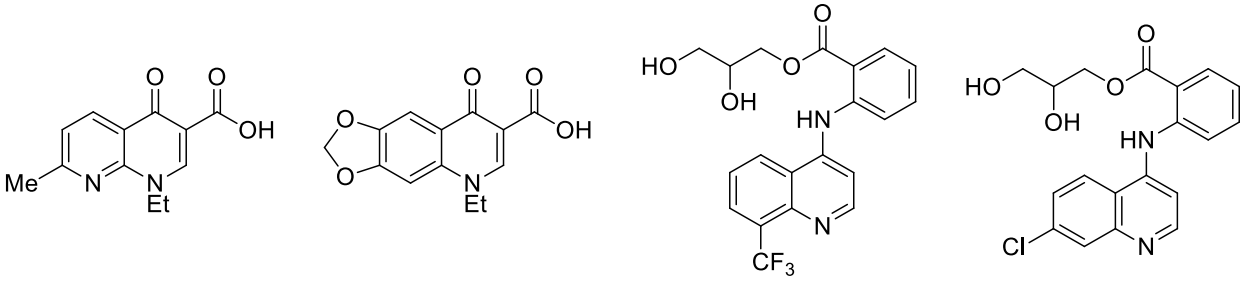
Utilization of High Temperature Chemistry



Andrew R. Bogdan,*, Manwika Charaschanya, Amanda Worthy, Ying Wang and Stevan W. Djuric

Org. Letters (2016)

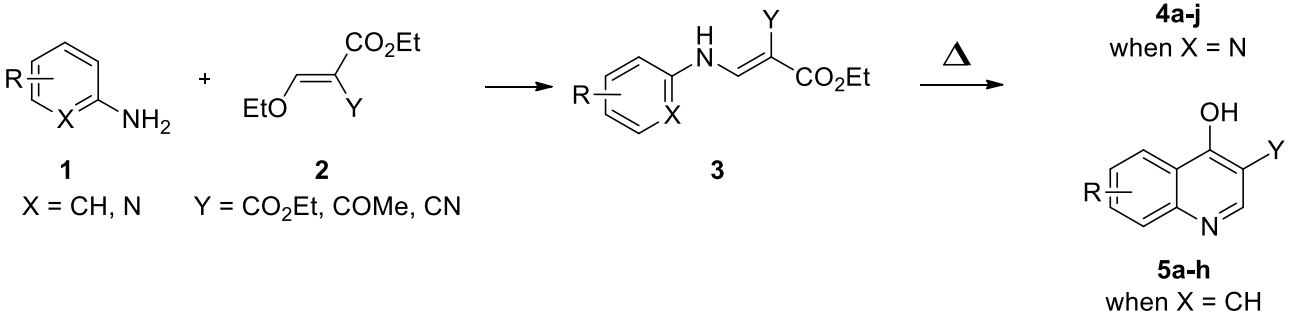
Synthesis of Fused Pyrimidinone and Quinolone Derivatives in an Automated High Temperature and High Pressure Flow Reactor



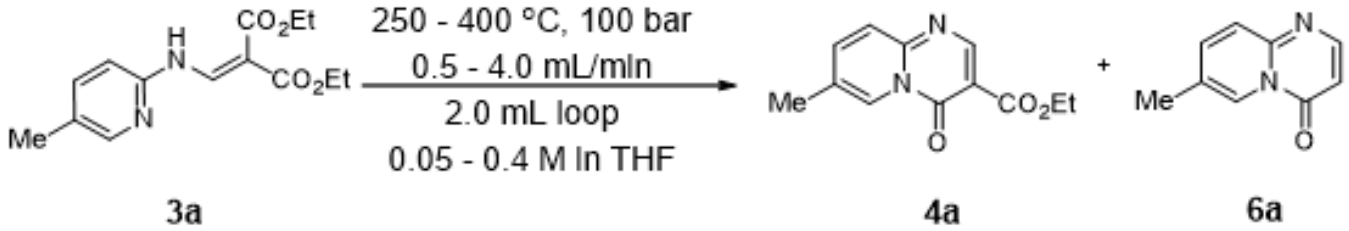
Quinolone Containing Drugs

Gould-Jacobs Reaction

- **>200^{0}C**
- **Long reaction times**
- **Dowtherm or diphenyl ether as solvents**

