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

\[
R \text{ and D Productivity } \sim \frac{WIP_p(TS)}{CT} \cdot \frac{1}{V} \cdot \frac{1}{C}
\]

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.*

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

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

Tecan liquid handler and plate reader

Matrix 2D bar-coded tubes

Synthesis
2-3 days – hours – 1 day

NMR

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

Acquity UPLC

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

Web-based library log in & design tools
AbbVie High Throughput Chemistry Engine

**Cycle Times**

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*

Small Molecule Library Synthesis Using Segmented Flow

Christina M. Thompson 1,a, Jennifer L. Poole 2, Jeffrey L. Cross 1, Irini Akritopoulou-Zanze 1 and Steven 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**

**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

DOI: 10.1002/anie.200906095

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**Reviews**

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

Ryan L. Hartman, Jonathan P. McMullen, and Klaas J. Jensen

DOI: 10.1002/anie.201004637

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

**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
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*
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
**SWIFT – Synthesis With Integrated Flow Technology**

**Flow Library Synthesis Process**

- **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 types**
- Acylation
- Urea formation
- Sulfonylation
- Reductive amination
- 2-step acylation & deprotection
- 2-step reductive amination & deprotection
- Various heterocycle formations
- Pyrazole acylation
- Epoxide openings
- Carbamate formation
- One-pot Click chemistry

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

Calculated Physicochemical Properties

in silico ADME Properties
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

F508del Homozygous 47%
F508del Heterozygous 39%
Nonsense/ Other 10%
Gating 8%
CFTR Correctors - Assays

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 (leq) current changes
- Gold standard for CFTR function and clinical efficacy correlation

Localization Assays
CSE-HRP (Cell Surface Expression)
- CSE-HRP-tagged

Co-incubate Correctors with Potentiator overnight
Measure leq in TECC after Forskolin activation of CFTR

Primary Human bronchial epithelial cells
SWIFT Platform applied to CFTR C1 corrector program

![Chemical Reaction](image)

**Proprietary amines** → **Proprietary acids**

**AbbVie Collection of Fragments**
- Filter by MW, alerts
- Enumerate virtual library
- Filter by calculated properties

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

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Fully integrated synthesis and purification

Registration and dispersal

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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

AbbV/GLPG Med Chem

Tier 1 ADME
- Metabolic stability
- Solubility
- Permeability

CSE - HRP

MPO score ($C_{\text{ub}} \times EC_{50}$)
Efficacy $\geq 70$

RAT PK

TECC
F508del CFTR
HBE

Tier 2 ADME
- CYP inhibition/induction
- CYP phenotyping

MoA Studies

Low Clp,u
Clean DDI profile

Rat CV & Higher Species PK

Candidate
Chromane SAR Exploration via Segmented Flow Based Libraries

- 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**

<table>
<thead>
<tr>
<th>Compound</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSE-HRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(EC&lt;sub&gt;50&lt;/sub&gt; µM, Max. Act% C1 Control)</td>
<td>2.7, 110%</td>
<td>12, 33%</td>
<td>4.1, 77%</td>
<td>0.80, 92%</td>
<td>0.21, 119%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In Vitro ADME</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat/Human Clint,u (L/hr/kg)- hep</td>
<td>470/49</td>
<td>580/110</td>
<td>460/110</td>
<td>230/77</td>
<td></td>
</tr>
<tr>
<td>PAMPA Peff (x10-6 cm/s)</td>
<td>0.04</td>
<td>0.3</td>
<td>0.26</td>
<td>0.03</td>
<td>0.3</td>
</tr>
</tbody>
</table>

- 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)
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?*

  ![Image of laboratory equipment]


- 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

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**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).
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 $C_{sp^3}$–H oxidation enabled by decatungstate photocatalysis in flow.

- **a) Direct oxidation of $C_{sp^3}$–H Bonds**
  \[
  \text{Fe, Pd, Co, Mn, Ir} \rightarrow \text{Thermally} \rightarrow \text{O} \]
  - strong oxidants
  - complex catalytic system
  - high temperature

- **b) Electrochemical oxidation of $C_{sp^3}$–H Bonds (Baran)**
  \[
  \text{mediator, electrolyte} \rightarrow \text{Electrochemically} \rightarrow \text{O} \]
  - broad scope
  - requires mediators, electrolyte, ...

