Process Research Over 25 Years

A Personal Perspective

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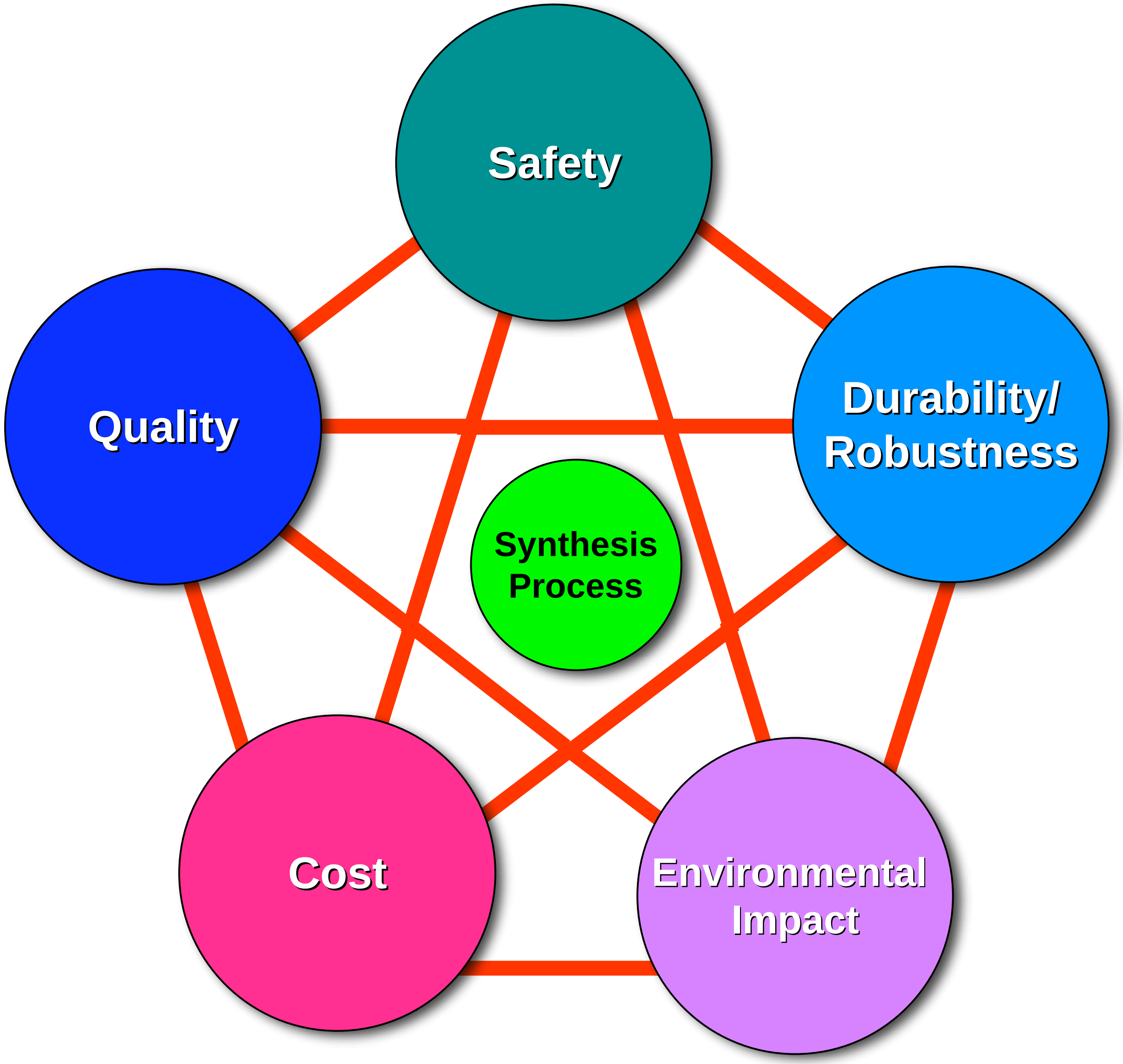
"It does, for example, no good to offer an elegant, difficult and expensive process to an industrial manufacturing chemist, whose ideal is something to be carried out in a disused bathtub by a one-handed man who cannot read, the product being collected continuously through the drain hole in 100% purity and yield."

Sir John Cornforth, *Chem. Brit.* 1975, 342.

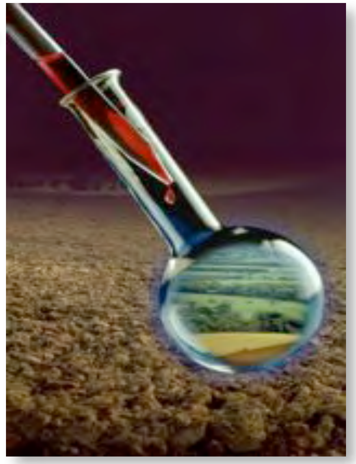
Major Route Design Factors and Their Interactions

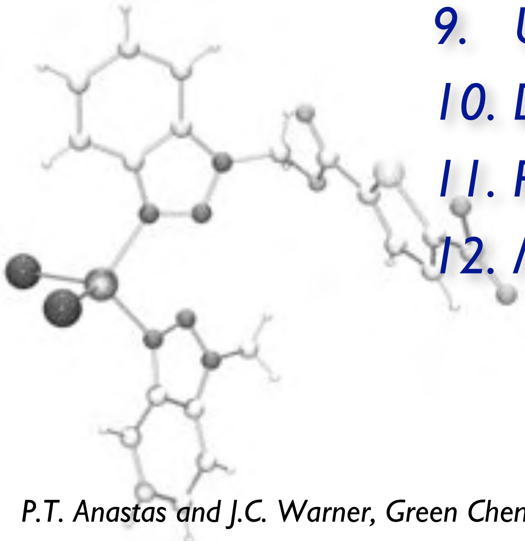


T.Y. Zhang, *Chem. Rev.*, 2006, *106*, 2583.

Twelve Principles of Green Chemistry

1. Prevent waste rather than treat/clean it up later
2. Invoke atom economy
3. Design safer chemicals
4. Use & generate less toxic substances
5. Massively reduce quantities of solvents used
6. Design syntheses for energy efficiency
7. Renewable feedstock for large scale processes
8. Minimize steps in synthesis
9. Use of highly-selective catalytic reagents
10. Design materials that innocuously degrade
11. Real-time monitoring for pollution prevention
12. Minimise potential for accidents



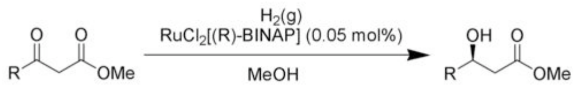


P.T. Anastas and J.C. Warner, Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998, p.30.

Landmark Papers – A Personal Selection Strategically Important Processes

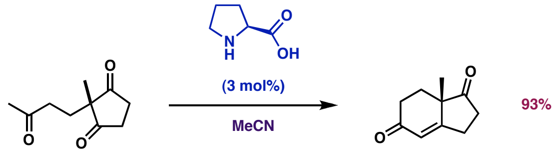
Noyori asymmetric hydrogenation (reduction of β-keto-esters)

R. Noyori, T. Okhuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akuragawa, J. Am. Chem. Soc. ***1987****, 109, 5856-5858*



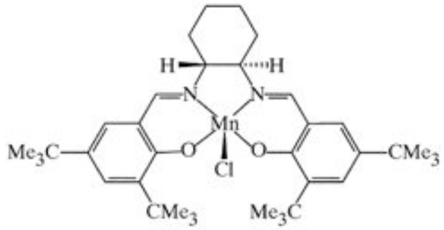
Hajos-Parrish (orgcat)

Z. G. Hajos and D. R. Parrish
J. Org. Chem. **1974**, *39*, 1615



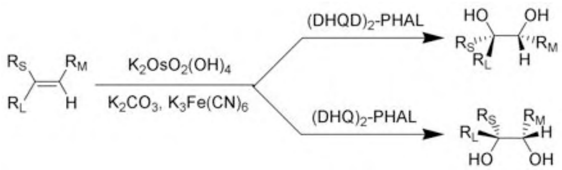
Jacobsen's Catalyst

E.N. Jacobsen, J.F. Larrow, Y. Gao, Y. Hong, X. Nie, C.M. Zepp
J. Org. Chem., 1994, **59**, 1939.



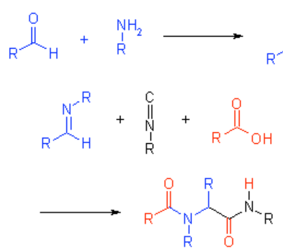
Sharpless asymmetric dihydroxylation

E.N. Jacobsen, I. Marko, W.S. Mungall, G. Schroeder, K.B. Sharpless J. Am. Chem. Soc. ***1988****, 110, 1968*



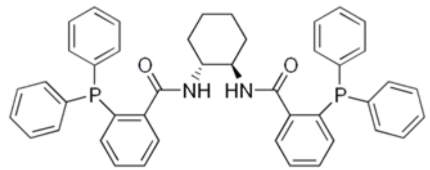
UGI multi-component coupling

I. Ugi, R. Meyr, U. Fetzer, C. Steinbruker. Angew. Chem. ***1959****, 71, 386.*



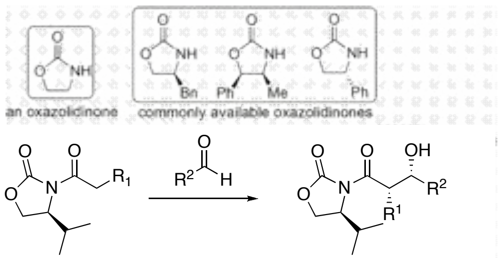
Trost's Ligand (Asymm.Allylic Alkylation)

B.M. Trost, D.L. Van Vranken, C. Bingel
J. Am. Chem. Soc., 1992, **114**, 9327.



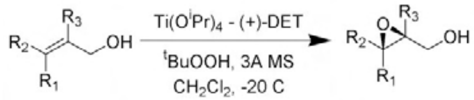
Evans chiral auxiliary

D.A. Evans, Aldrich. Acta, ***1982****, 15, 23*

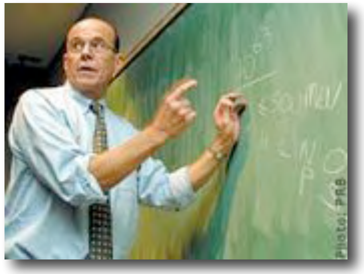


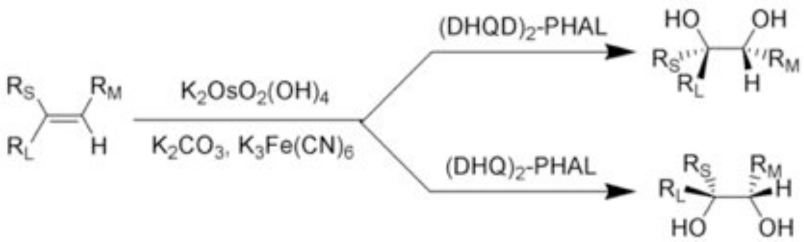
Sharpless epoxidation

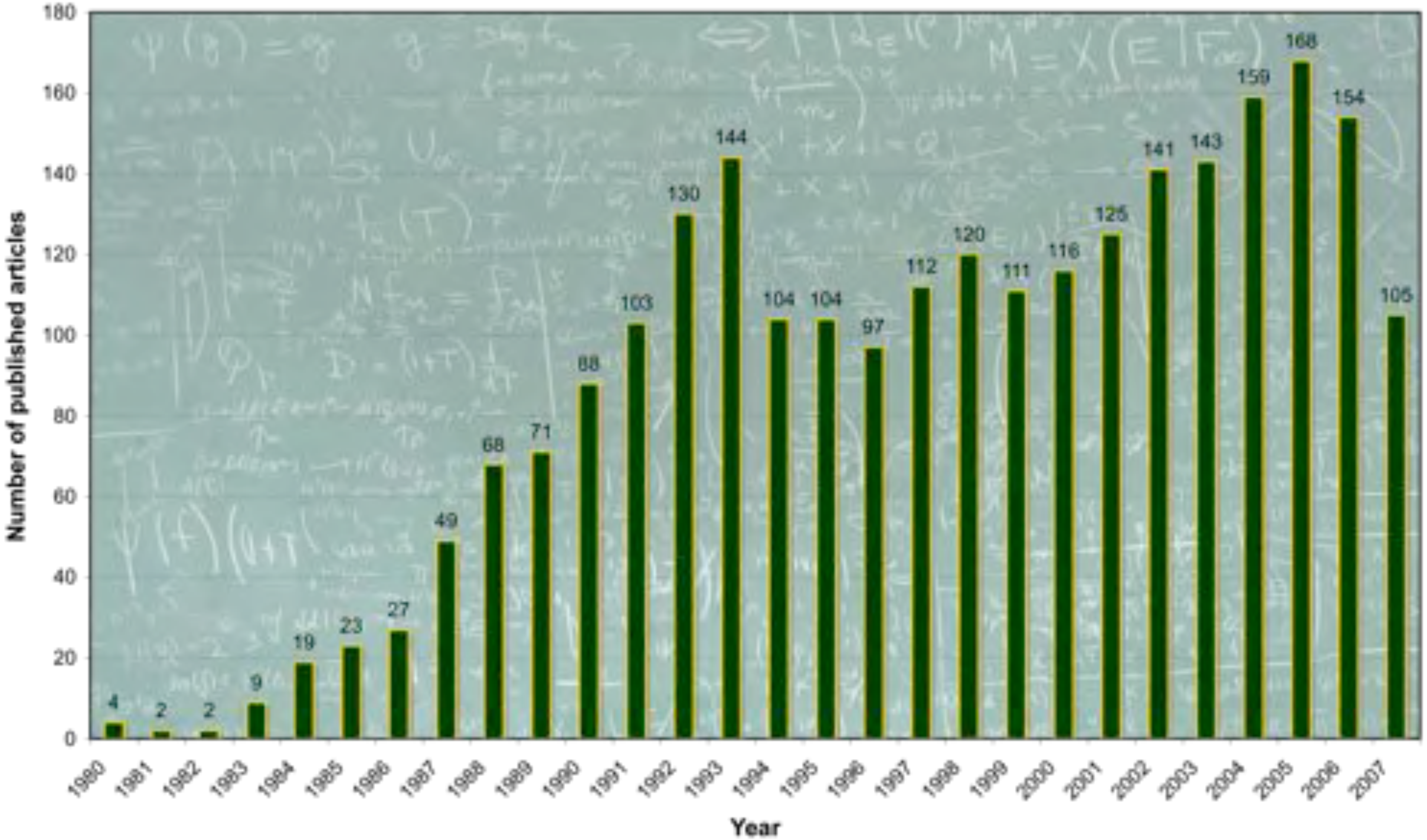
T. Katsuki and K.B. Sharpless J. Am. Chem. Soc. ***1980****, 102, 5974*



Sharpless Asymmetric Dihydroxylation Reaction







Landmark Papers – A Personal Selection Strategically Important Processes

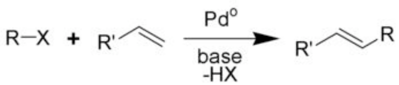
Suzuki reaction

N. Miyaura and A. Suzuki
J. Chem. Soc., Chem. Commun, ***1979****, 3427*

BASF plant in Guaratingueta, Sao Paulo, Brazil, where the fungicide boscalid is manufactured.

Heck reaction

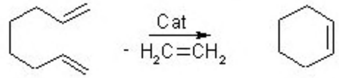
R.F. Heck, J.P.J. Nolley,
J. Org. Chem. ***1972****, 37, 2320.*



Metathesis reactions

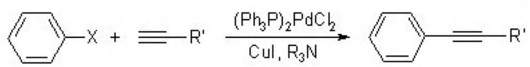
Cross; Ring-closing; Enyne; Ring-opening; ROMP, Acyclic dienes; Alkyne; Alkane.

e.g. R.R. Schrock *et al.*, *J. Am. Chem. Soc.*, 1990, *112*, 3875.
R.H. Grubbs *et al.*, *J. Am. Chem. Soc.*, 1993, *115*, 9858.
R.H. Grubbs *et al.*, *Angew. Chem., Int. Ed. Engl.*, 1995, *34*, 2039.