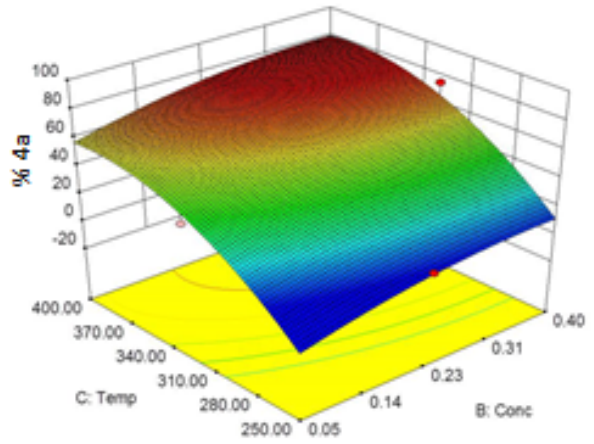


Reaction Optimization using DoE

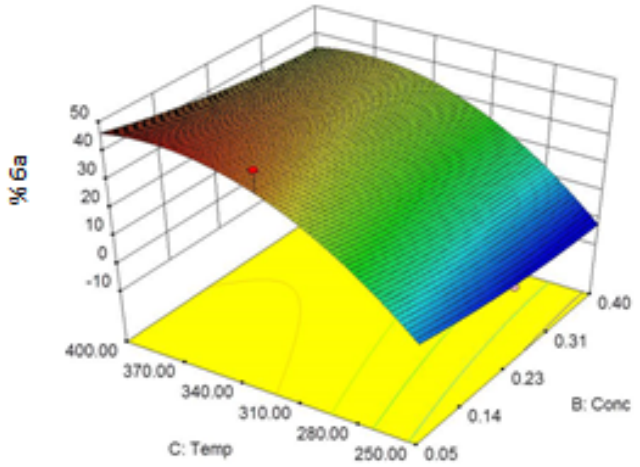


3a **4a** **6a**

a: Flow rate: 4 mL/min (rt = 0.5 min)



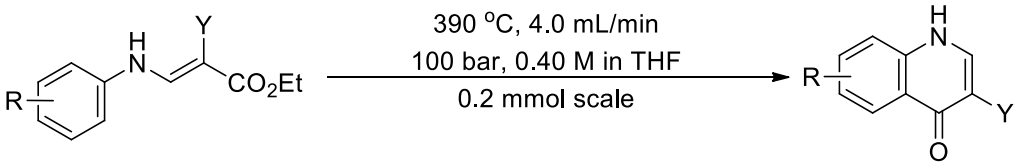
b: Flow rate: 0.5 mL/min (rt = 4 min)



*Response surface models designed using Box-Behnken design on Stat-Ease Design Expert 7 (16 runs, 5 centre points).
DoE = Design of Experiment; rt = residence time.

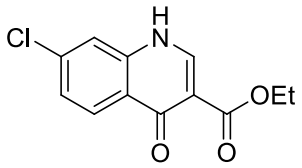
Predicted conditions for 4a: T = 390 °C, P = 100 bar
flow rate = 4.0 mL/min
conc. = 0.4 M in THF

Synthesis of Quinolones

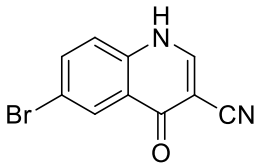


3
Y = CO_2Et, CN, COMe

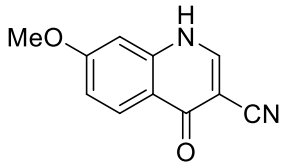
5



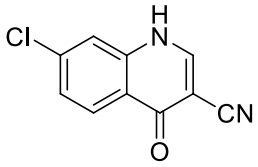
5a (32%)



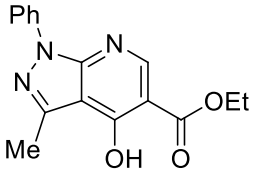
5b (92%)



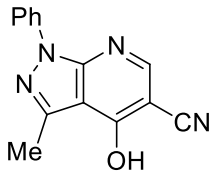
5c (45%)[b]



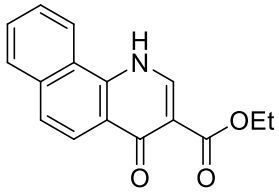
5d (35% 7-Cl; 13% 5-Cl)



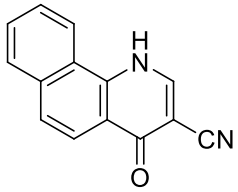
5e (68%)[c]



5f (95%)