- **c) This Work: Photocatalytic aerobic oxidation of activated and unactivated $C_{sp^3}$–H Bonds**
  \[
  \text{O}_2, \text{TBADT (5 mol%)} \rightarrow \text{365 nm LEDs} \rightarrow \text{continuous-flow} \rightarrow \text{O} \]
  - inexpensive catalyst
  - simple reaction conditions
  - oxygen as green oxidant
  - chemoselective
  - broad scope
  - sustainable
  - late-stage modification
Scheme 2. Substrate scope of the Csp$^3$–H oxidation enabled by deca-tungstate photocatalysis in flow.

\[
\begin{array}{c}
\text{O}_2, \text{TBADT (2-5 mol\%)} \\
365 \text{ nm LEDs} \\
\text{CH}_2\text{CN} / 1\text{M HCl (2.5:1)} \\
\text{RT, 45 min}
\end{array}
\]

*continuous-flow*

**Activated C-H Bonds**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>70%*</td>
</tr>
<tr>
<td>4</td>
<td>43%</td>
</tr>
<tr>
<td>5</td>
<td>91% (a:b 1:1)</td>
</tr>
<tr>
<td>5</td>
<td>84% (a:b 10:1)b</td>
</tr>
<tr>
<td>6</td>
<td>47%</td>
</tr>
<tr>
<td>7</td>
<td>50%</td>
</tr>
<tr>
<td>8</td>
<td>87%</td>
</tr>
<tr>
<td>9</td>
<td>54%</td>
</tr>
<tr>
<td>10</td>
<td>66%</td>
</tr>
<tr>
<td>11</td>
<td>86%b</td>
</tr>
<tr>
<td>12</td>
<td>71%</td>
</tr>
<tr>
<td>13</td>
<td>41%</td>
</tr>
<tr>
<td>14</td>
<td>23%c</td>
</tr>
<tr>
<td>15</td>
<td>69%</td>
</tr>
<tr>
<td>16</td>
<td>43%d</td>
</tr>
<tr>
<td>17</td>
<td>57%c</td>
</tr>
</tbody>
</table>

**Unactivated C-H Bonds**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>35%a</td>
</tr>
<tr>
<td>2a</td>
<td>82%a</td>
</tr>
<tr>
<td>19</td>
<td>79%a</td>
</tr>
<tr>
<td>20</td>
<td>65% (y:δ 5:1)</td>
</tr>
<tr>
<td>21</td>
<td>51% (y:δ 2:1)b</td>
</tr>
<tr>
<td>22</td>
<td>67%a</td>
</tr>
<tr>
<td>23</td>
<td>52%</td>
</tr>
<tr>
<td>24</td>
<td>49% (α:β 1.1:1)b</td>
</tr>
<tr>
<td>25</td>
<td>42%</td>
</tr>
<tr>
<td>26</td>
<td>56%</td>
</tr>
<tr>
<td>27</td>
<td>68%</td>
</tr>
<tr>
<td>28</td>
<td>63% (α:β 1.1:1)</td>
</tr>
<tr>
<td>29</td>
<td>44% (2:1 4.8:1)b</td>
</tr>
<tr>
<td>30</td>
<td>55%b,c</td>
</tr>
</tbody>
</table>

*XX%* 1.4 g scale
For many common chemical reactions at room temperature, the reaction rate doubles for every 10 degree Celsius increase in temperature.

**The Arrhenius Equation**

\[ k = A e^{-\frac{E_a}{RT}} \]

- \( k \) is the rate constant at \( T \)
- \( E_a \) is the activation energy
- \( R \) is the energy gas constant
  \[ R = 8.3145 \text{ J/(mol K)} \]
- \( T \) is the Kelvin temperature
- \( A \) is the collision frequency factor

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 $S_N$Ar between 2-chloroquinazoline and benzylamine

<table>
<thead>
<tr>
<th>Temperature ($^\circ$C)</th>
<th>Pressure (MPa)</th>
<th>Flow rate (mL/min)</th>
<th>Product$^a$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>8</td>
<td>2.5</td>
<td>46</td>
</tr>
<tr>
<td>250</td>
<td>10</td>
<td>4.0</td>
<td>29</td>
</tr>
<tr>
<td>250</td>
<td>10</td>
<td>1.0</td>
<td>75</td>
</tr>
<tr>
<td>250</td>
<td>12</td>
<td>2.5</td>
<td>42</td>
</tr>
<tr>
<td>325</td>
<td>8</td>
<td>1.0</td>
<td>37</td>
</tr>
<tr>
<td>325</td>
<td>8</td>
<td>4.0</td>
<td>20</td>
</tr>
<tr>
<td>325</td>
<td>8</td>
<td>2.5</td>
<td>34$^b$</td>
</tr>
<tr>
<td>325</td>
<td>10</td>
<td>1.0</td>
<td>62</td>
</tr>
<tr>
<td>325</td>
<td>12</td>
<td>4.0</td>
<td>47</td>
</tr>
<tr>
<td>325</td>
<td>12</td>
<td>2.5</td>
<td>25</td>
</tr>
<tr>
<td>325</td>
<td>12</td>
<td>1.0</td>
<td>37</td>
</tr>
<tr>
<td>400</td>
<td>8</td>
<td>4.0</td>
<td>27</td>
</tr>
<tr>
<td>400</td>
<td>10</td>
<td>2.5</td>
<td>37</td>
</tr>
<tr>
<td>400</td>
<td>10</td>
<td>1.0</td>
<td>27</td>
</tr>
<tr>
<td>400</td>
<td>12</td>
<td>2.5</td>
<td>37</td>
</tr>
</tbody>
</table>