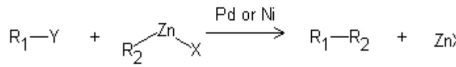
Sonogashira cross-coupling

K. Sonogashira, Y. Tohda, N. Hagihara
Tetrahedron Lett., 1975-4467.



Negishi cross-coupling

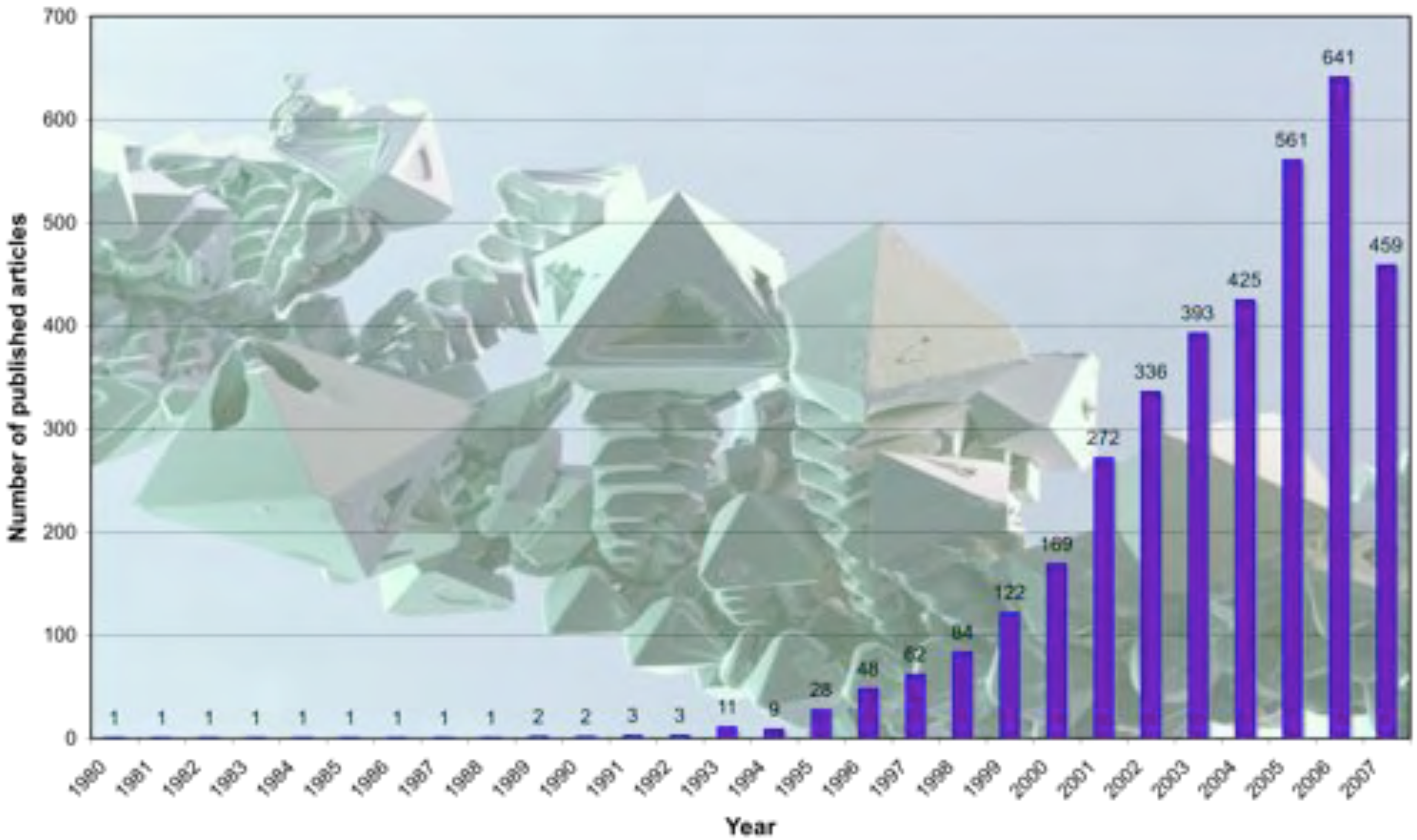
E. Negishi et al., J. Org. Chem. ***1977****, 42, 1821.*



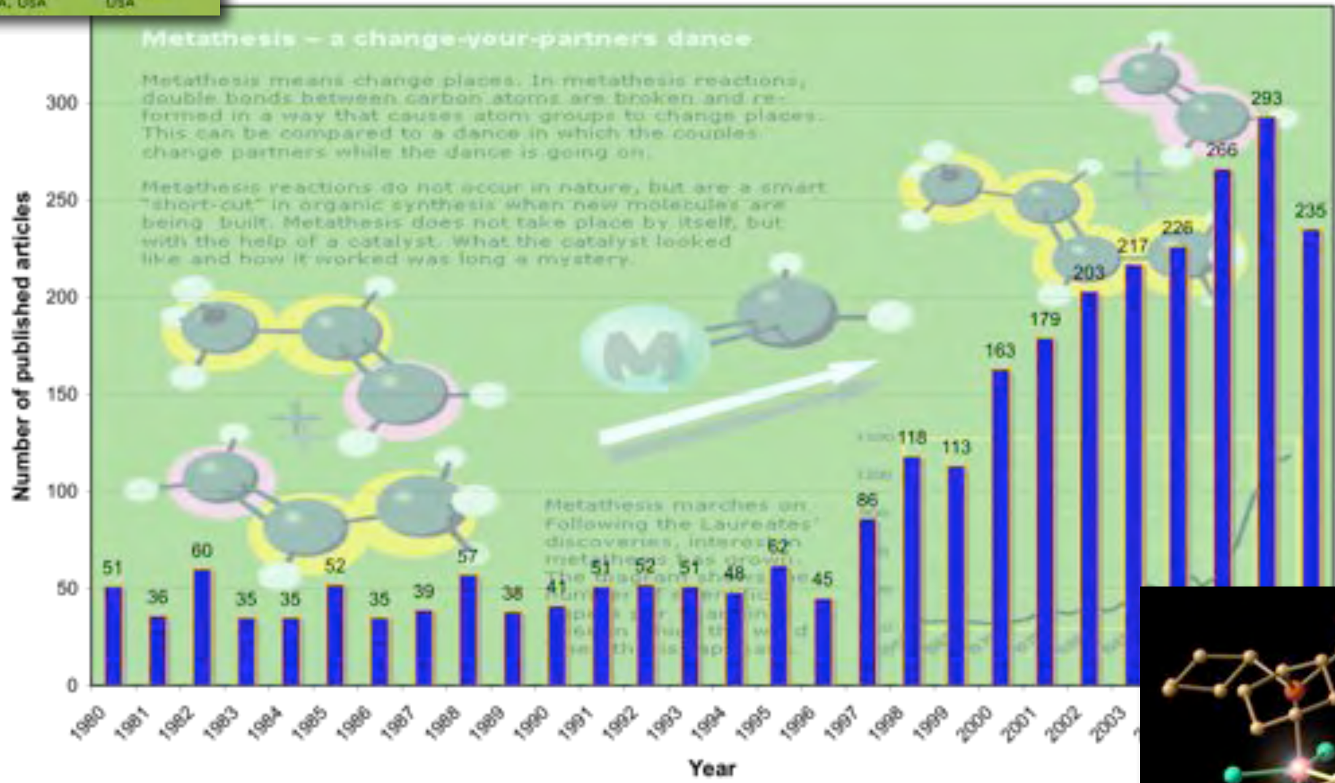
X, Y = halogen
R_1 = alkenyl, aryl, allylic, benzylic
R_2 = alkenyl, aryl, alkynyl,alkyl,allylic, benzylic

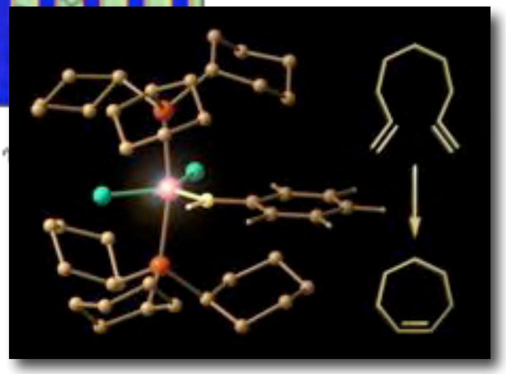
The Suzuki Reaction – a Key Organic Process

$$R^1\text{-}B(R)_2 \quad + \quad R^2\text{-}X \xrightarrow{\text{cat. Pd(0), base, ligand}} R^1\text{-}R^2 \quad + \quad X\text{–}B(R)_2$$



Alkene Metathesis





Analysis of Reactions Used for Drug Candidate Synthesis

*In carrying out this survey, the syntheses of **128 drug candidate molecules** were analysed, these were divided between the three companies and covered all therapeutic and geographic areas that the companies have R&D interests.*

Headline Data	AstraZeneca	GlaxoSmithKline	Pfizer	Total
Number of syntheses	45	39	44	128
Total number of chemical transformations	371	310	358	1039
Average number of chemical transformations per synthesis	8.2	7.9	8.1	8.1
Number of chiral compounds	25	23	21	69
Number of chiral centres	46	52	37	135
Number of chiral centres generated	22	19	20	61
Number of substituted aromatic starting materials	64	79	63	206
New aromatic heterocycles formed	14	11	29	54

Analysis of the reactions used for the preparation of drug candidate molecules
J.S. Carey, D. Laffan, C. Thomson and M.T. Williams, *Org. Biomol. Chem.*, 2006, *4*, 2337-2347.

Summary of Reaction Categories

Reaction Categories	AstraZeneca	GlaxoSmith Kline	Pfizer	Total/% of total reactions
Heteroatom alkylation and arylation	87	57	52	196 (19%)
Acylation	41	37	50	128 (12%)
C-C bond forming reaction	31	41	44	116 (11%)
Aromatic heterocycle formation	16	10	26	52 (5%)
Deprotection	54	56	49	159 (15%)
Protection	18	16	27	61 (6%)
Reduction	27	24	43	94 (9%)
Oxidation	17	7	16	40 (4%)
Functional group interconversion	43	34	27	104 (10%)
Functional group addition	13	8	12	33 (3%)
Resolution	14	8	8	30 (3%)
Miscellaneous	10	12	4	26 (3%)
Totals	**371**	**310**	**358**	**1039**

Analysis of the reactions used for the preparation of drug candidate molecules
J.S. Carey, D. Laffan, C. Thomson and M.T. Williams, *Org. Biomol. Chem.*, 2006, *4*, 2337-2347.

New Reactions – Trends, Drivers & Changes

- Metal-catalyzed aryl and olefin amination
- C-H activation methods
- Organogold chemistry
- Metathesis
- New metal-based catalysts (recycle/containment)
- Asymmetric organocatalysis
- Control of radical reactions
- Alternative solvents (scCO_2, H_2O, ionic liquids)
- Greener chemistries
- Biotransformations, directed evolution techniques
- Effects of outsourcing

Emerging Technologies for Chemical Process R&D

- *High throughput screening and analysis methods*
- *DoE and principal component analysis methods*
- *Calorimetry measurement methods*
- *Real-time analysis and kinetics evaluation*
- *Polymorph and salt selection protocols*
- *Impurity profiling methods*
- *Reaction modeling and workflow analysis*
- *Route evaluation methods*
- *Continuous processing procedures*
- *Micro and meso flow reactors, spinning disc reactors, shear mixers*
- *Immobilization, particularly scavenging methodology*
- *Plug and segmental flow techniques*
- *Microwave/superheated flow tubes*

A.E. Rubin, S. Tummala, D.A. Both, C. Wang, E.J. Delaney, *Chem. Rev.*, 2006, *106*, 2794.

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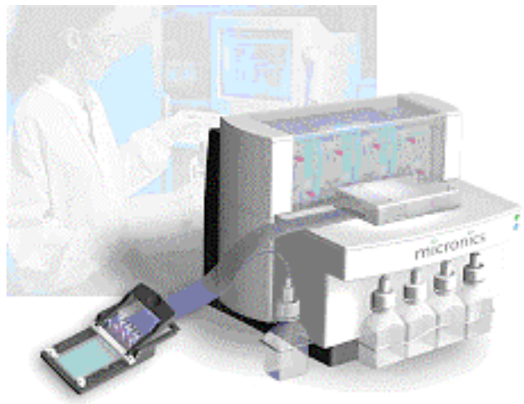
Change in Technology but a Massive Change in Philosophy

- Cost of the equipment in an ever changing environment and time needed for effective assessment of the relevant competitive technologies
- Lack of relevant experience and knowledge of flow chemistry;
    - there is a need for training
    - future development of the relevant skill base (and management)
- The problem of solids / slurries (oscillation methods, high temperatures / pressures, protecting group strategies, disk reactors,etc.
- The cost of investment in existing plant and infrastructure leads to a level of inflexibility
- Regulatory issues batch to flow yet to be properly addressed
- Enforced conservatism as opposed to the bold solution



Some Early Decisions

- Single vs. Multi-step
- Reaction understanding needs to be high
- Use of immobilized systems – reagents, scavengers, catch and release tagging and phase switch techniques
- Versatility of the equipment – rapidly reconfigured modular devices or designed for specific operations
- Plug flow and segmentation vs. steady-state continuous processing
- Scale 10^{17} range in quantity requirements – nano - full scale production
- Need for effective cross disciplinary interactions

New Tools for Molecule Makers

NEW CHEMISTRY DEVICES

Microarrays, Calorimetry, Flow reactors
Nanoscience/ technology
Mini reactor wells, Microfluidic reactors
Diagnostic reporter devices
Novel solvents: *ionic liquids, CO_2, H_2O, fluorous phase*
Wireless devices

BIOCHEMISTRY TOOLS

Gene shuffling
Phage display techniques
Multi-enzymes in synthesis
Directed evolution techniques

AUTOMATION TOOLS

Multi-channel mass spectroscopy
Robotic equipment: *polymorph hunting devices, salt selectors*
Preparative autoseparation devices
DoE, PCA & ReactArray methods
Flow and MAS NMR techniques
HT X-ray crystallography
Databases & informatics

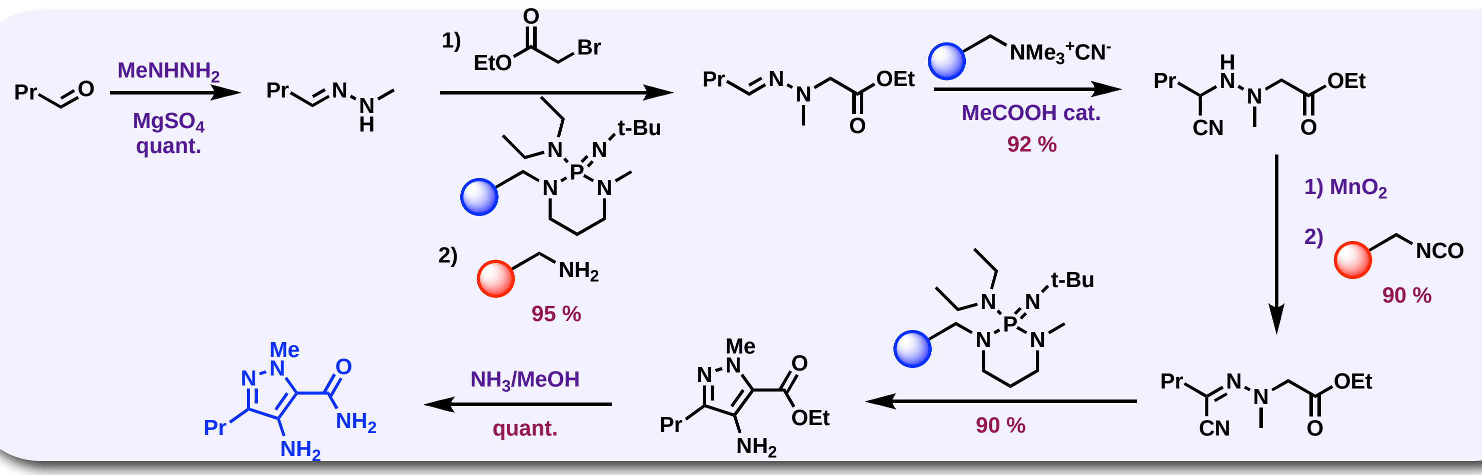
CHEMISTRY TOOLS

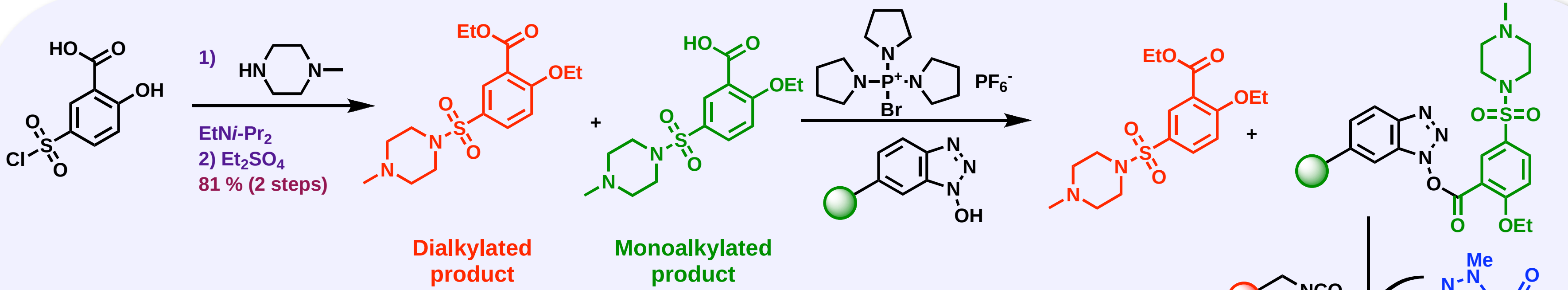
Polymer-supported reagents
Scavenger resins
Capture & release techniques
Multi-parallel synthesis
Fast serial processing
Microwaves, microfluidics
Dynamic and Self Assembly methods
Molecular imprinting
Rapid catalyst discovery
Structural morphing techniques

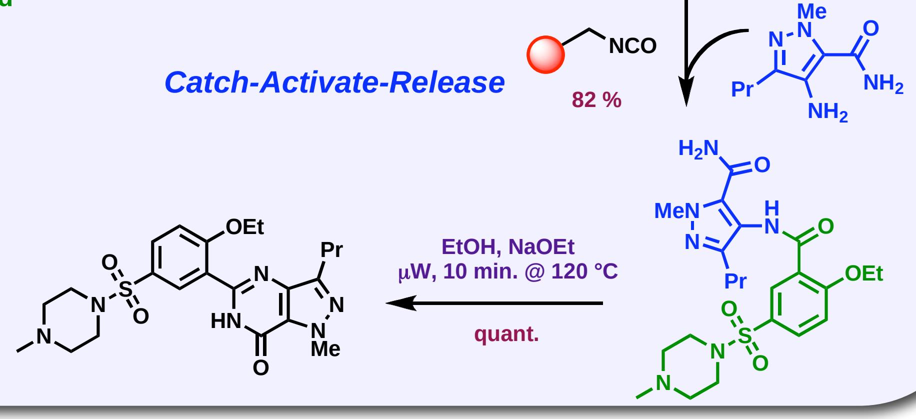
COMPUTATIONAL TOOLS

Conformation, shape & cluster analysis, Compound design, Diversity algorithms

Synthesis of Sildenafil (Viagra™)



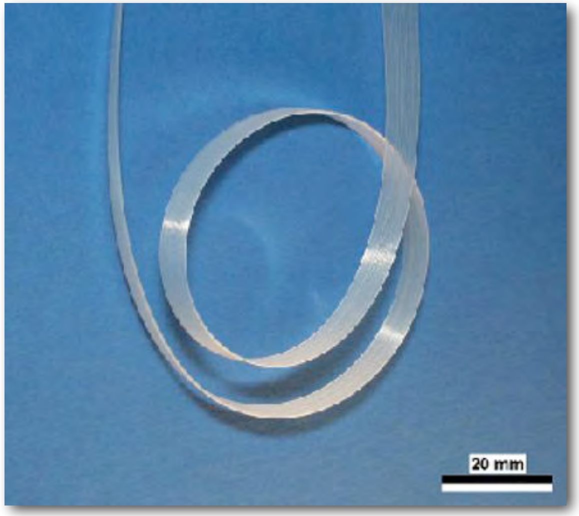


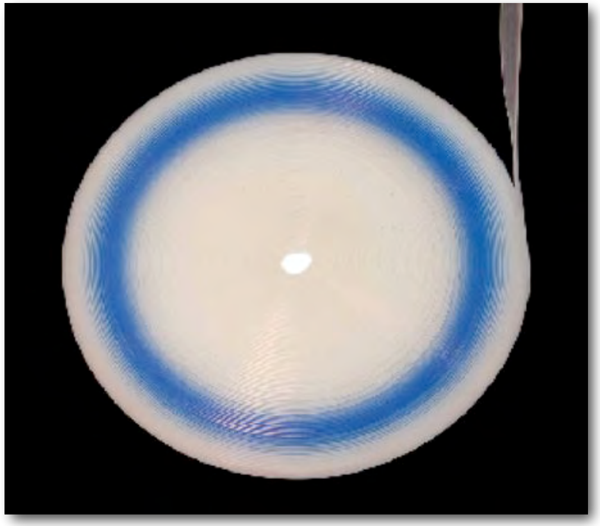


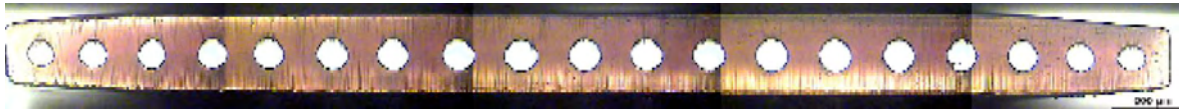
- 11 steps (8 longest linear, 64% overall)
- no aqueous workup
- no column chromatography
- analytically pure

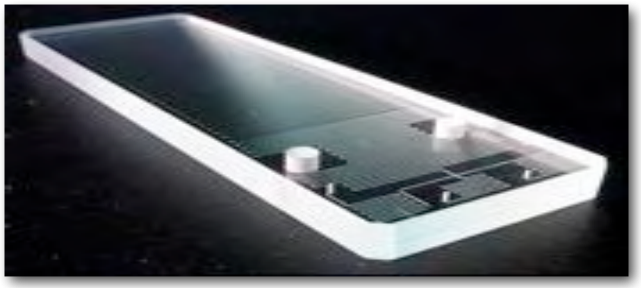
Polymer-Supported Reagents for Multi-Step Organic Synthesis: Application to the Synthesis of Sildenafil
I.R. Baxendale and S.V. Ley, *Bioorg. Med. Chem. Lett.*, 2000, *10,* 1983-1986.