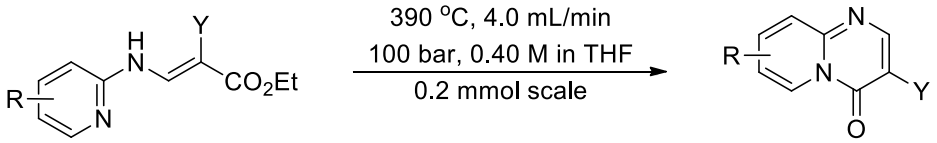
5g (48%)[d]



5h (82%)

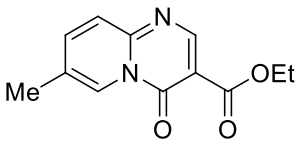
Synthesis of Pyrimidones

J.Tsoung, A.R.Bogdan, S.Kantor, Y. Wang,
M. Charaschanya, and S. W. Djuric,
Journal of Organic Chemistry,
DOI: 10.1021/acs.joc.6b02520

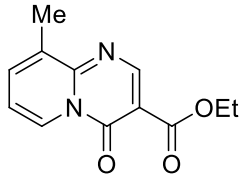


3
Y = CO_2Et, CN, COMe

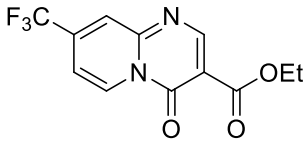
4



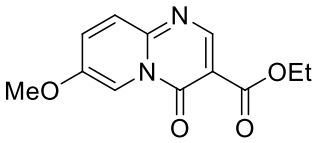
4a (96%)



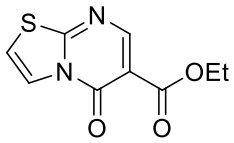
4b (96%)



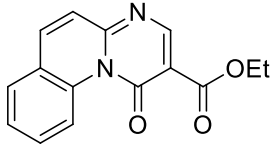
4c (88%)



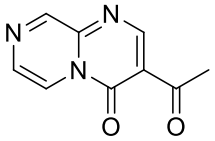
4d (96%)



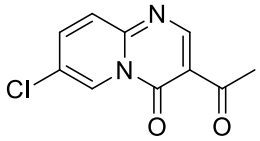
4e (94%)



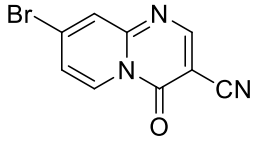
4f (94%)



4g (91%)



4h (96%)



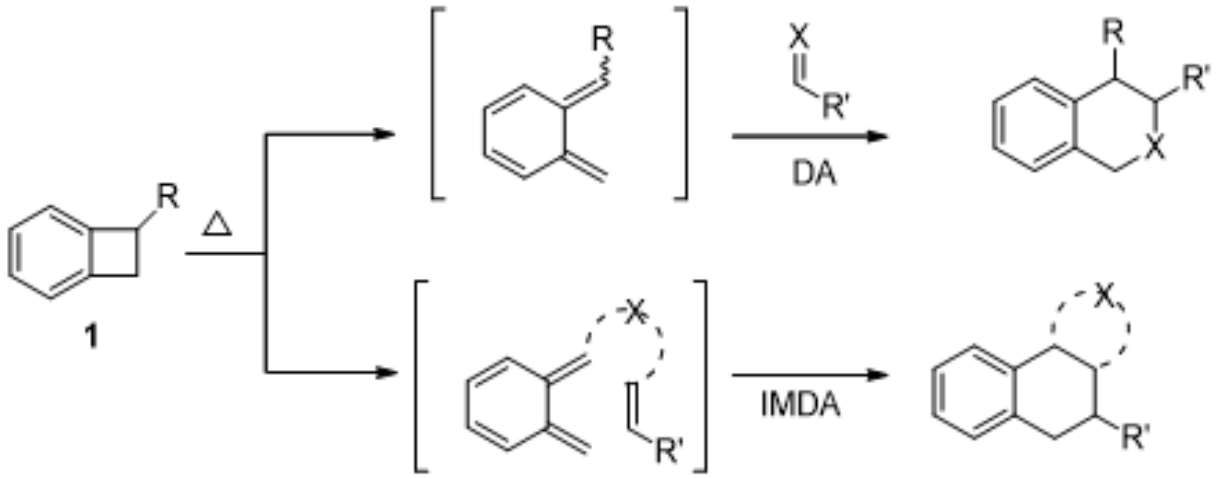
4i (77%)

Synthesis of Building Blocks and Fragments

Utility of High temperature Chemistry

Expedient Diels-Alder Cycloadditions with *ortho*-Quinodimethanes in a High Temperature/Pressure Flow Reactor

Jennifer Tsoung,[a] Ying Wang*,[a] and Stevan W. Djuric[a]