$^a$ Percent product by analytical HPLC.
$^b$ Center point, average of 4 runs.

<table>
<thead>
<tr>
<th>2-Aminoquinazoline product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>38</td>
</tr>
<tr>
<td>10</td>
<td>71</td>
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<tr>
<td>11</td>
<td>79</td>
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<td>66</td>
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<td>15</td>
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<td>16</td>
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<td>17</td>
<td>66</td>
</tr>
<tr>
<td>18</td>
<td>60</td>
</tr>
<tr>
<td>19</td>
<td>63</td>
</tr>
<tr>
<td>20</td>
<td>39</td>
</tr>
</tbody>
</table>
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

Gould-Jacobs Reaction
- $>200^\circ\text{C}$
- Long reaction times
- Dowtherm or diphenyl ether as solvents

Quinolone Containing Drugs

Gould-Jacobs Reaction

![Chemical Structures]

1. \( R - X - \text{NH}_2 \)
2. \( \text{EtO} - Y - \text{CO}_2\text{Et} \)
3. \( R - X - \text{NH} - Y - \text{CO}_2\text{Et} \)

4a-j when \( X = N \)
5a-h when \( X = \text{CH} \)
Reaction Optimization using DoE

Chemical reaction:

\[
\text{Me} \quad \text{H} \quad \text{CO}_2\text{Et} \quad 250 - 400 \degree \text{C}, 100 \text{ bar} \\
2.0 \text{ mL loop} \\
0.5 - 4.0 \text{ mL/min} \\
\text{Me} \quad \text{N} \quad \text{CO}_2\text{Et} \rightarrow 2 \text{ mL/min} \quad \text{Me} \quad \text{N} \quad \text{CO}_2\text{Et} + \text{Me} \quad \text{N} \quad \text{CO}_2\text{Et}
\]

Flow rates:

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

Predicted conditions for 4a:

\[
T = 390 \degree \text{C}, P = 100 \text{ bar} \\
\text{flow rate} = 4.0 \text{ mL/min} \\
\text{conc.} = 0.4 \text{ M in THF}
\]

*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.
Synthesis of Quinolones

3

Y = CO₂Et, CN, COMe

5

390 °C, 4.0 mL/min
100 bar, 0.40 M in THF
0.2 mmol scale

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

\[
\begin{align*}
\text{Y} & = \text{CO}_2\text{Et}, \text{CN}, \text{COMe} \\
\text{3} & \xrightarrow{390 \degree C, 4.0 \text{ mL/min}, 100 \text{ bar, 0.40 M in THF}} \xrightarrow{0.2 \text{ mmol scale}} \\
& \quad \text{4a (96%), 4b (96%), 4c (88%), 4d (96%), 4e (94%), 4f (94%), 4g (91%), 4h (96%), 4i (77%)}
\end{align*}
\]
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 Tsonug, Ying Wang, and Stevan W. Djuric

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


http://dx.doi.org/10.1039/C7RE00058H
High Temperature intramolecular Diels-Alder reaction: 

**Examples**

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**Table 3** Intramolecular Diels-Alder cycloadditions of oQDM precursors 3

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>300 °C, 100 bar, 0.05 M in THF, rt = 4.0 min</td>
<td>8a: 93%, (2.9:1), 8b: 69% (1:1)</td>
</tr>
</tbody>
</table>

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**Table 2** Intramolecular Diels-Alder cycloaddition of benzocyclobutene 4

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>300 °C, 100 bar, 0.05 M in THF, rt = 0.5 min</td>
<td>5a: 64%, 5b: 79%, 5c: 75%</td>
</tr>
</tbody>
</table>

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

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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**

**Useful for Chemists**

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**Experimental**

**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 anthropomorphomorphic 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