Different Formats for Supported Reagents

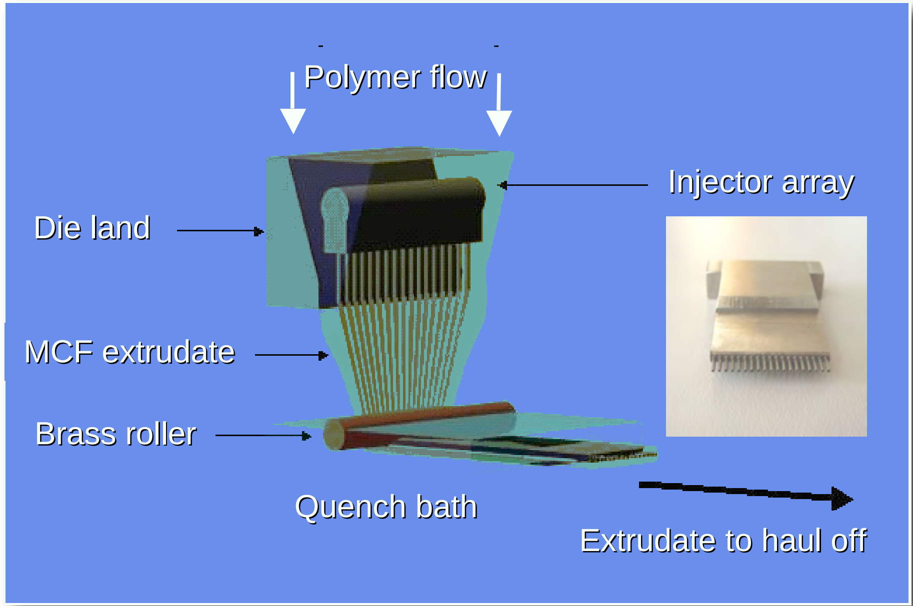


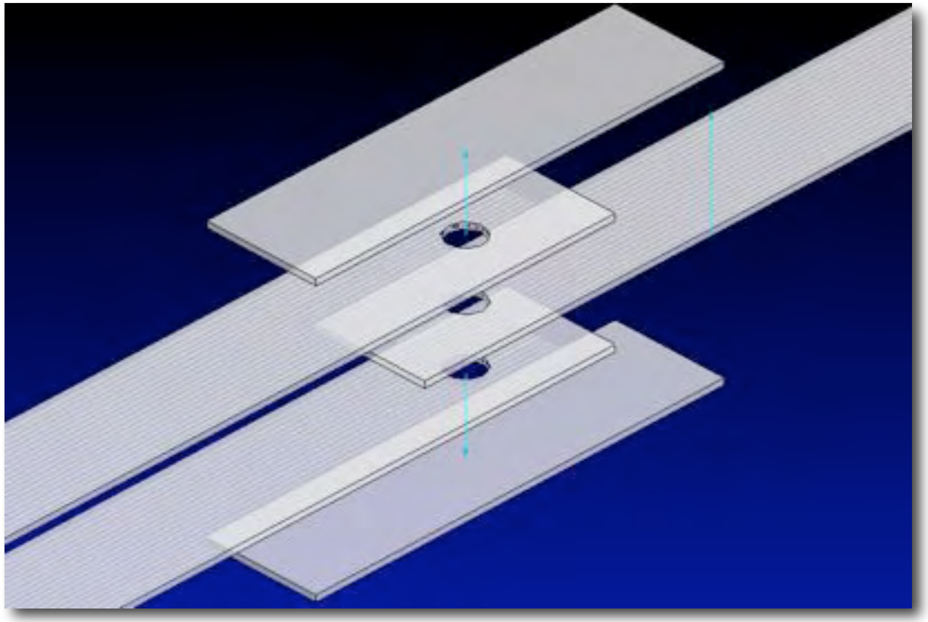


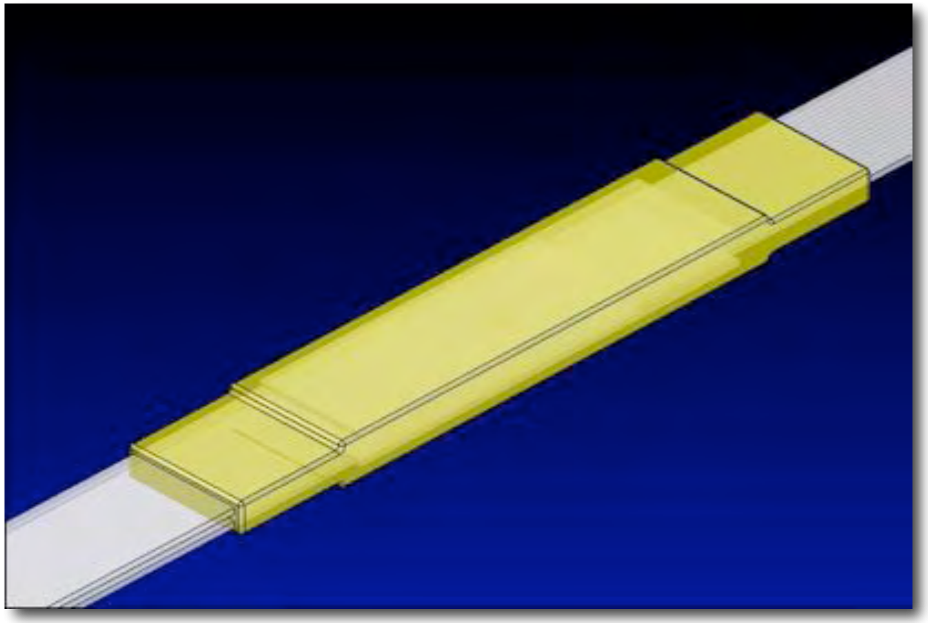


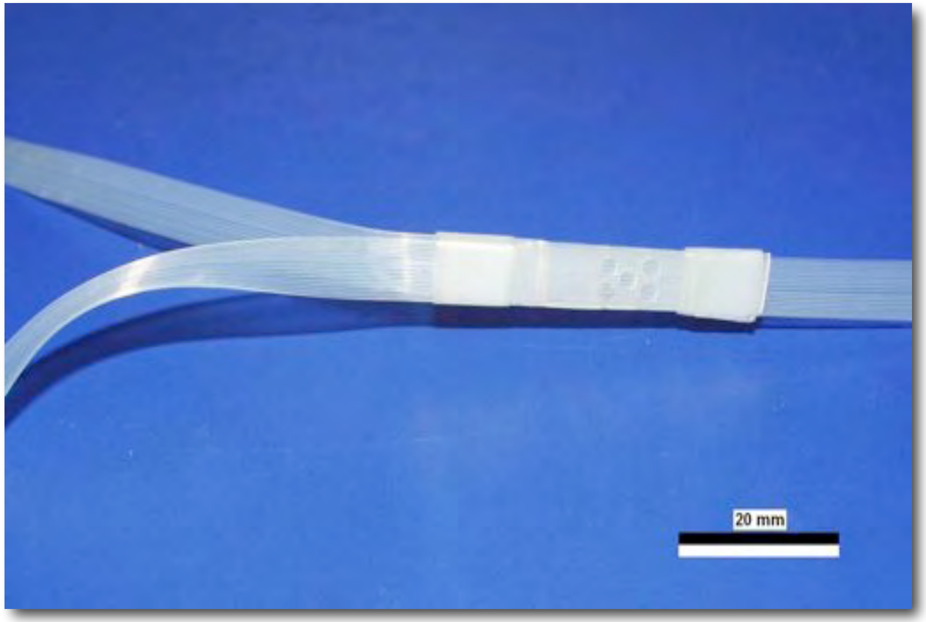


Microcapillary Reactor & Mixing Device

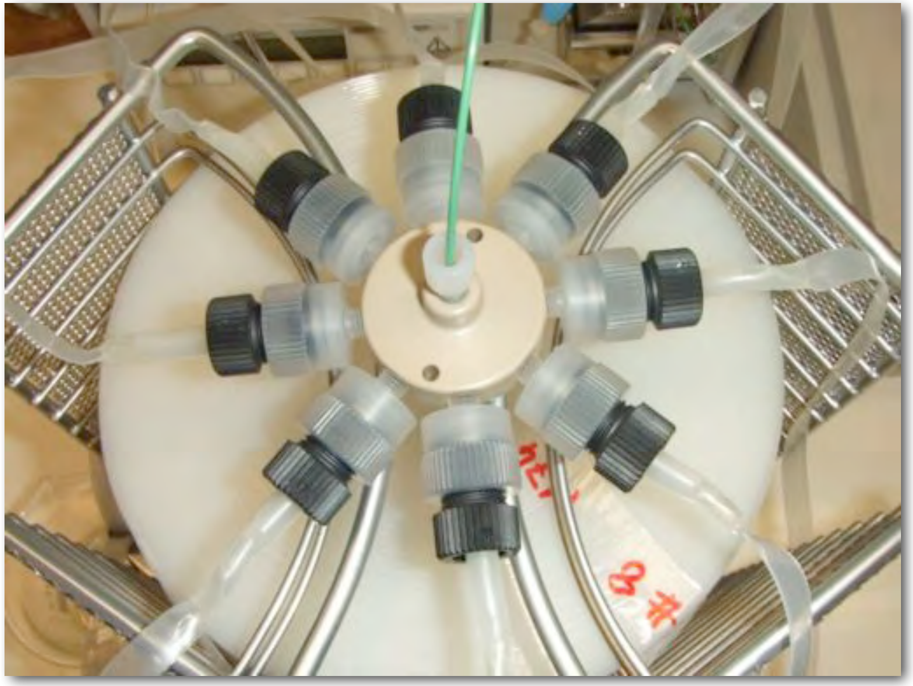


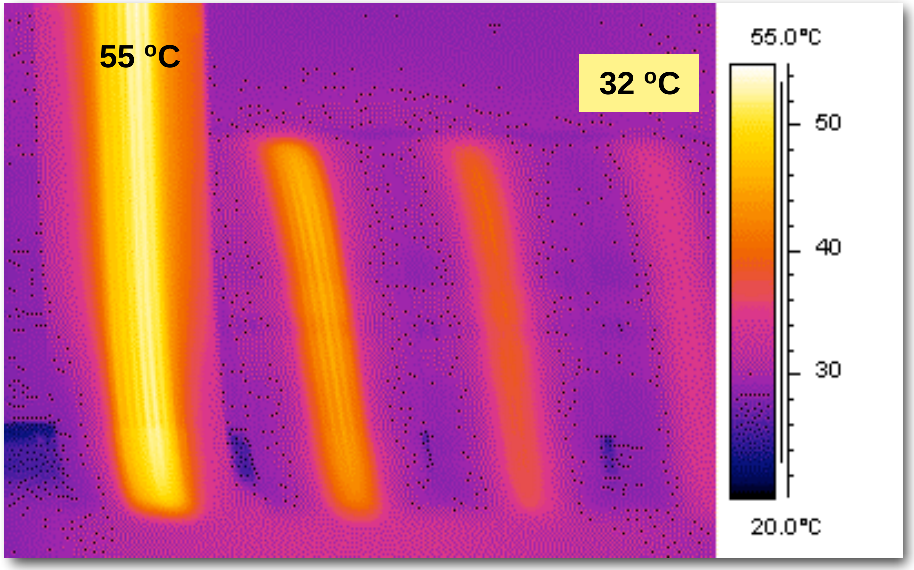




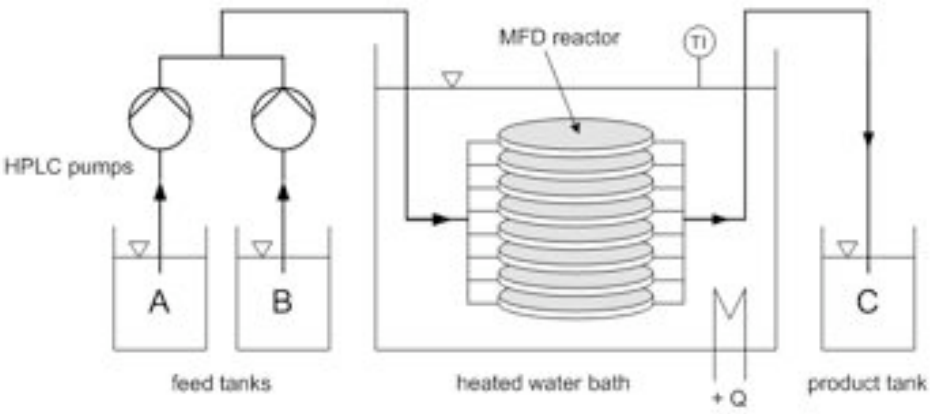


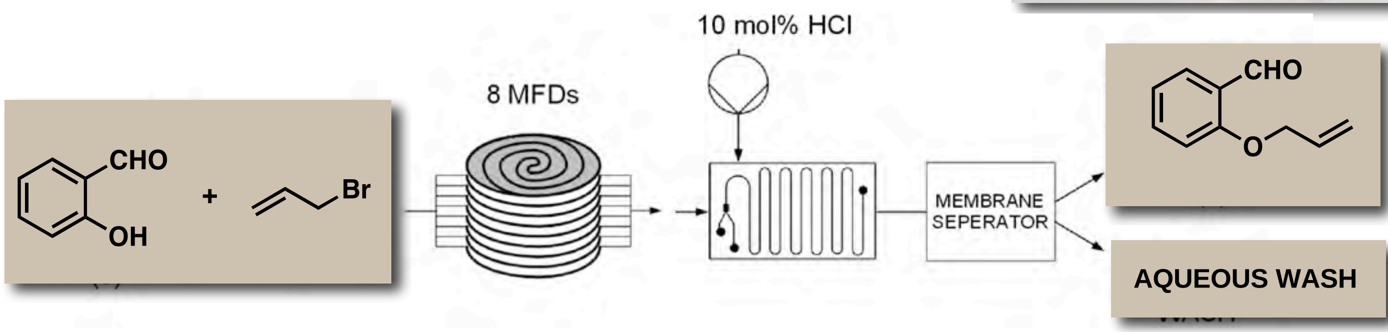
Microcapillary Reactor



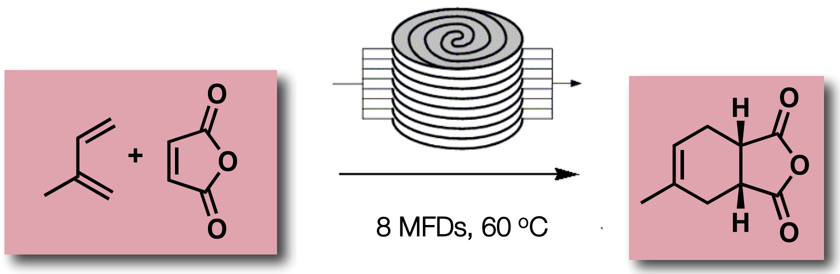


MFD Reactor





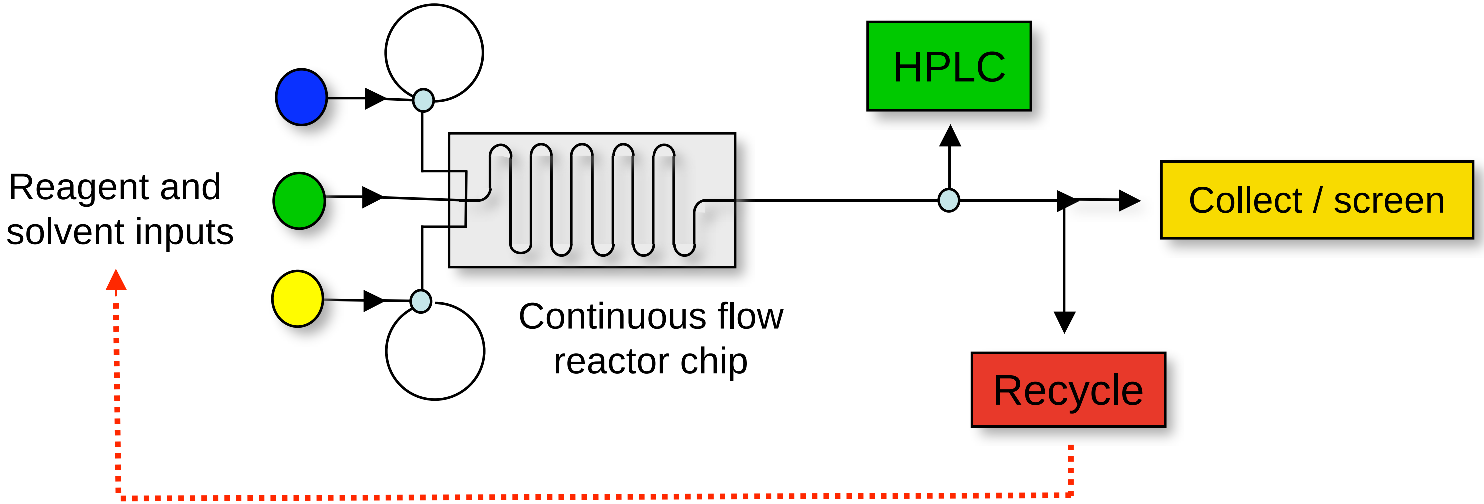
98% isolated yield; 4 ml/min
output 0.37 g/min or 0.526 kg/day

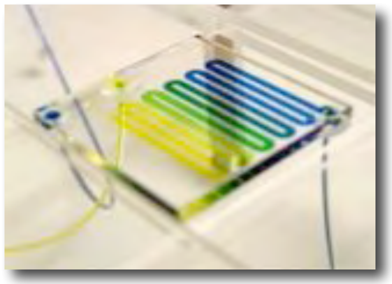
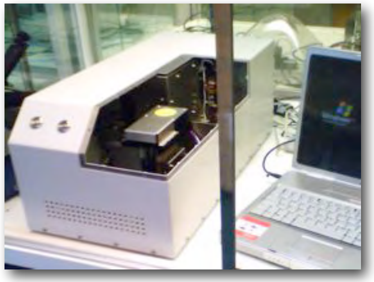


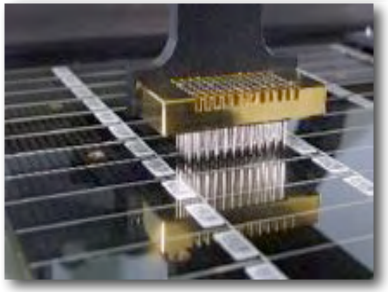
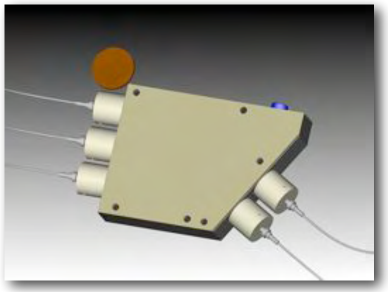
93 % conversion (98% isolated yields) 6 ml/min; output of 2.73 g/min or 3.93 kg/day

A Novel Microcapillary Flow Disc (MFD) Reactor for Organic Synthesis
C.H. Hornung, M.R. Mackley, I.R. Baxendale and S.V. Ley and, *Org. Proc. Res. Dev.*, 2007, *11*, 399.