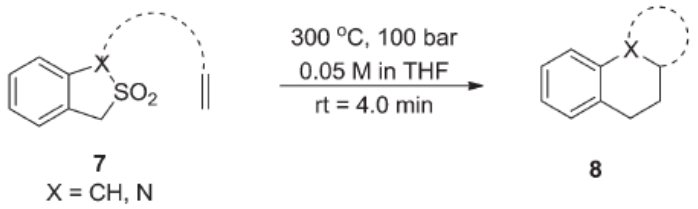


Scheme 1 – Inter- and Intra-molecular Diels-Alder cycloadditions of *o*-QDMs

React. Chem. Eng., 2017, Advance Article
http://dx.doi.org/10.1039/C7RE00058H

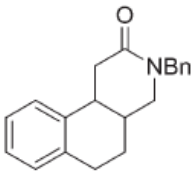
High Temperature intramolecular Diels-Alder reaction: *Examples*

Table 3 Intramolecular Diels–Alder cycloadditions of *o*QDM precursors 3[a]

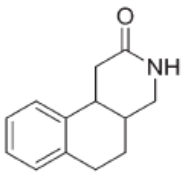


7
X = CH, N

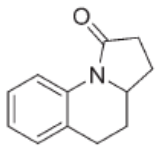
8



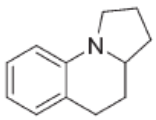
8a, 93%, (2.9 : 1)



8b, 69% (1 : 1)



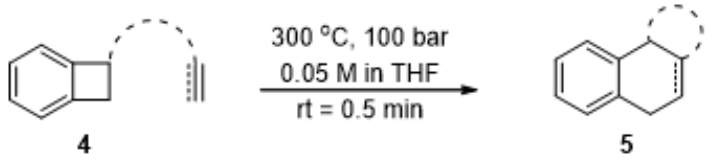
8c, 55%



8d, 14%

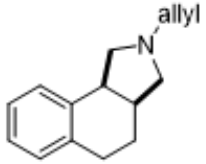
[a] Reported as isolated yields. *Cis*/*trans* ratios are reported in parantheses and determined by 1H NMR spectroscopic analysis of the crude reaction mixture.

Table 2 – Intramolecular Diels-Alder cycloaddition of benzocyclobutene 4

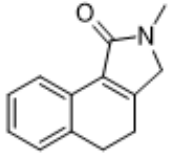


4

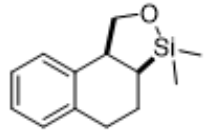
5



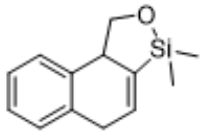
5a, 64%



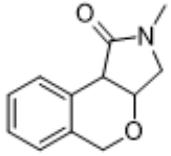
5b, 79%



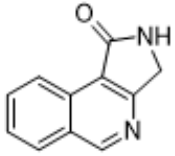
5c, 75%



5d, 21%

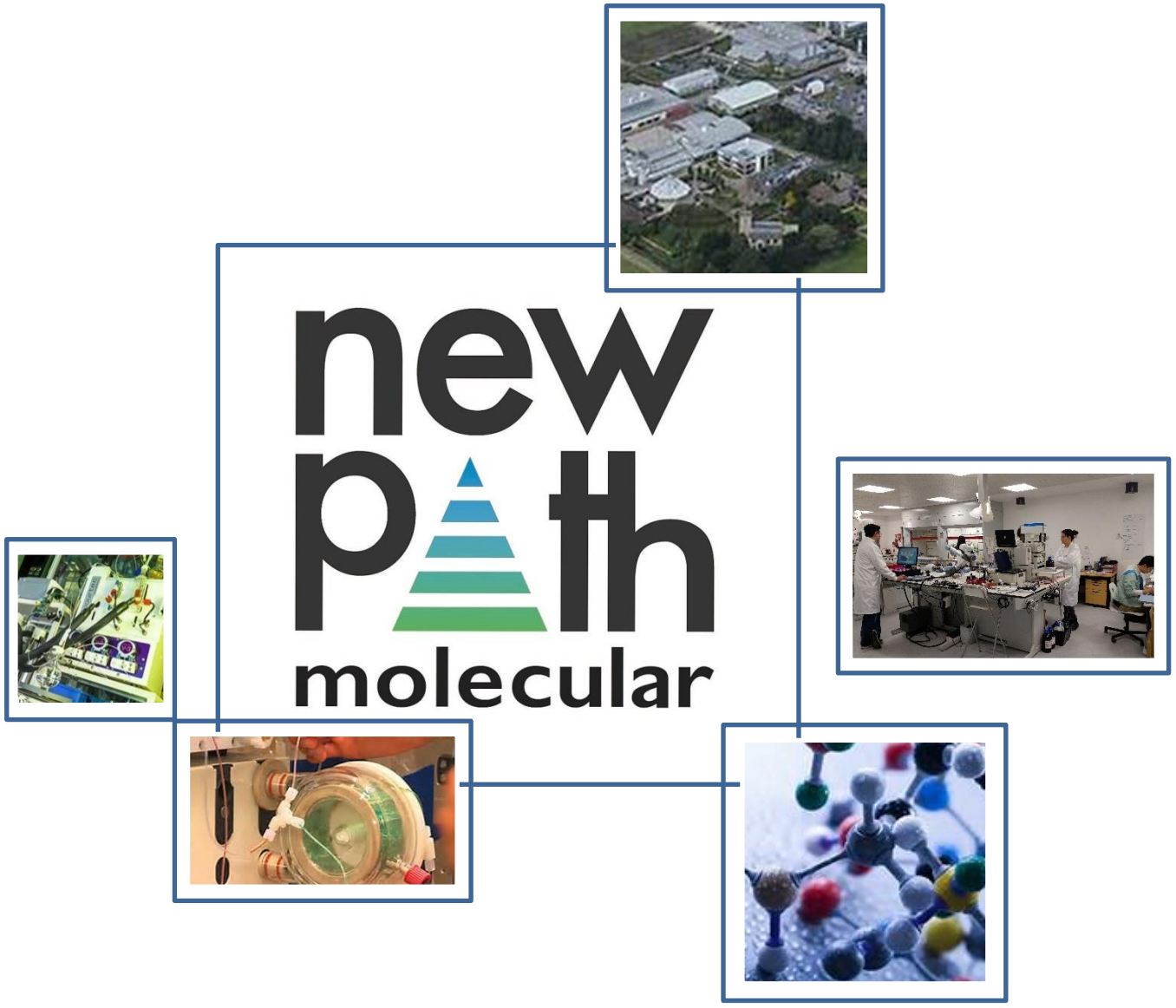


5e, 51% (1.7:1)



5f, 58%

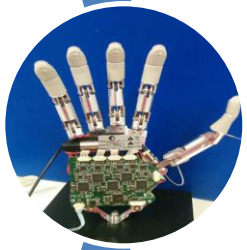
[a] Reported as isolated yields. *Cis/trans* ratios are reported in parantheses and determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.


new
path
molecular

Solving Problems with Innovative Chemistry and Technology

Innovative machine assisted chemistry

Process intensification: technologies to handle challenging aspects of synthesis; e.g. flow chemistry, reactor engineering, photochemistry, biocatalysis



Automation for preparative purposes, reaction optimisation and route scouting. Use of robotics and novel optimisation method

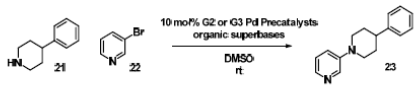
Modern chemical methodologies: e.g. photochemistry, electrochemistry , lead diversification

Example Project: The Challenge of Meaningful Automation

Easy to Automate

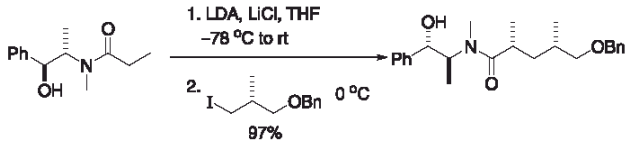
Experimental

Experiment 1. Pd C-N Coupling Reactions of 4-Phenylpiperidine 21 and 3-Bromopyridine 22: A Comparative Experiment between Reactions in 1536-Well and 96-Well Plate Microvials



Procedure for 96 Nanomolar Scale (1 uL volume) Reactions in a 1536-Well Plate (Run in Triplicate). Stock solutions of each of the reaction components were made as follows: 4-phenylpiperidine **21** (0.6 M in DMSO), 3-bromopyridine **22** (17, 0.4 M in DMSO), organic superbases (**24**-**29**, 0.8 M in DMSO, **Figure S3**), and Pd-precatalyst (**30**-**45**, 0.04 M in DMSO, **Figure S4**). For the 1536-well plate experiment, each of the solutions was dispensed in 75 uL charges to a 384-well source plate (source plate map is shown in **Figure S5**, components listed in **Table S1**).