Typical Flow Reactor Configuration



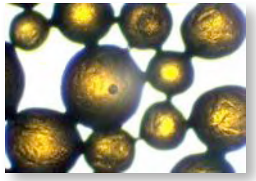



Make and Screen Opportunities

- Ready incorporation of analytics/diagnostics
- Information harvesting
- Reaction/reagent prospecting
- Rapid optimisation techniques
- Feedback mechanisms
- Closed loop operation

Make → **Screen**

Catalysts



Reagents

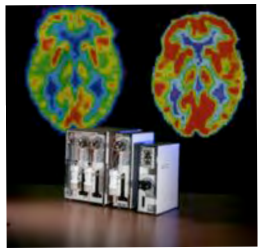
Reactions

Biology

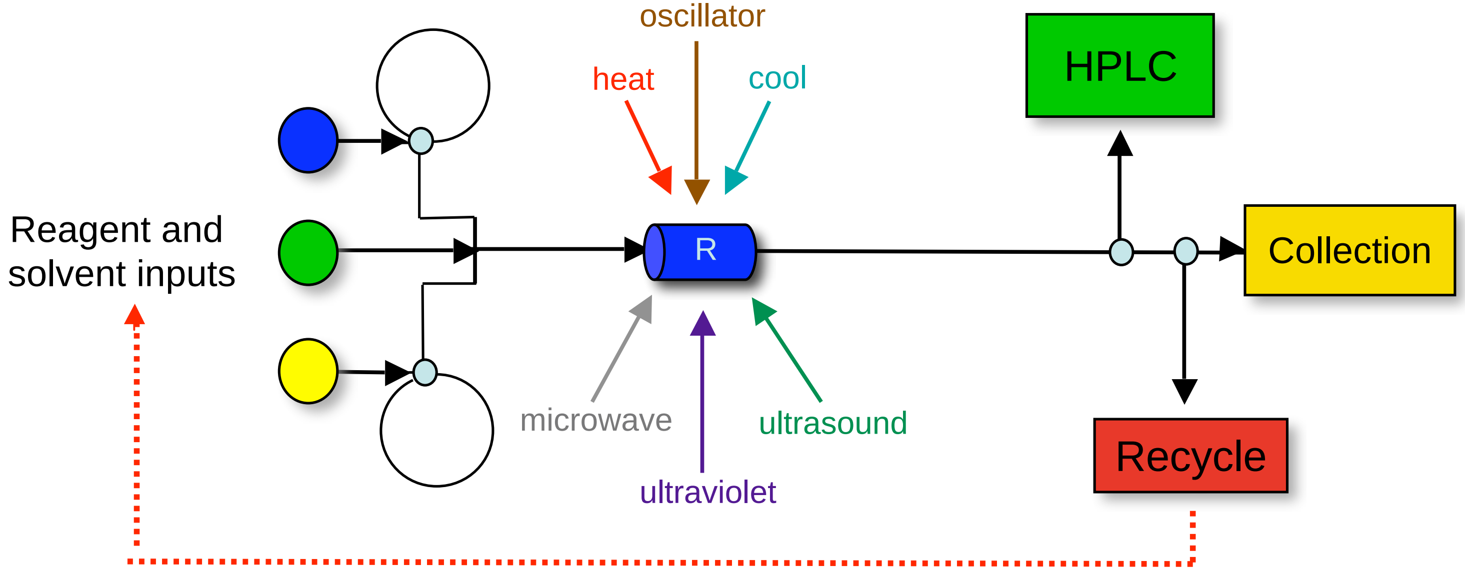
(Systems approach)

PET

(Translational medicine approach)

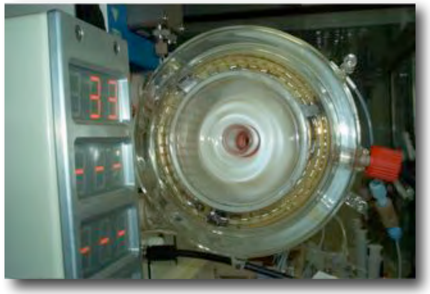


Typical Flow Reactor Configuration



Omnifit Column (6.6 mm ID, 100 mm)

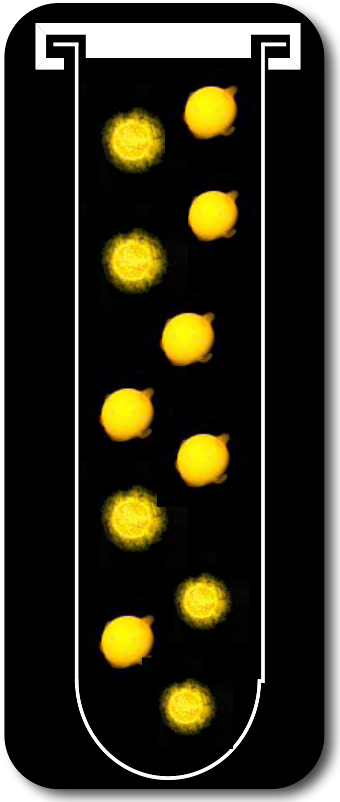
The Flow Coil Reactors

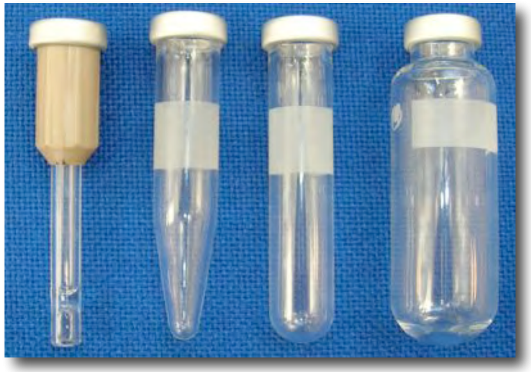


Flow Synthesis Equipment Configuration

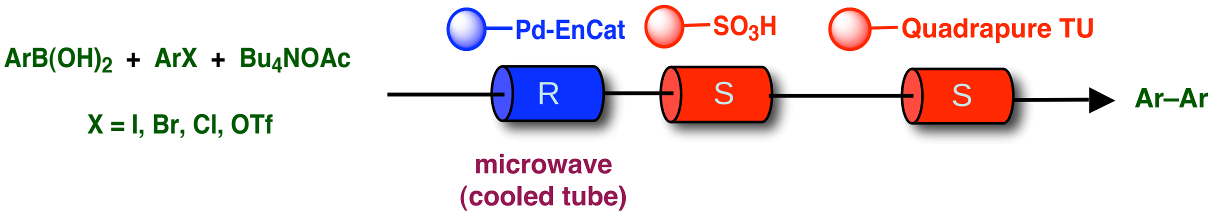
Flow Synthesis Equipment Configuration

Reaction Activation – Microwaves





Suzuki Couplings

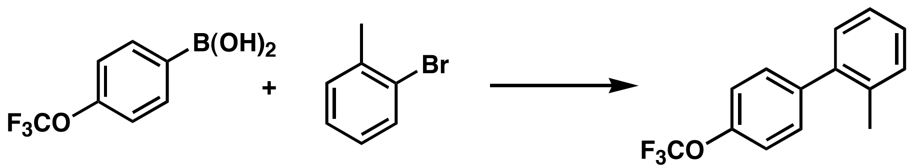


Batch Run

374 *examples from* ***11*** *boronic acids and* ***34*** *halides. Pyridine, thiophene, quinoline, pyrimidine, pyrazole, benzoxodiazole, benzofuran and biaryl compounds and sensitive functional groups e.g. aldehyde, benzyl bromide, benzyl alcohol.*

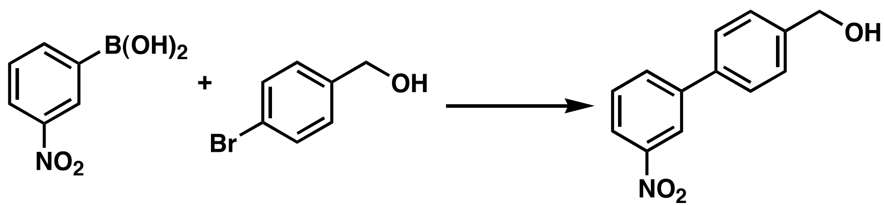
193 >80% yield, >90% purity

Batch to Flow Comparison



Batch
120 ^{o}C, 10 min — **Purity 84%**

Flow
0.1 ml/min, 0.01M, 50W with cooling — **Purity >98%**



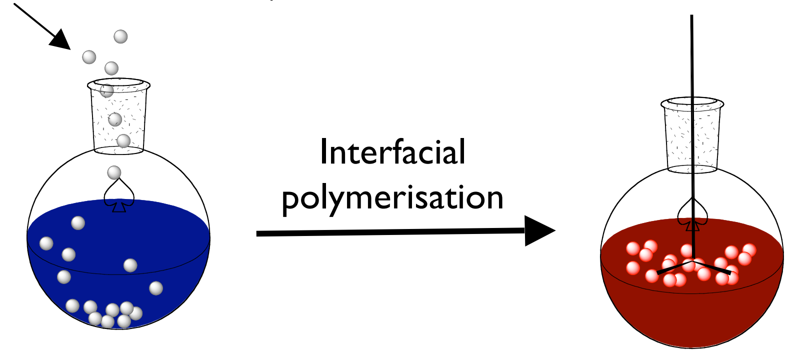
Batch
120 ^{o}C, 10 min — **Purity 34%**

Flow
0.1 ml/min, 0.01M, 50W with cooling — **Purity >98%**

Microwave Assisted Suzuki Coupling Reactions with an Encapsulated Palladium Catalyst for Batch and Continuous Flow Transformations
I.R. Baxendale, C.M. Griffiths-Jones, S.V. Ley and G. Tranmer, *Chem. Eur. J.*, 2006, 12, 4407-4416.

Microcapsules Manufacturing by Interfacial Polymerisation

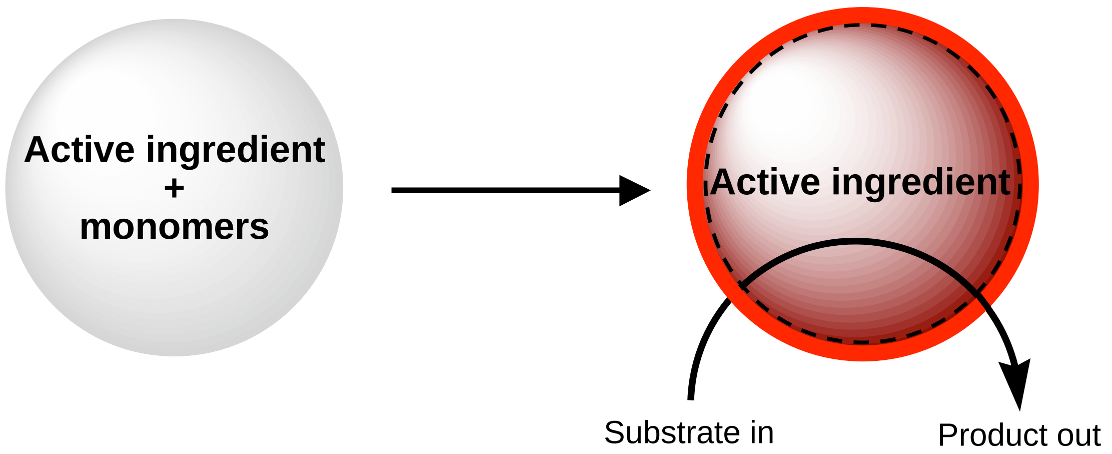
Oil
(Active ingredient + monomers)



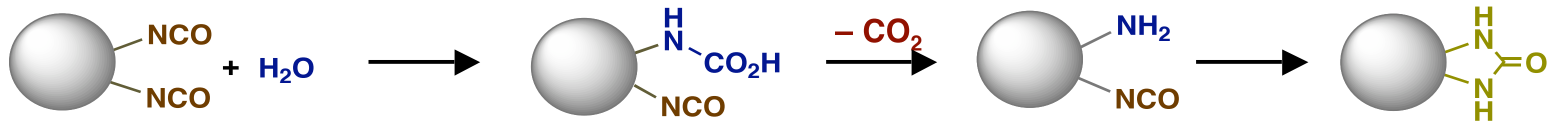
Aqueous: water, colloid stabilisers, emulsifiers

Wall formation

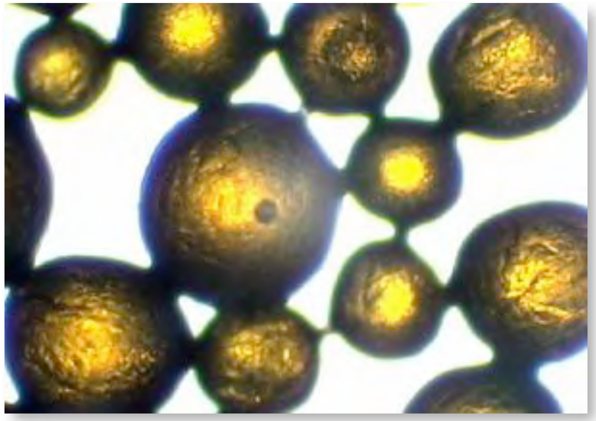
Filtered & dried EnCat™ (50-300 µm)