Useful for Chemists



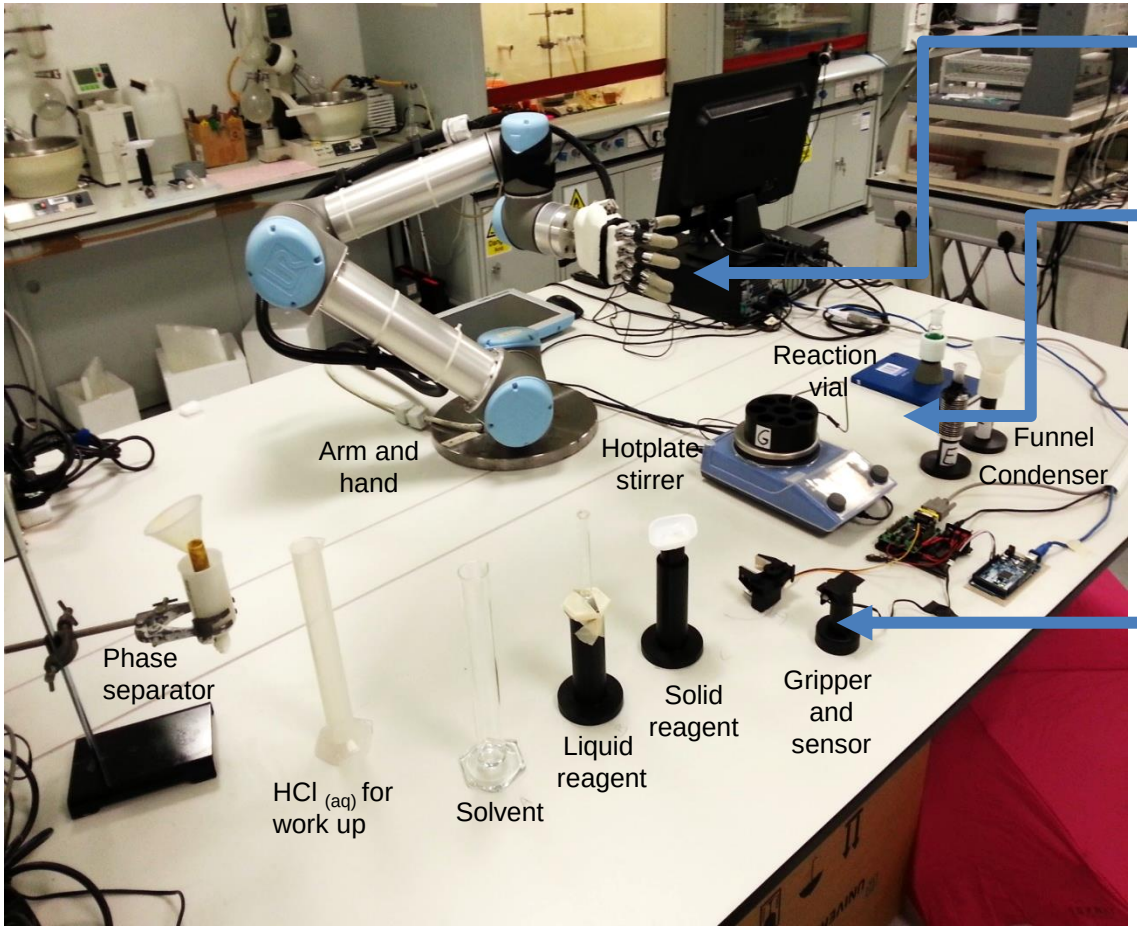
Procedure: A solution of *n*-butyllithium (2.50 M in hexanes, 27.96 mL, 69.9 mmol) was added via a cannula to a suspension of lithium chloride (9.39 g, 222 mmol) and diisopropylamine (10.6 mL, 75.3 mmol) in THF (50 mL) at -78 °C. It has been noted that the lithium chloride must be anhydrous and flame-dried immediately before use. The resulting suspension was warmed to 0 °C briefly and then cooled to -78 °C. An ice-cooled solution of the amide (8.12 g, 36.7 mmol) in THF (100 mL, followed by a 4 mL rinse) was added via a cannula. The mixture was stirred at -78 °C for 1 h, at 0 °C for 15 min at 23 °C for 5 min. The mixture was cooled to 0 °C and the iodide (5.08 g, 17.5 mmol) was added neat to the reaction via a cannula. After being stirred for 18.5 h at 0 °C, the reaction mixture was treated with half-saturated aqueous ammonium chloride solution (180 mL), and the resulting mixture was extracted with EtOAc (4 . 100 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with ether:hexanes (65:35) to afford 6.52 g (97%) of the amide as a white solid.

Novel Automation: a "Collective Intelligence" Approach

The system should be capable of:

- learning to interact with new objects and devices as the need to use these items arises
- Improved dexterity by using an anthropomorphic hand to replace the expensive and limited end-tool changing approach
- Usable Artificial Intelligence:
  - various parts of the system may work without being aware of the rest of the system, making decisions just based on the input from simple sensors
  - The final outcome though appears intelligent to the outside observer (*cf* ants and bees)
  - This is in contrast to conventional AI which uses top-to-bottom decision making

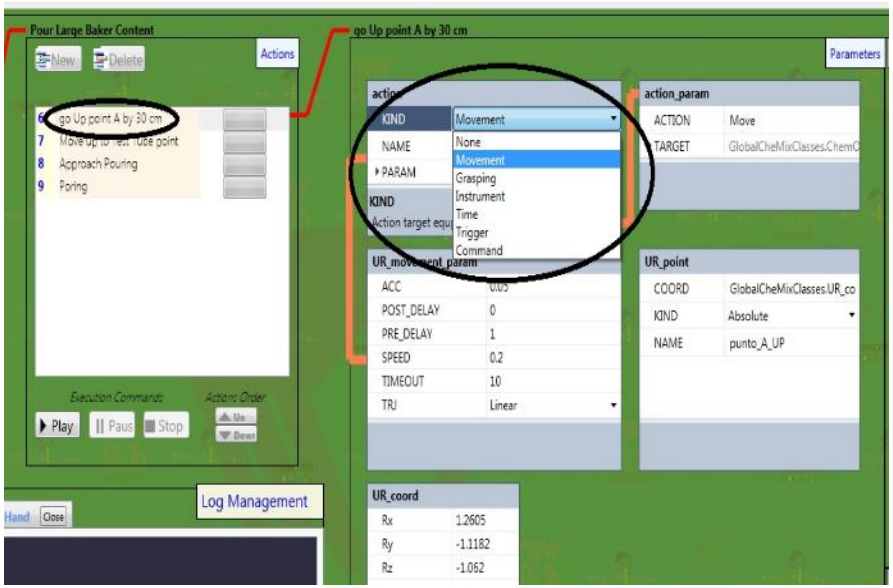
Anthropomorphic Automation With Collective Intelligence



- Anthropomorphic automation
- Standard labware
- Collective intelligence devices
- This set up for a Heck reaction

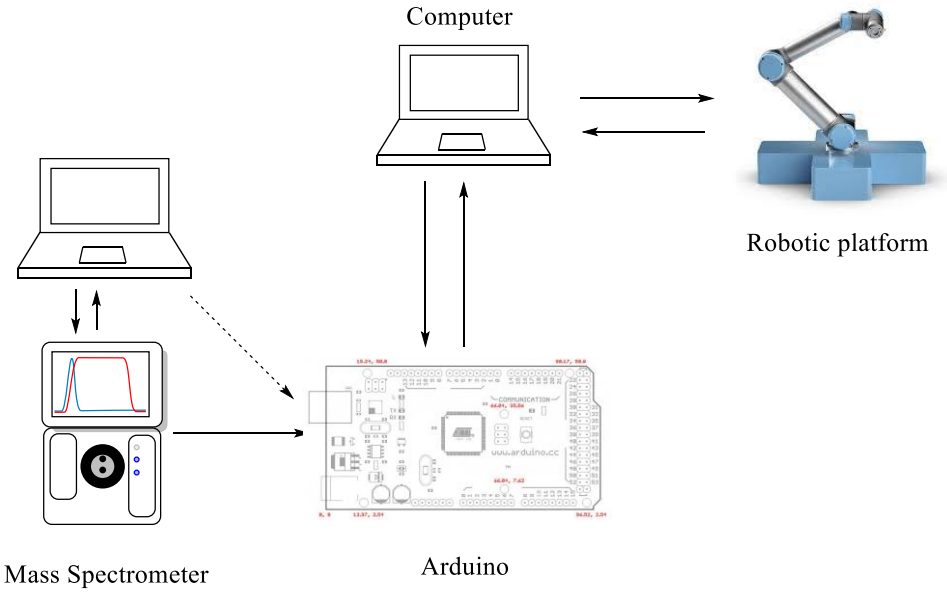
Intuitive, Flexible Software

A chemist can easily set up another reaction which uses different reagents and glassware using what the system has learned so far