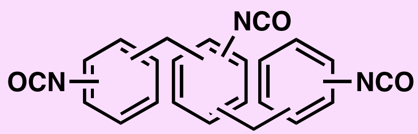


Polyurea Microcapsules Made by In-situ Interfacial Polymerisation

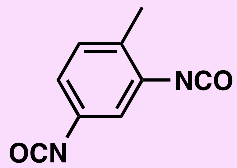


Oil droplet

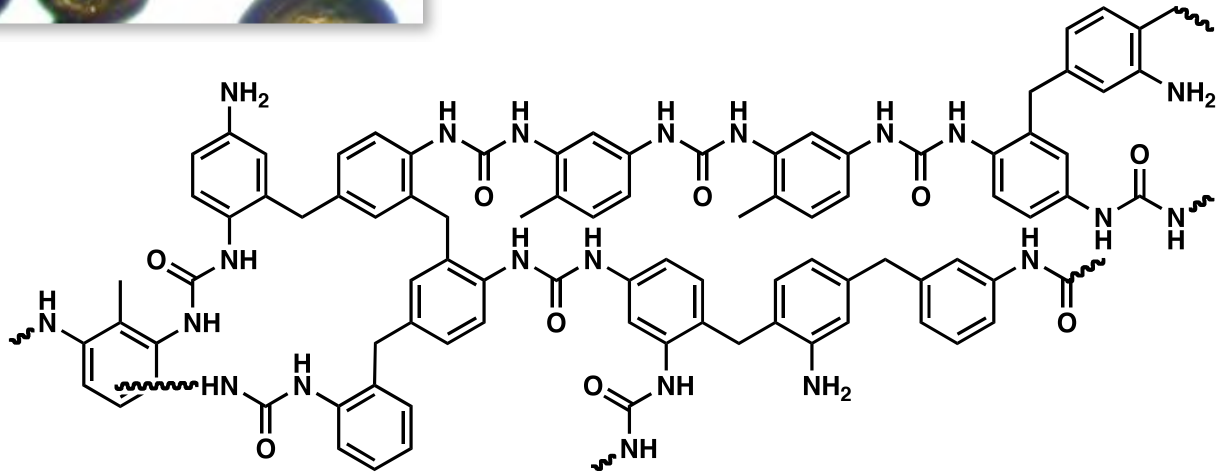




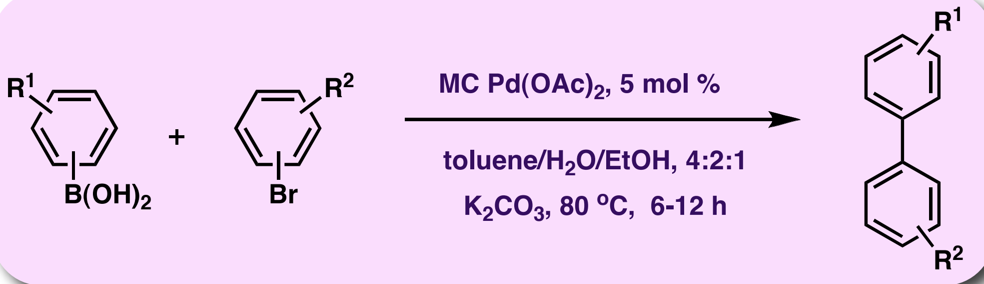
Polymethylenepolypropylene isocyanate



Toluene diisocyanate



Synthesis of Biaryls Using $Pd(OAc)_2$ Encapsulated in Polyurea

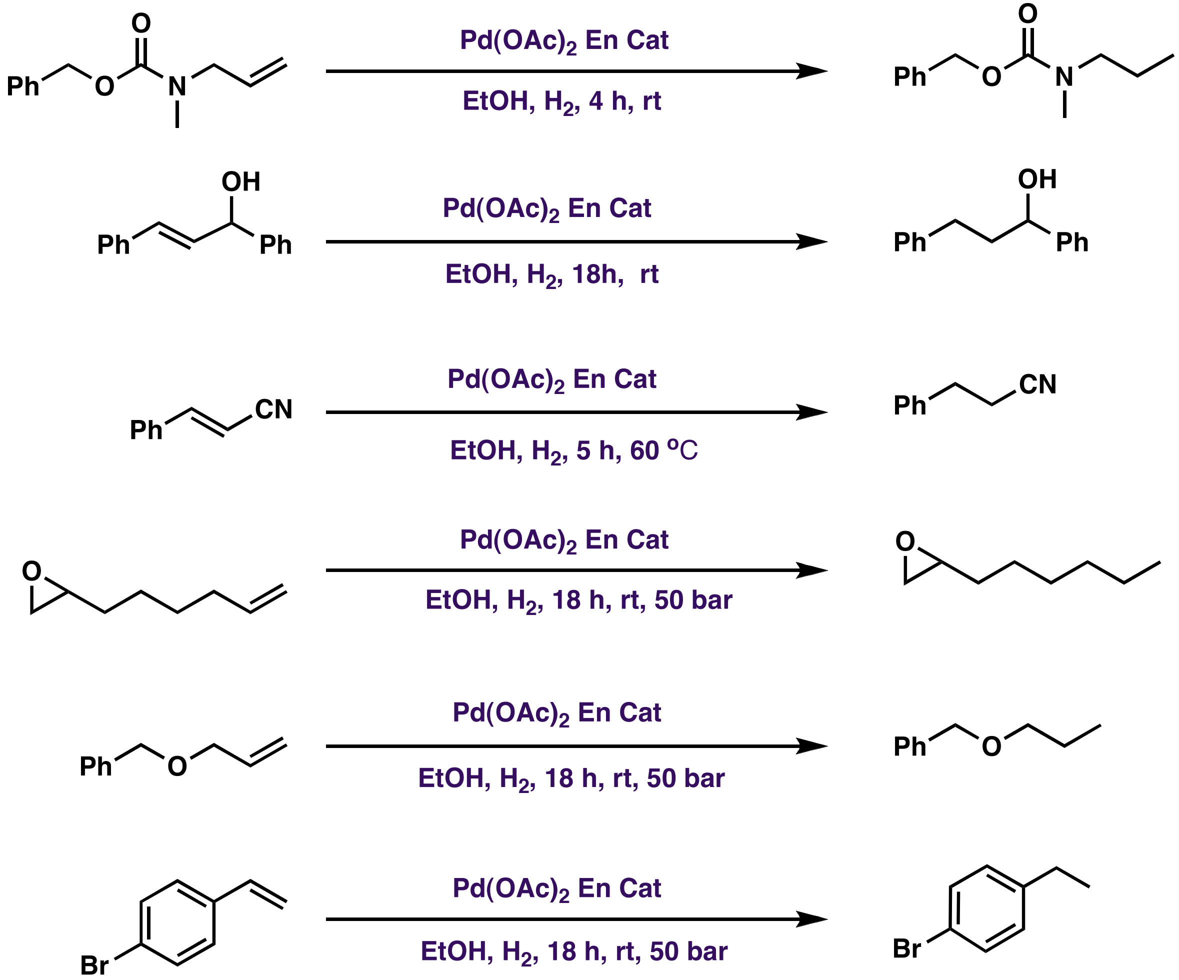


Entry	R^1	R^2	Yield/%†
1	*p*-OMe	*p*-OMe	87
2	*p*-OMe	*p*-F	89
3	*p*-OMe	*p*-NO_2	91
4	*p*-OMe	*p*-OMe	71
5	*p*-Ac	*p*-OMe	84
6	*p*-Ac	*p*-F	90
7	*p*-Ac	*p*-NO_2	97
8	H	*p*-OMe	94
9	H	*p*-F	93
10	H	*p*-NO_2	97

† *(%) based on isolated products. ICP Pd analysis typically 0.5-5 ppm*

300 examples
Works in $scCO_2$
Can entrap various phosphorous ligands
Flow reactor version

$Pd(OAc)_2$ EnCats in Hydrogenation

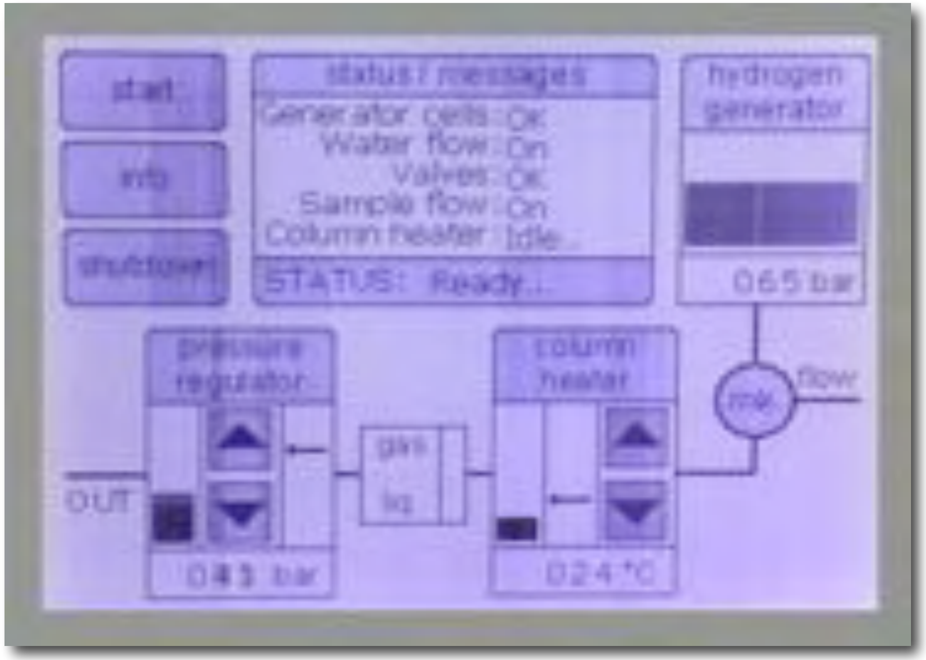


Quantitative yield up to 30x recycle

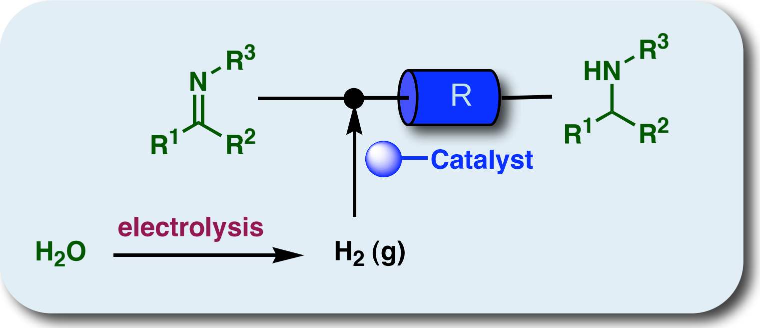
N.Bremeyer, S.V.Ley, C.Ramarao, I.M.Shirley, S.C.Smith, *Synlett*. 2002, 1843.

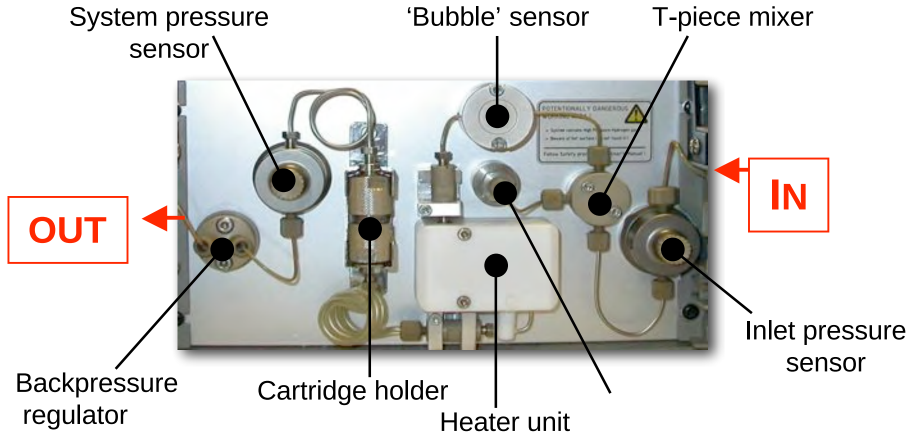
H-Cube Flow Hydrogenator

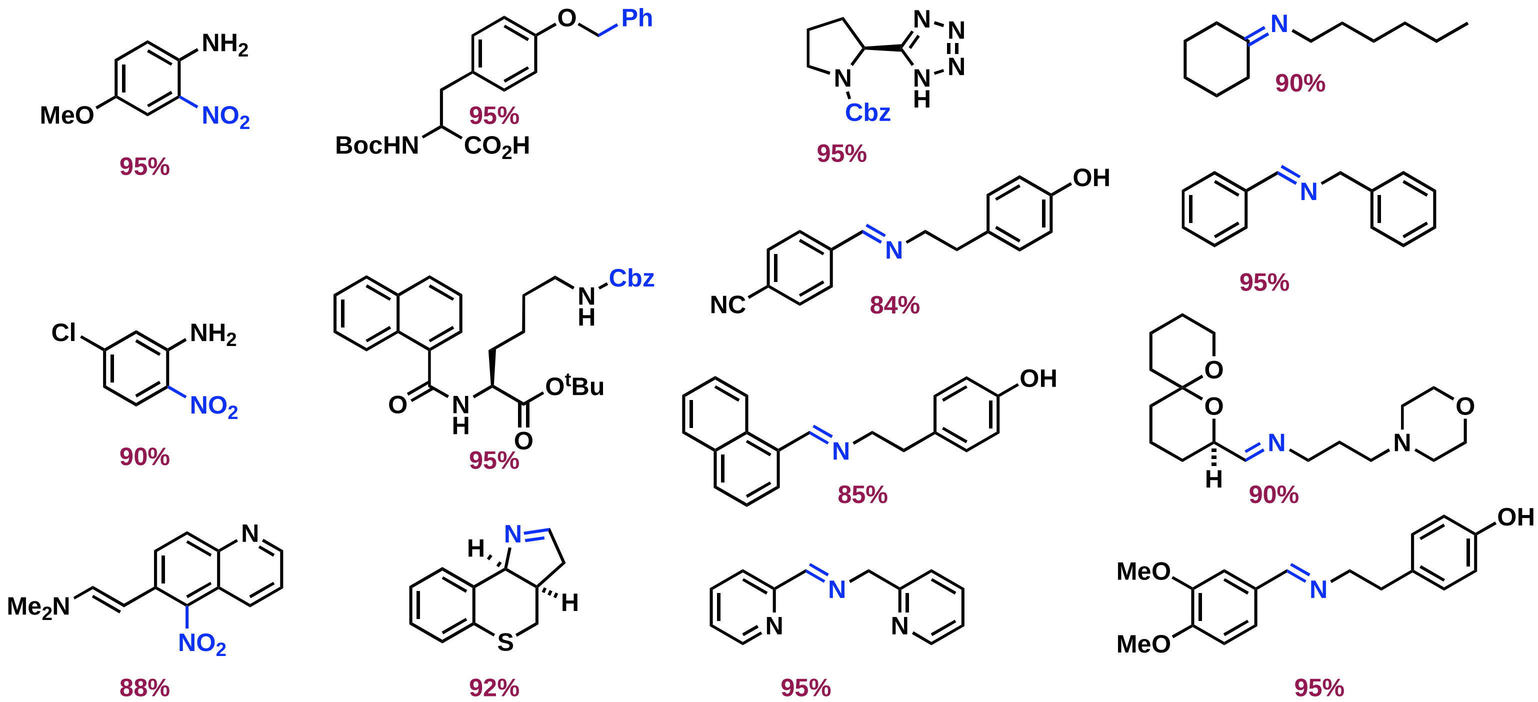
- H-Cube generates H_2 gas *in situ* from the electrolysis of water (< 8 cm^3).
- H_2 gas and a flowing solution of the substrate are mixed at a T-piece to form a mixture of gas and liquid ('bubbles').
- Mixture flows through an interchangeable metal cartridge containing a hydrogenation catalyst.
- Product mixture then flows through a backpressure regulator to a collection vial.
- **System pressure** controllable up to 100 bar
- **System temperature** is variable up 90 ^{O}C



Flow Hydrogenation in Action

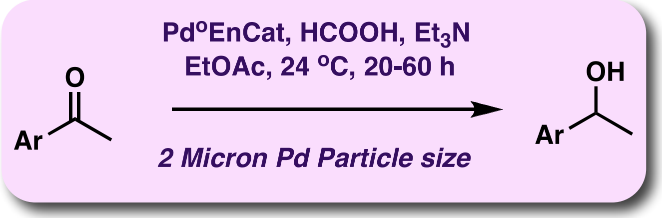


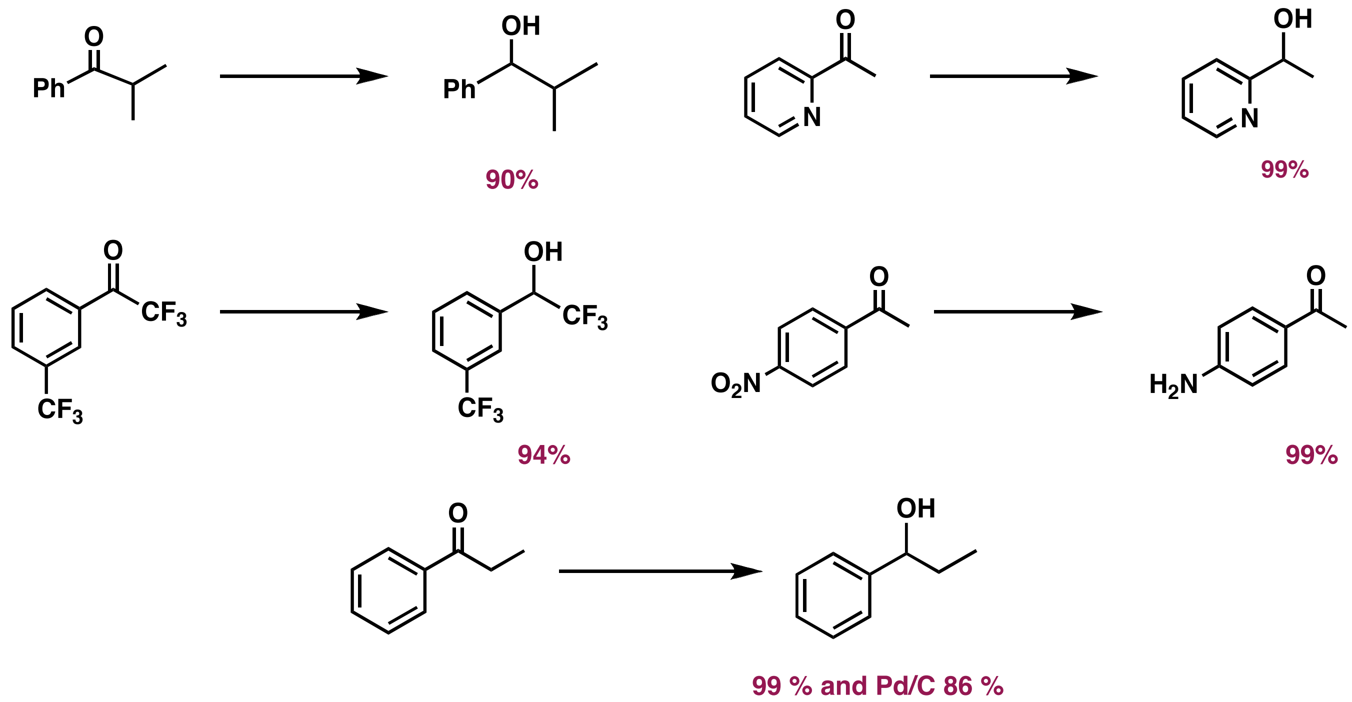




The use of a Continuous Flow-Reactor Employing a Mixed Hydrogen-Liquid Flow Stream for the Efficient Reduction of Imines to Amines
S. Saaby, K.R. Knudsen, M. Ladlow and S.V. Ley, *J. Chem. Soc., Chem. Commun.*, **2005**, 2909-2911.
Optimisation of Conditions for *O*-Benzyl and N-Benzyloxycarbonyl Protecting Group Removal using an Automated Flow Hydrogenator
K.R. Knudsen, J. Holden, S.V. Ley and M. Ladlow, *Adv. Syn. Cat.*, **2007**, *349*, 535-538

EnCat Pd(0) in Polyurea – For Hydrogen Transfer Reduction of Aryl Ketones

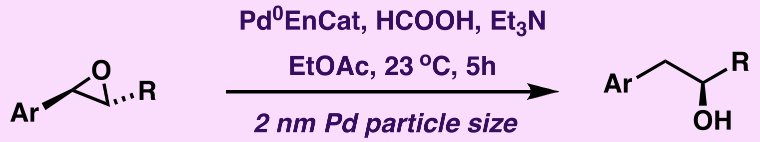


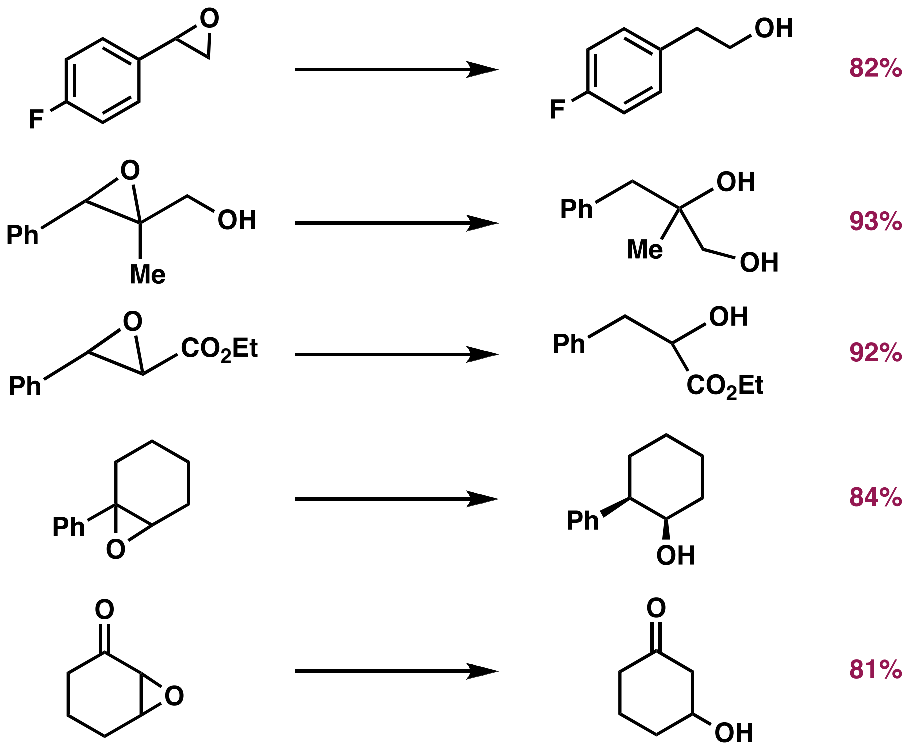


Recycle up to 10+ times

Transfer Hydrogenation using Recyclable Polyurea-Encapsulated Palladium: Efficient and Chemoselective Reduction of Aryl Ketones
J-Q Yu, H-C. Wu, C. Ramarao, J.B. Spencer and S.V. Ley, J. Chem. Soc., Chem. Commun., 2003, 678.

EnCat Pd(0) in Polyurea – For Hydrogenolysis of Epoxides

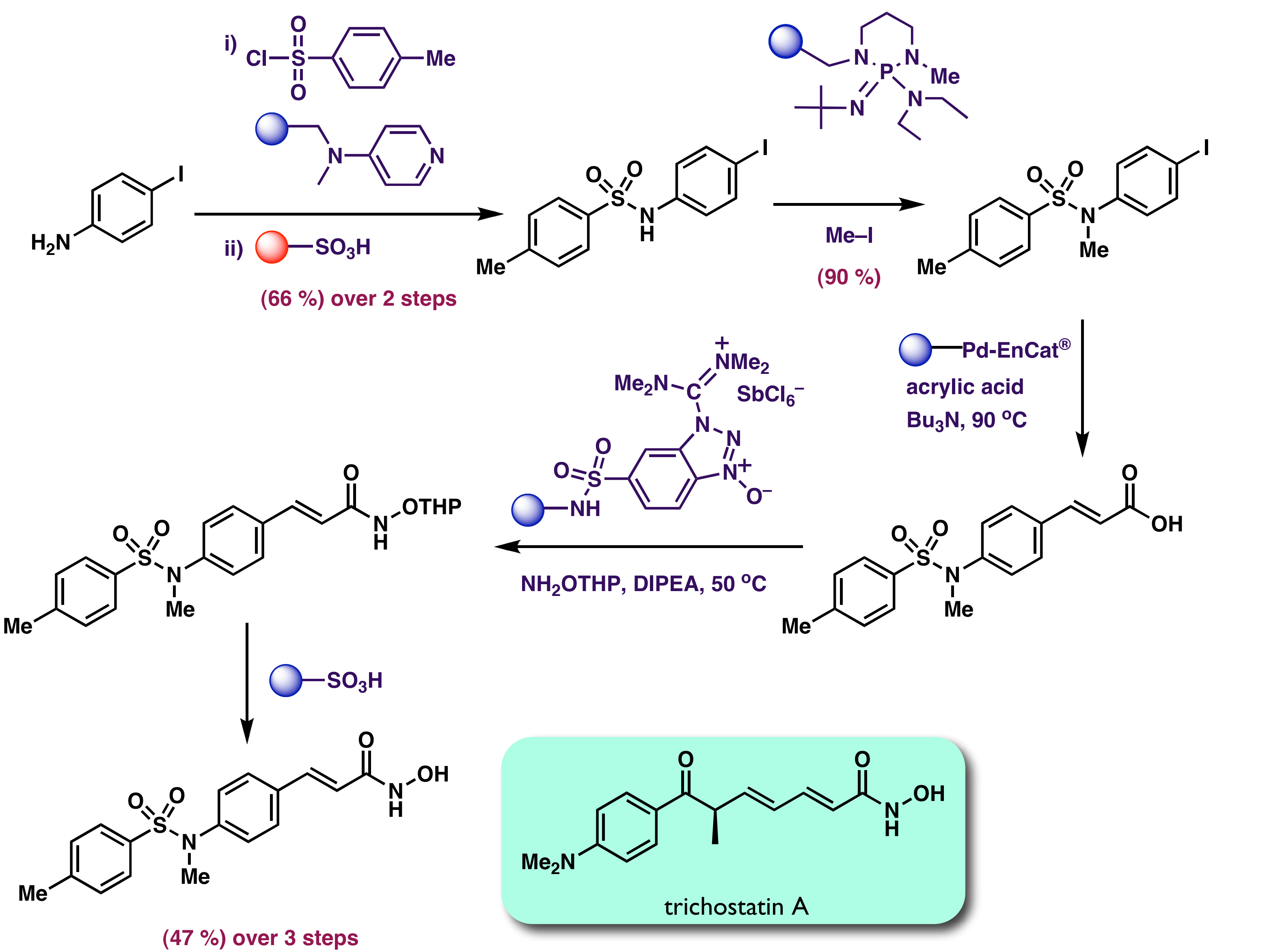




Recycle up to 10+ times

Recyclable Polyurea-Microencapsulated Pd(0) Nanoparticles: An Efficient Catalyst for the Hydrogenolysis of Epoxides, C. Mitchell, D. Pears, S.V. Ley, J-Q. Yu and W. Zhou, *Org. Lett.*, 2003, *5*, 4665.

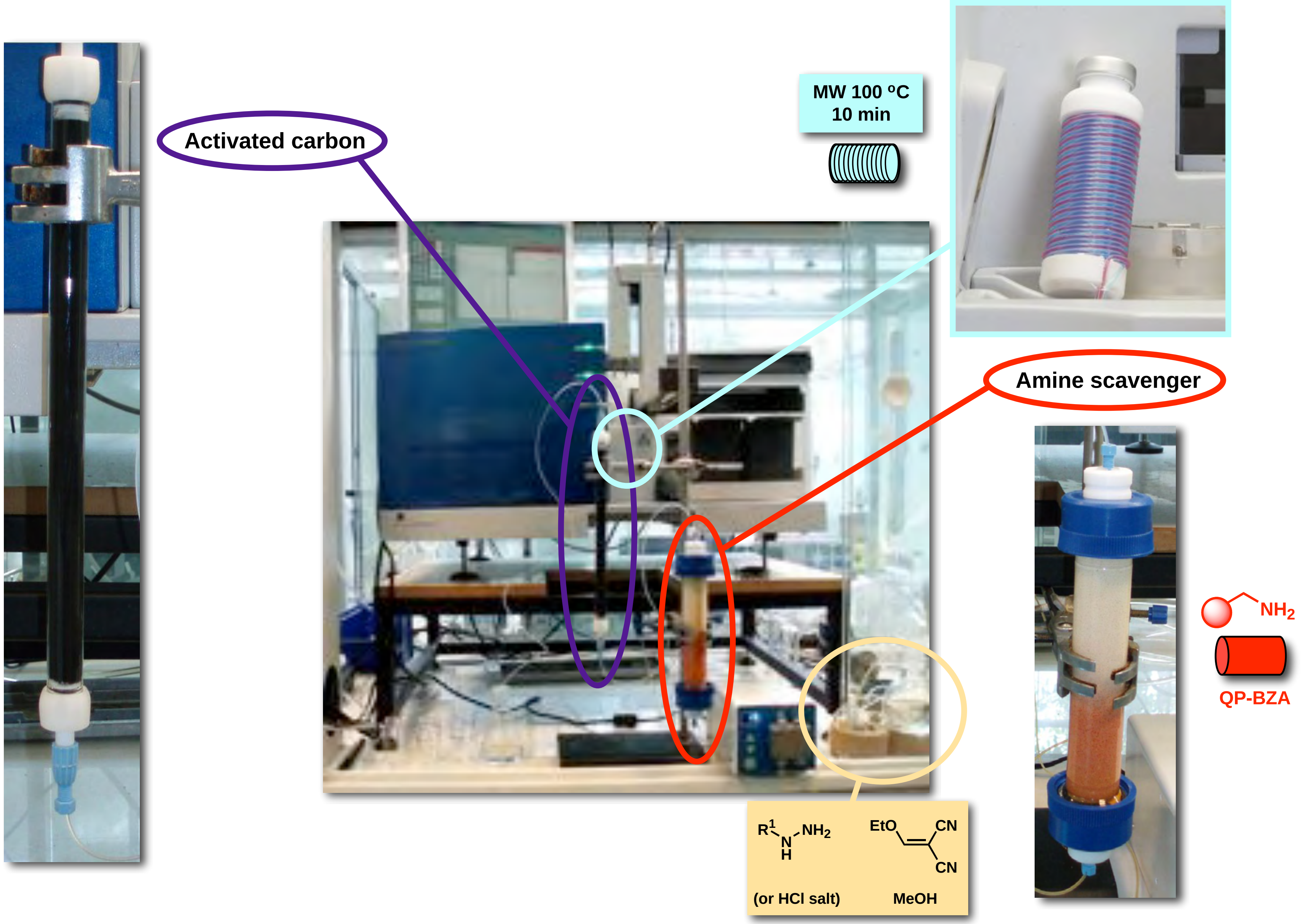
Synthesis of Histone Deacetylase Inhibitors



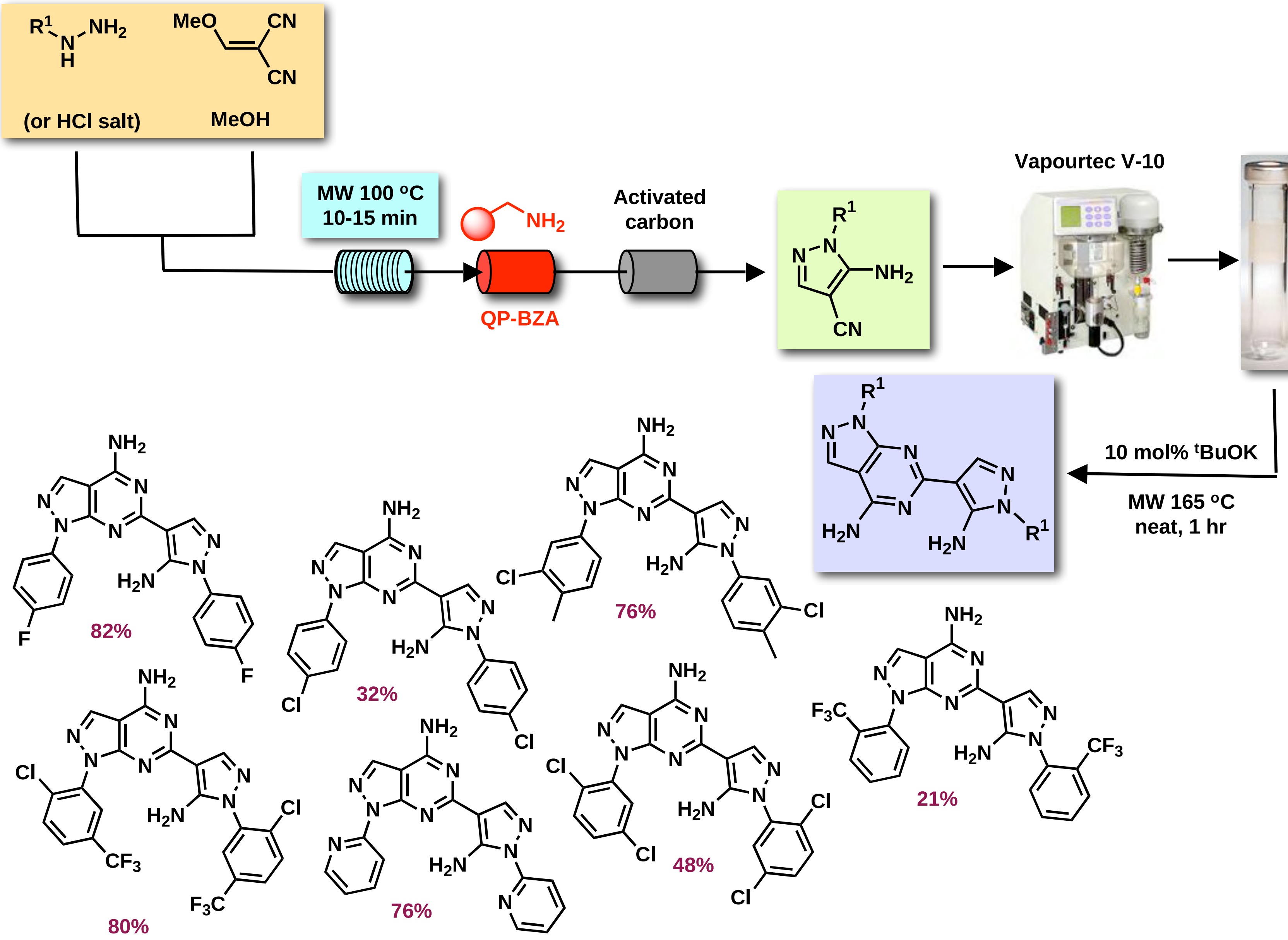
Polymer-Assisted Multistep Solution Phase Synthesis and Biological Screening of Histone Deacetylase Inhibitors

A. Bapna, M. Ladlow, E. Vickerstaff, B.H. Warrington, T-P. Fan and S.V. Ley, Org. Biomol. Chem., 2004, 2, 611

Synthesis of Pyrazole Dimers



Synthesis of Pyrazole Dimers

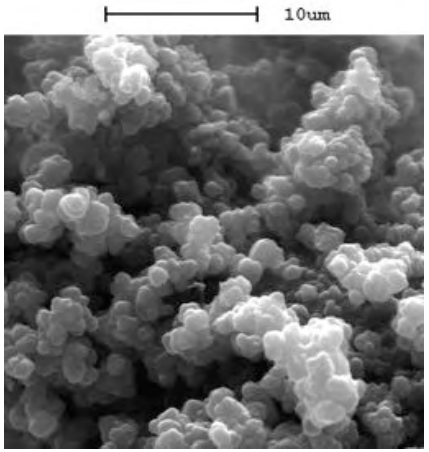


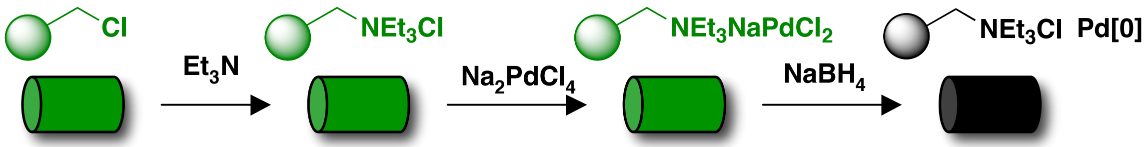
I.R. Baxendale, C.J. Smith, S.V. Ley *et al. Org. Biomol. Chem.*, 2007, *5*, 2758-2761.

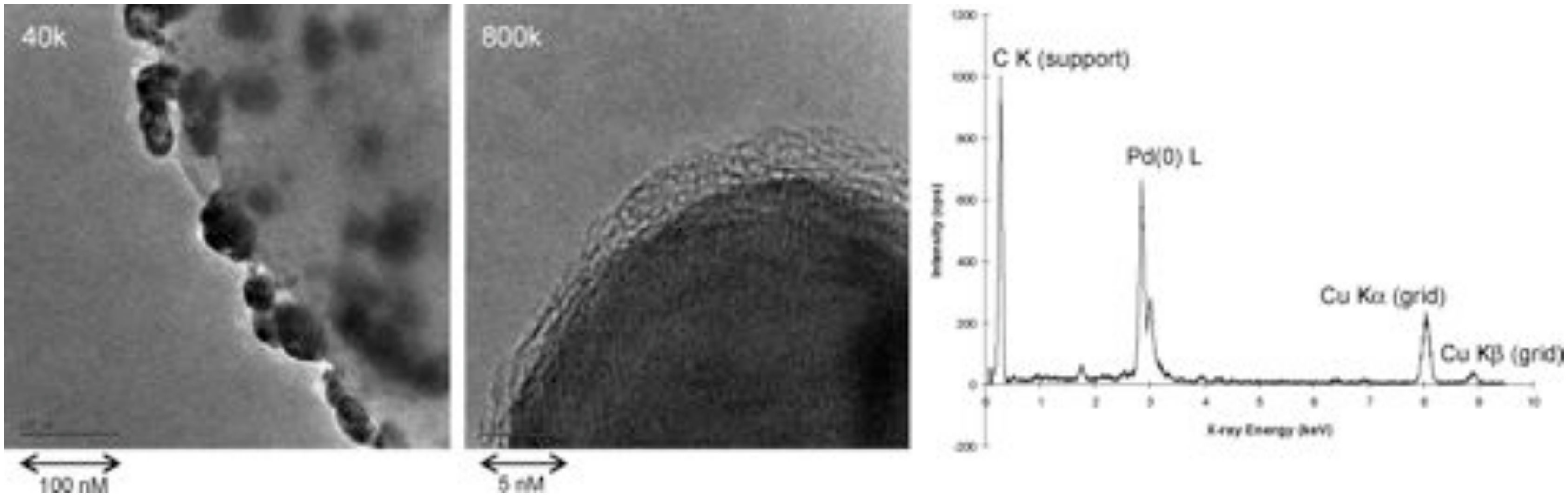
Monolith Preparation

High loading capacity
Macroporous polymer
Inexpensive
Easy to prepare
Available in a variety of materials

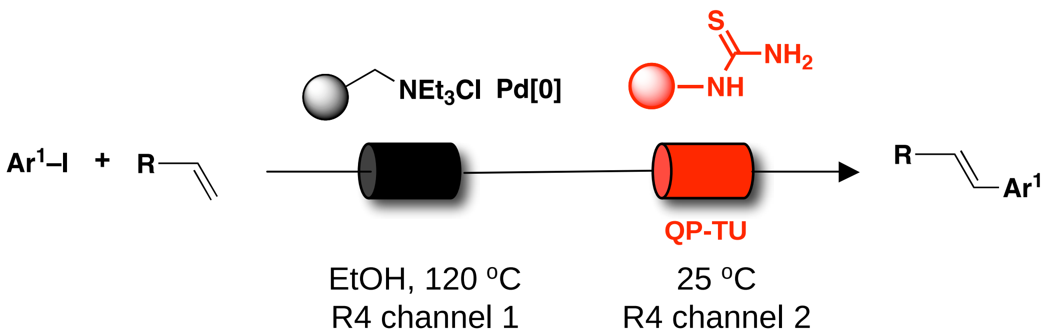
Nanoparticular Monolith Pd



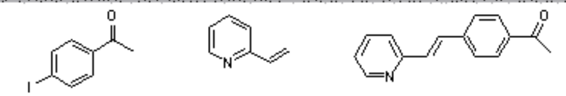
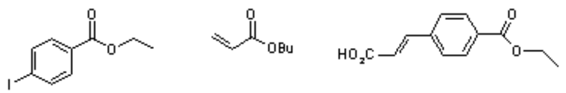
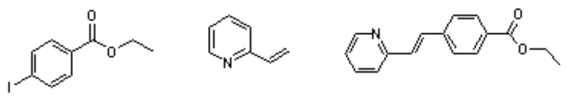
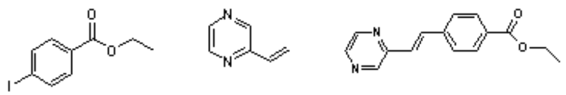
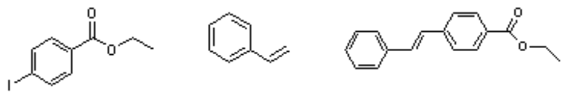
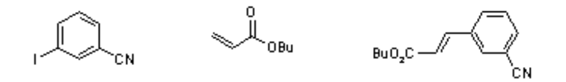
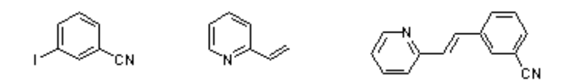
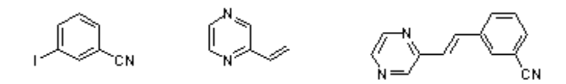
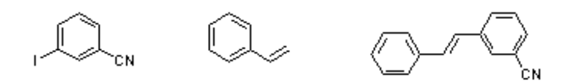