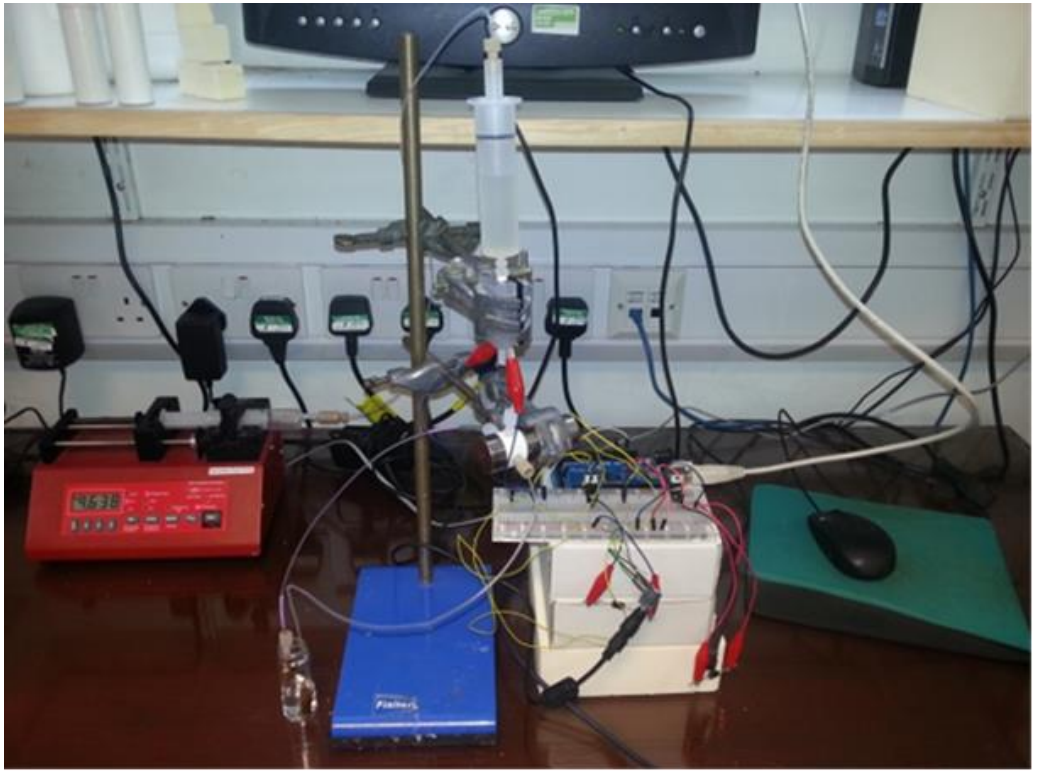
Flexible Interaction with New Instruments: Analysis Trigger

- User can add a “look for value” command to actions
- Software will look for a required value e.g. mass ion or % conversion before proceeding
- Communication via Arduino



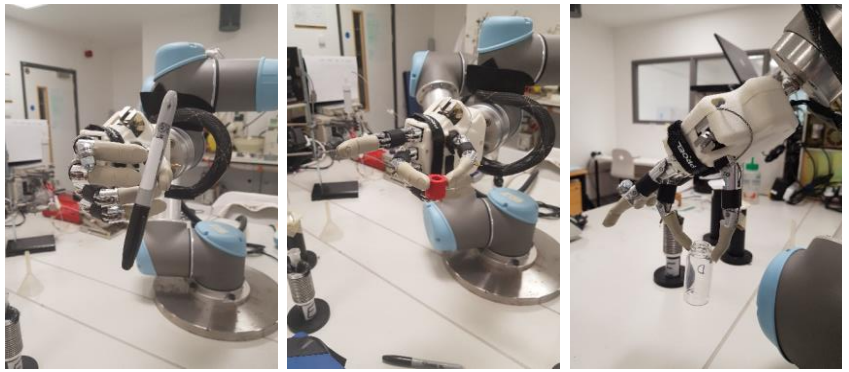
Flexible Interaction with New Instruments: Phase Separation

- Collective intelligence approach
  - Sensor triggered by robot gesture to initiates work up
  - Works up and delivers back to system for next step
- Conductivity cell
  - Microfluidic cell with sintered electrodes
- Proprietary algorithm
  - Determines phase boundary even if partially miscible solvents)e.g. DMF) drag salts into organic phase
- Aspiration through cell breaks emulsions (tested with Sonogashira and DiBAL reductions)



Improved Dexterity: Fine Motor Grasps

- Additional software to enable easier programming of fine motor manipulations
- Robot can now handle small objects reliably:
  - Weighing boat
  - Vial
  - Pen
  - Screw top



(a) (b) (c)