Nanoparticular Monolith Pd in Heck Reactions

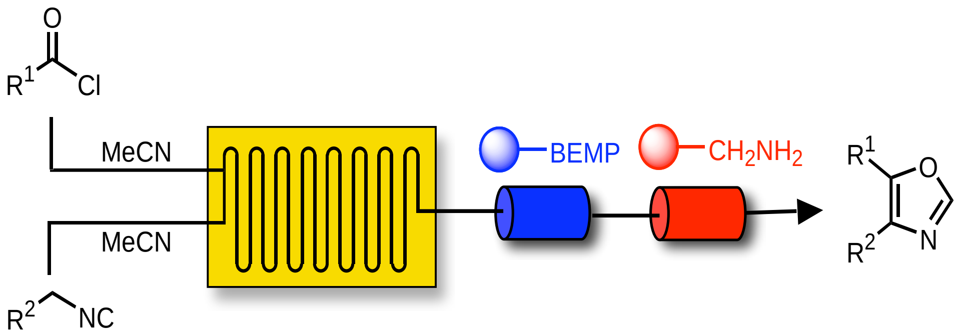


Flow rate 0.05 mL/min
ICP analysis <5 ppm Pd
Column reused 50 times
Lithograph surface area 5 m^2/g

Aryl Halide / Alkene / Product	Conversion (%)	Purity	Yield (%)
	100	>99	86
	100	>95	87
	100	>95	88
	100	>95	87
	100	>95	88
	100	>99	79
	100	>99	85
	100	>99	78
	100	>99	73

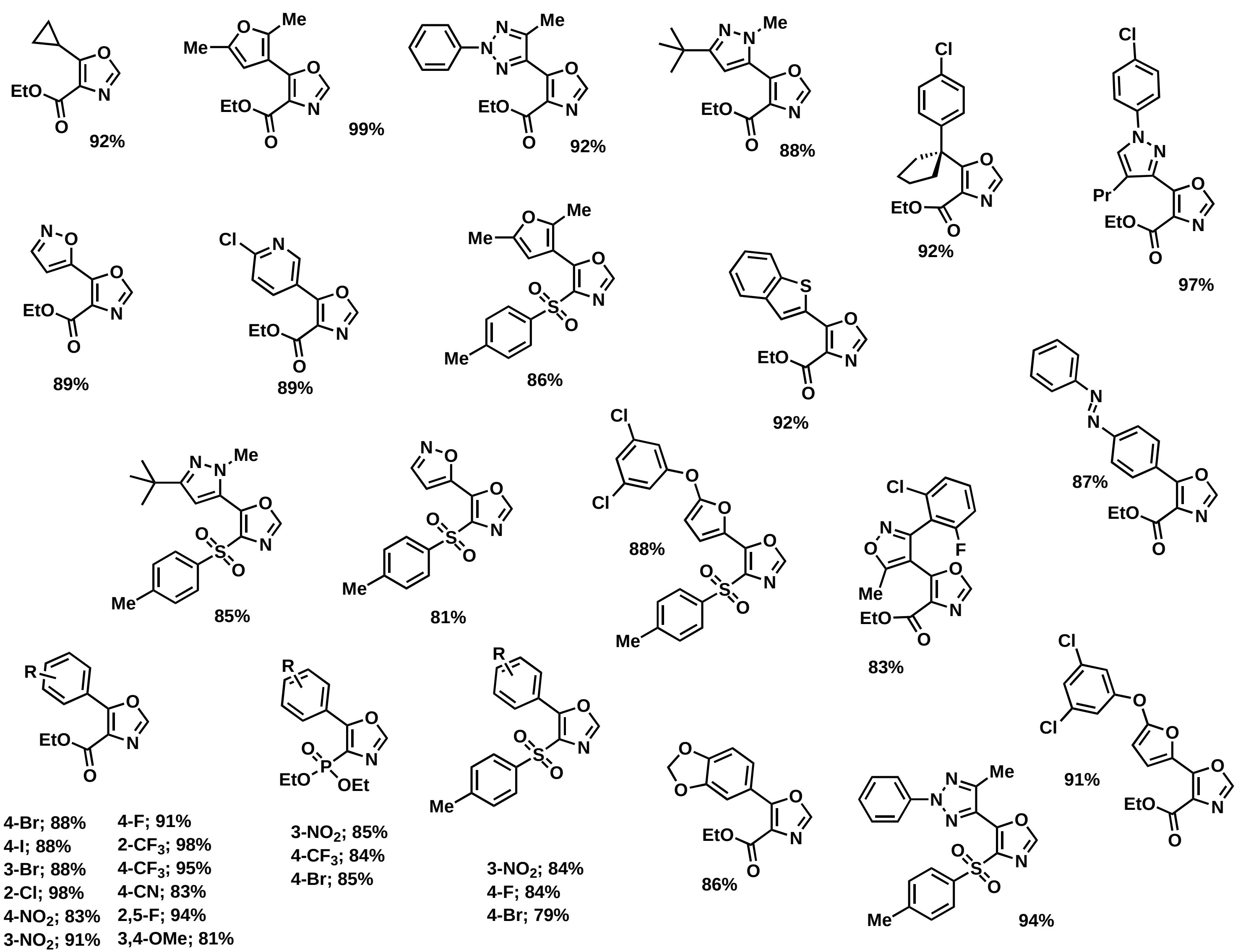
N. Nikbin, M. Ladlow, S.V. Ley, *Org. Proc. Res. Dev*. **2007**, *11*, 458

Synthesis of Oxazoles in Flow



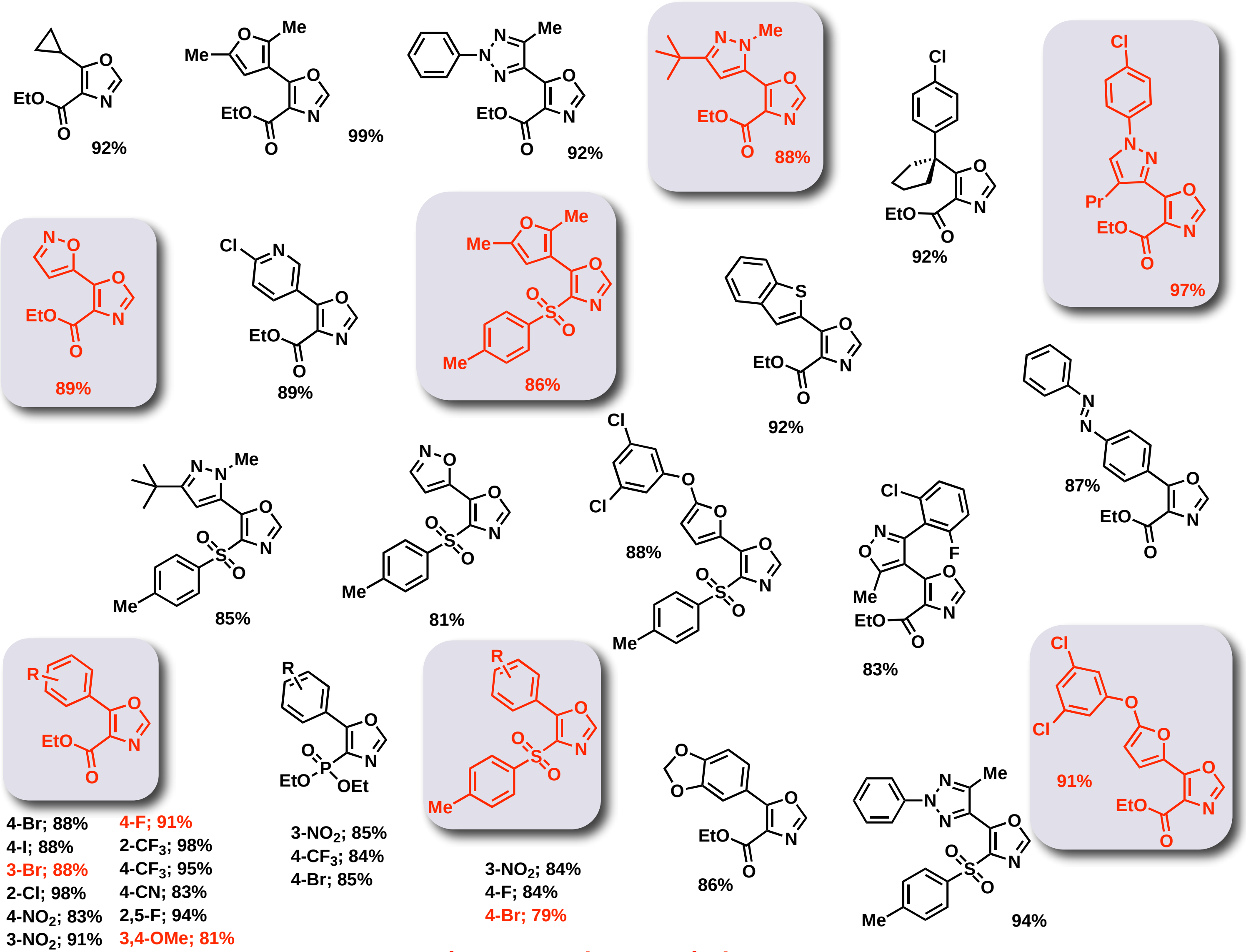
A Fully Automated Continuous Flow Synthesis of 4,5-Disbustituted Oxaxoles,
M. Baumann, I.R. Baxendale, S.V. Ley, C.D. Smith and G.K. Tranmer, *Org. Lett.,* 2006, *8,* 5231-5234.

Synthesis of Oxazoles in Flow



A Fully Automated Continuous Flow Synthesis of 4,5-Disbustituted Oxaxoles,
M. Baumann, I.R. Baxendale, S.V. Ley, C.D. Smith and G.K. Tranmer, *Org. Lett.,* 2006, *8,* 5231-5234.

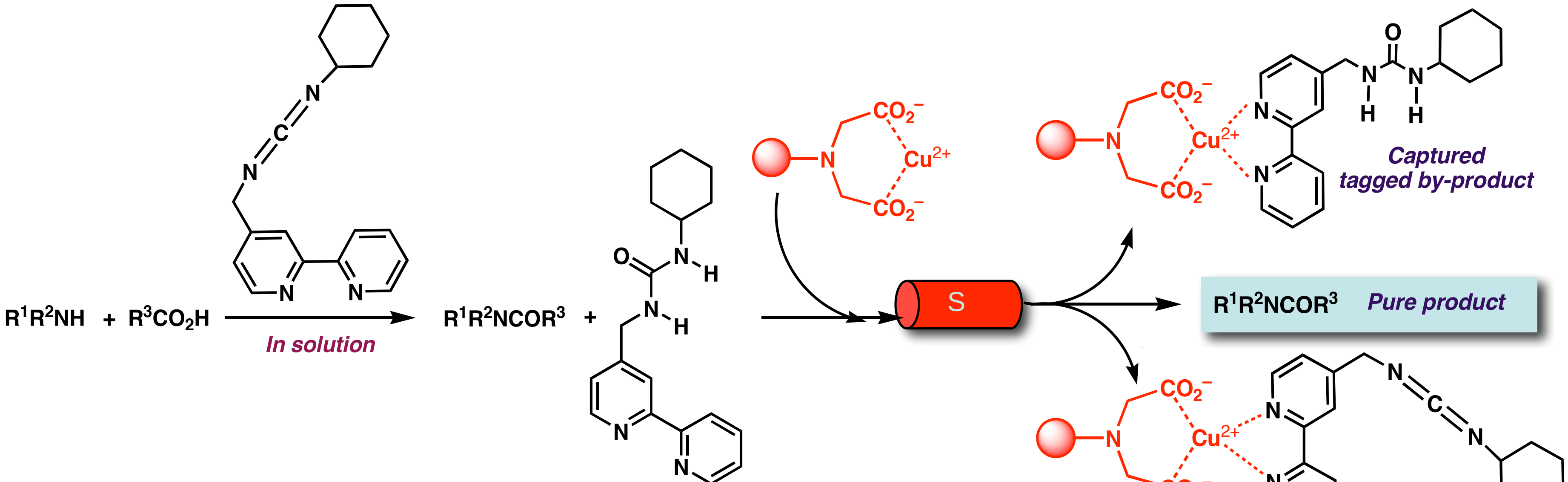
Synthesis of Oxazoles in Flow

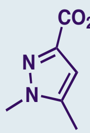
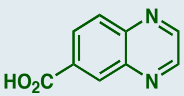
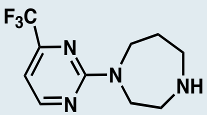
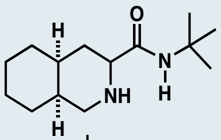
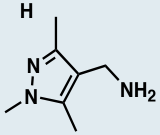


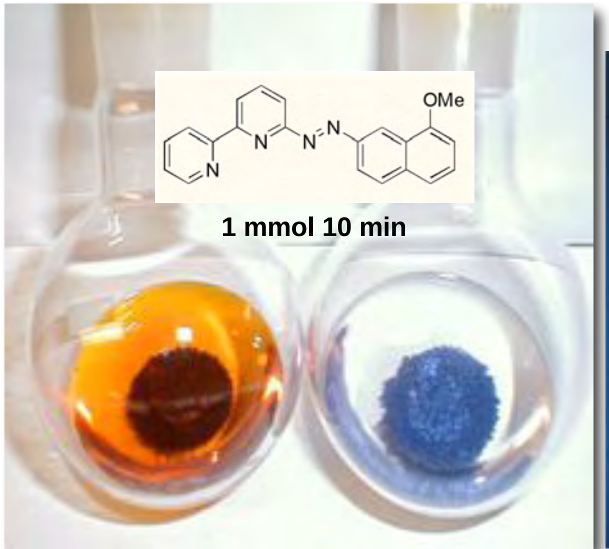
oxazole preparations scaled to >10g

A Fully Automated Continuous Flow Synthesis of 4,5-Disbustituted Oxaxoles,
M. Baumann, I.R. Baxendale, S.V. Ley, C.D. Smith and G.K. Tranmer, *Org. Lett.,* 2006, *8,* 5231-5234.

Reagent Phase Switch Tagging Techniques



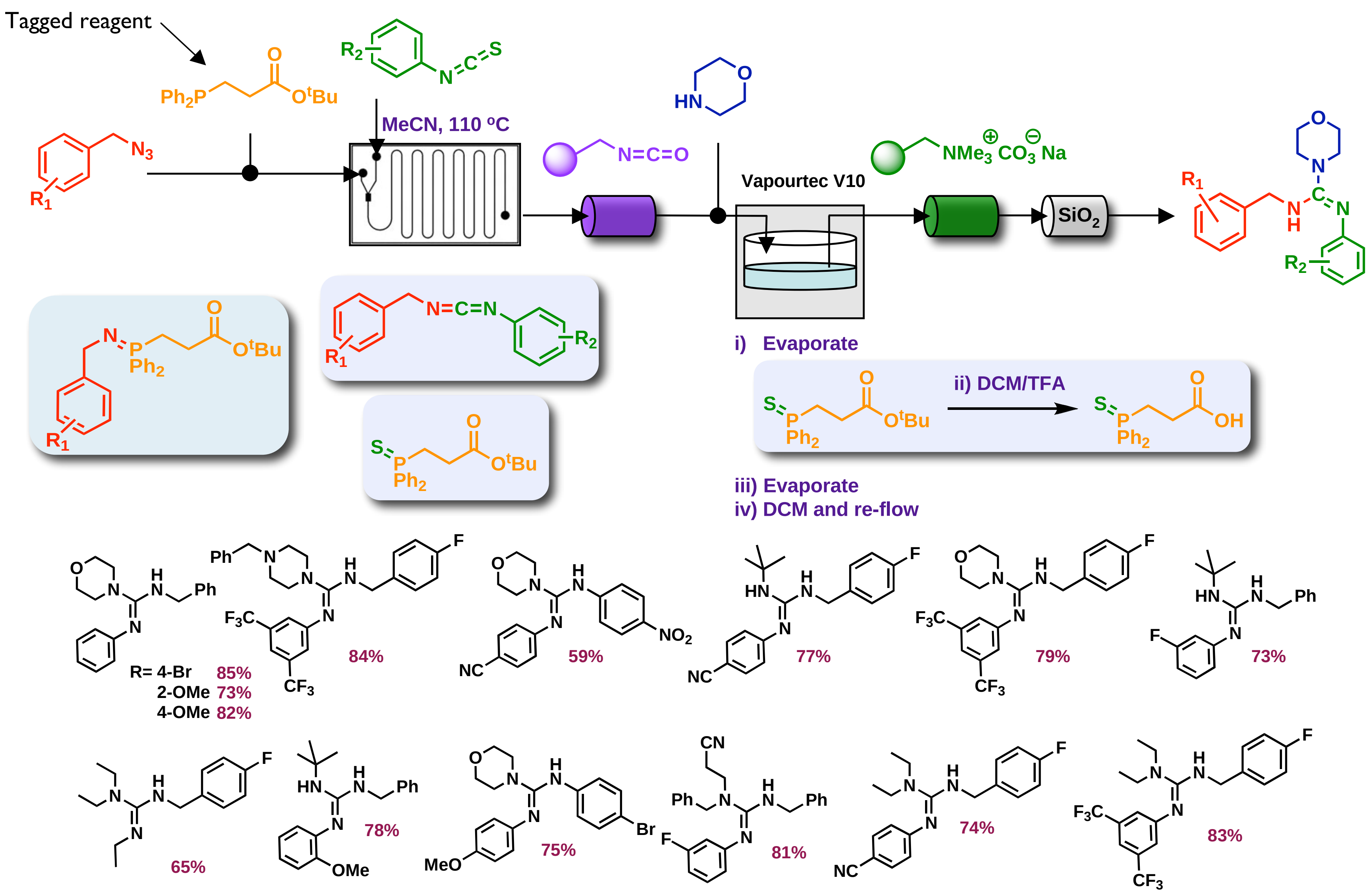
Amine		
	87%	83%
	91%	89%
	90%	85%



A Phase-Switch Purification Approach for the Expedient Removal of Tagged Reagents and Scavengers Following their Application in Organic Synthesis

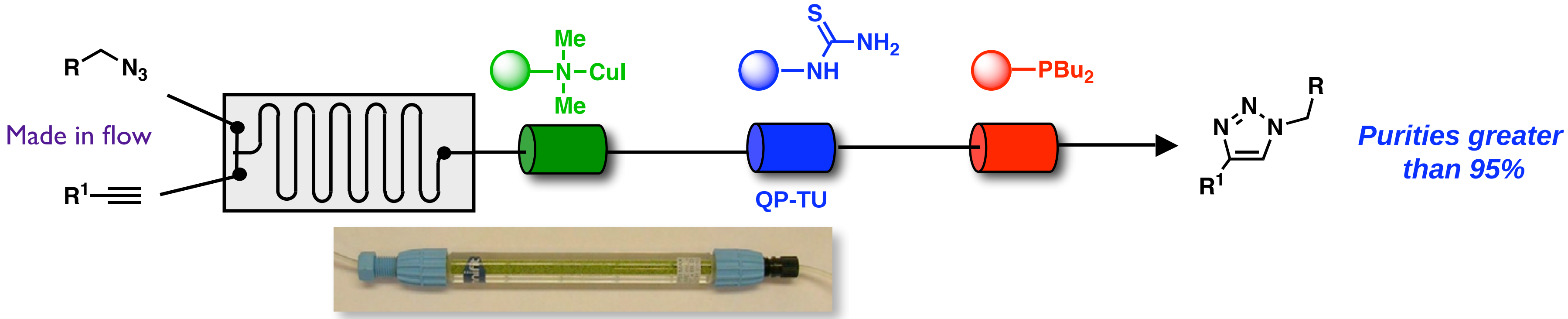
J. Siu, I.R. Baxendale, R.A. Lewthwaite and S.V. Ley, *Org. Biomol. Chem.,* 2005, *3,* 3140-3160.

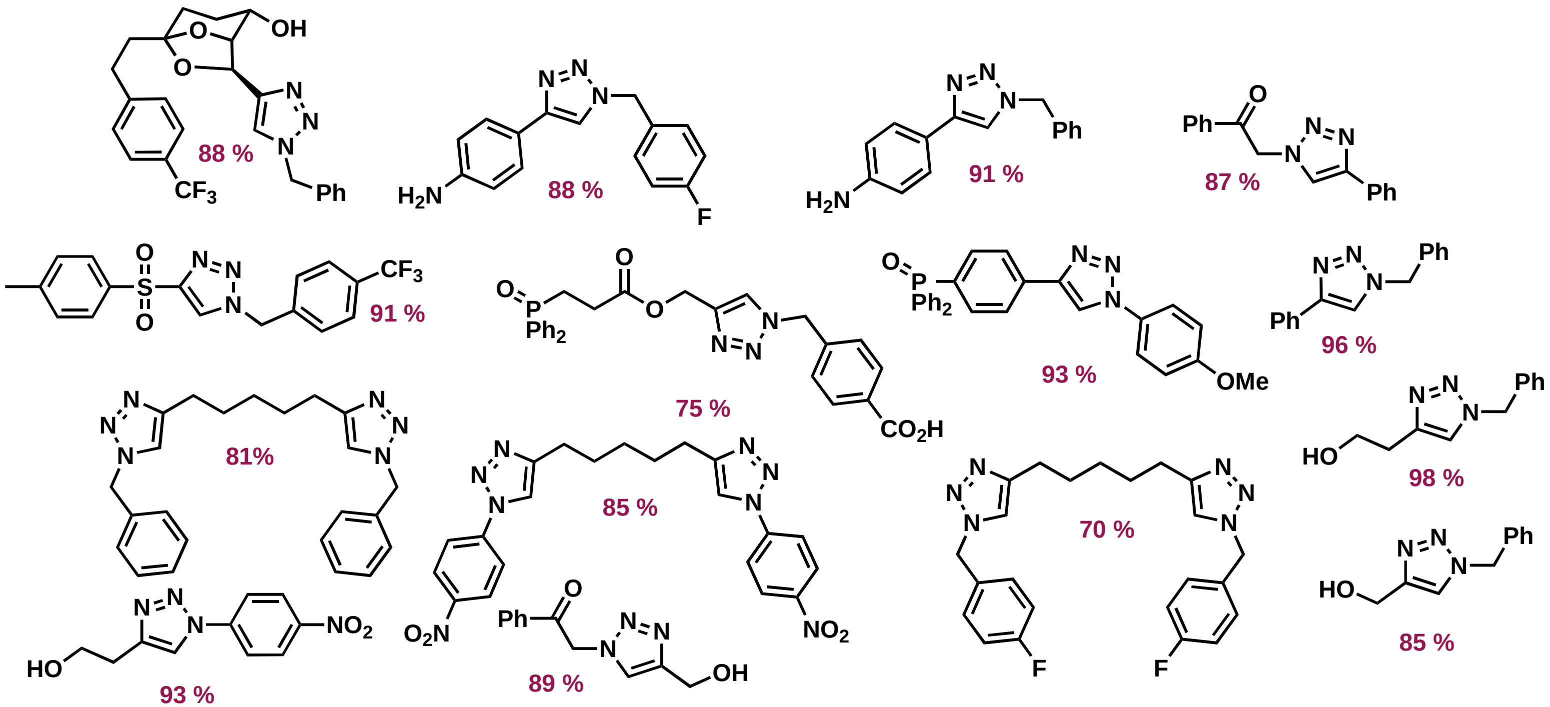
Tagged Reagents in Flow – Synthesis of Guanidines



Tagged Phosphine Reagents to Assist Reaction Work-up by Phase-Switched Scavenging Using a Modular Flow Reactor Process. C.D. Smith, I.R. Baxendale, G.K. Tranmer, M. Baumann, S.C. Smith, R.A. Lewthwaite and S.V. Ley, *Org. Biomol. Chem.*, 2007, *5*, 1562-1568

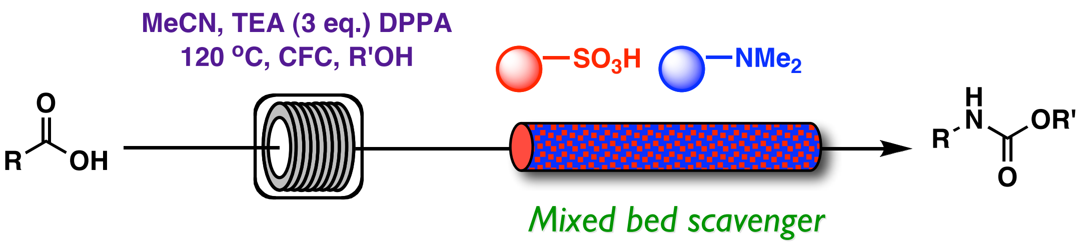
Azide Couplings in Flow



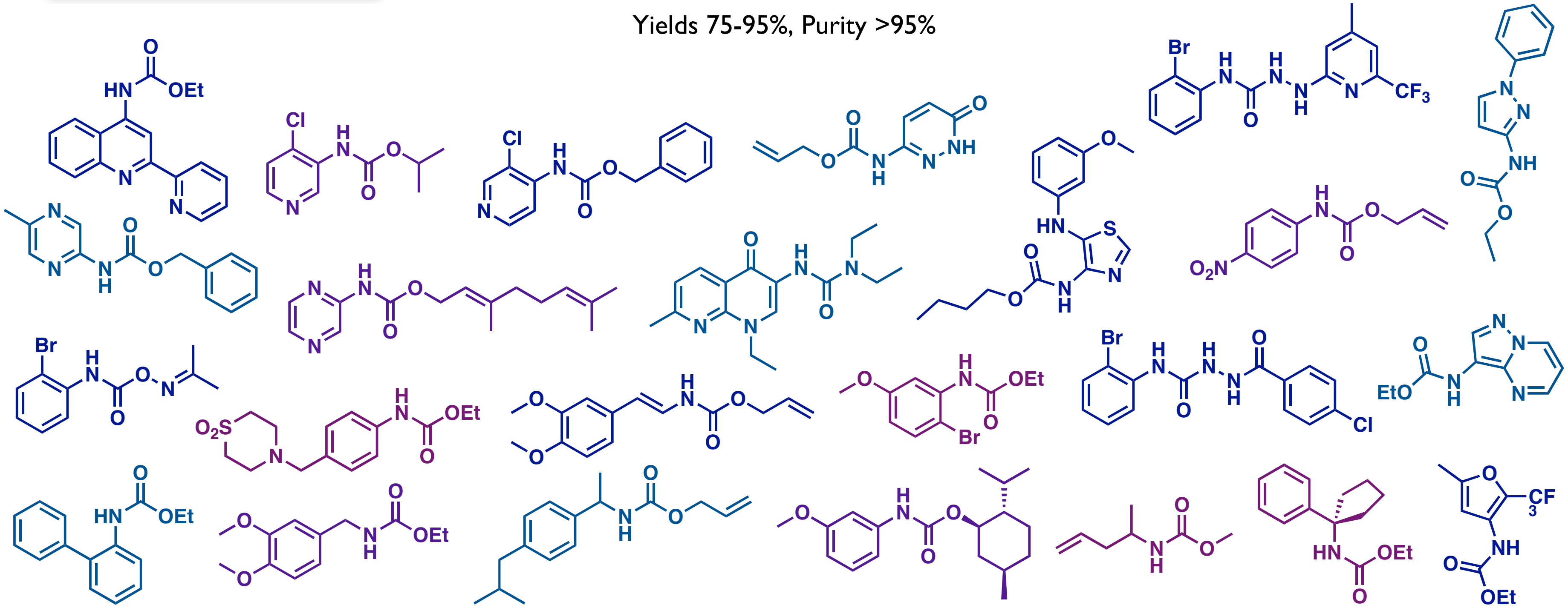


[3 + 2] Cycloaddition of Acetylenes with Azides to give 1,4-Disubstituted 1,2,3- Triazoles in a Modular Flow Reactor
C.D. Smith, I.R. Baxendale, S. Lanners, J.J. Hayward, S.C. Smith and S.V. Ley, *Org. Biomol. Chem.*, 2007, *5*, 1559-1561.

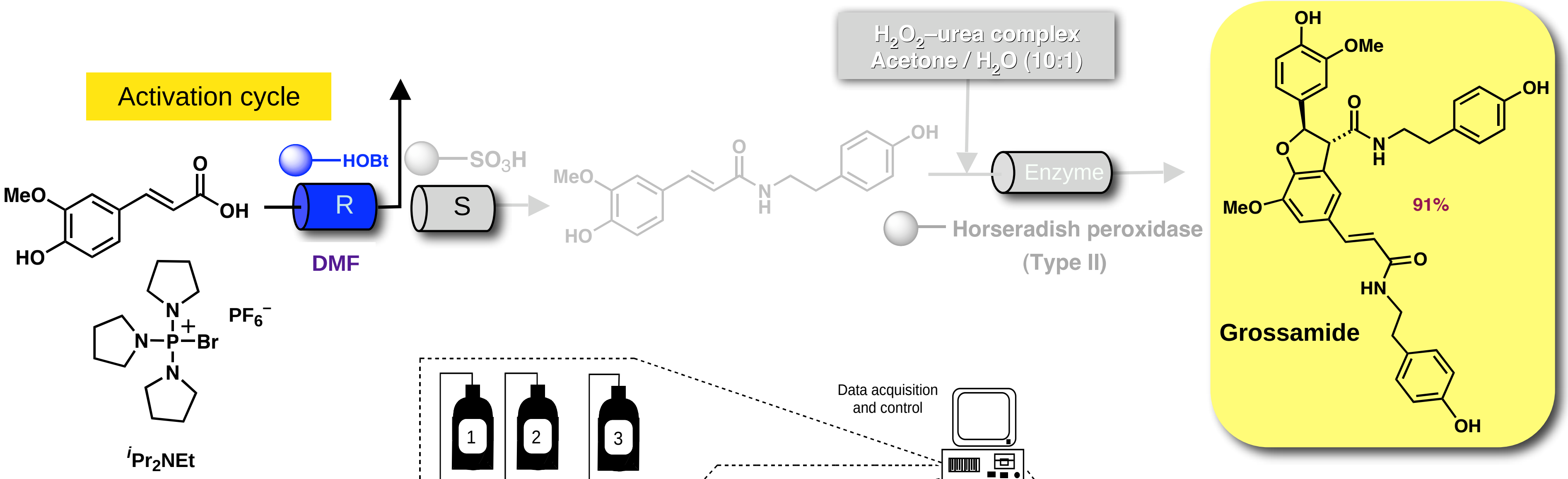
Curtius Rearrangements in Flow

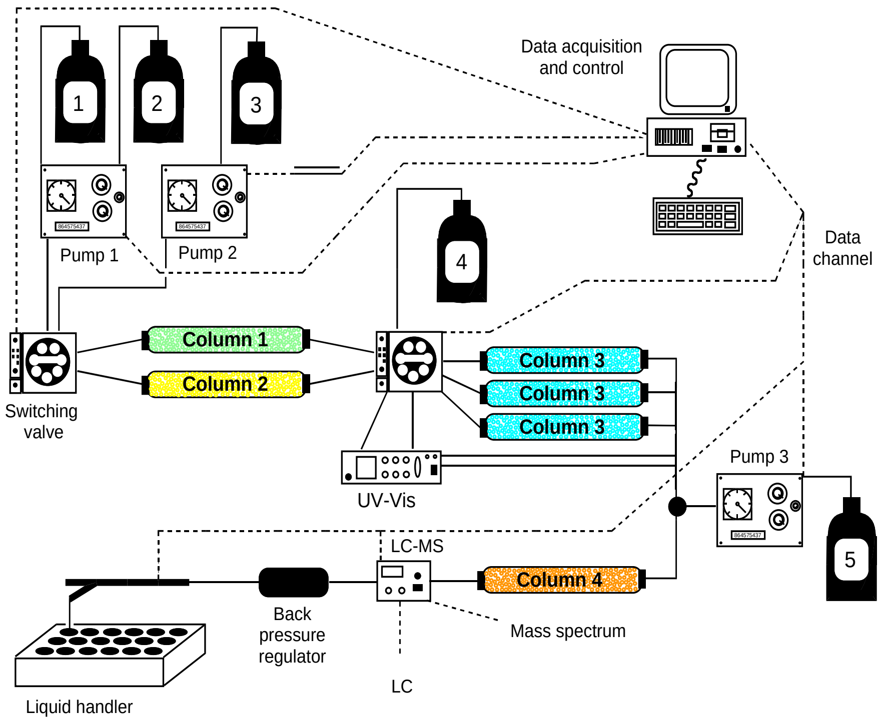


Yields 75-95%, Purity >95%



Flow Synthesis of Grossamide using Immobilized Enzymes





Column

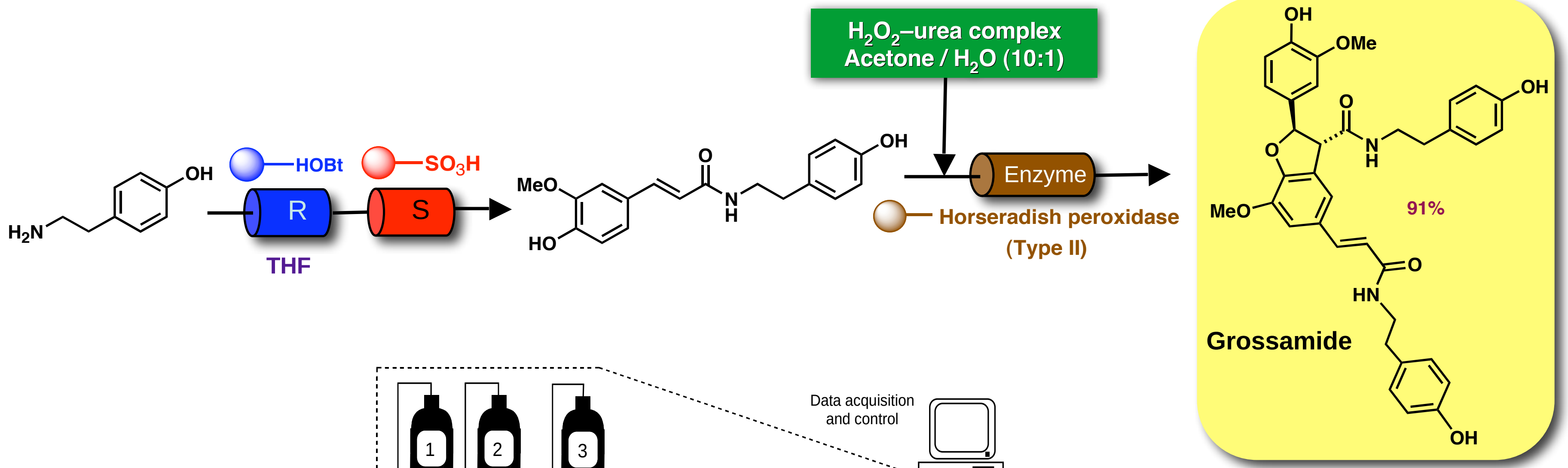
1 PS-HOBt
2 PS-HOBt
3 PS-SO_3H
4 Si-Horseradish peroxidase

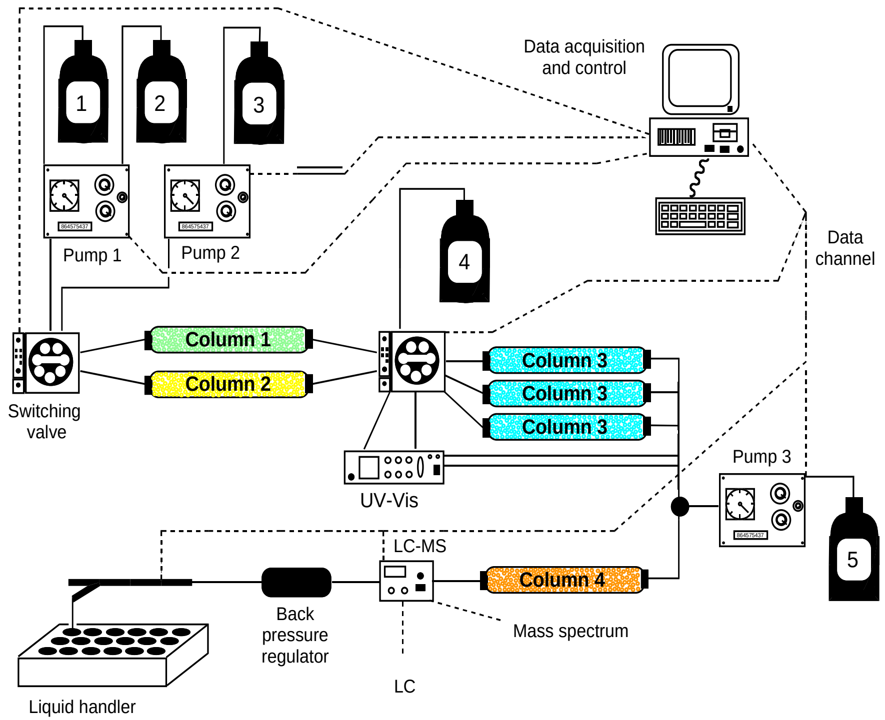
Container

1 Ferulic acid
2 PyBrOP, DIPEA
3 Amine solution
4 Washings
5 H_2O_2 urea complex
Buffer pH 4.5

Preparation of the Neolignan Natural Product Grossamide by a Continuous Flow Process
I.R. Baxendale, C.M. Griffiths-Jones, S.V. Ley and G.K. Tranmer, *Synlett*, 2006, 427-430

Flow Synthesis of Grossamide using Immobilized Enzymes





Column

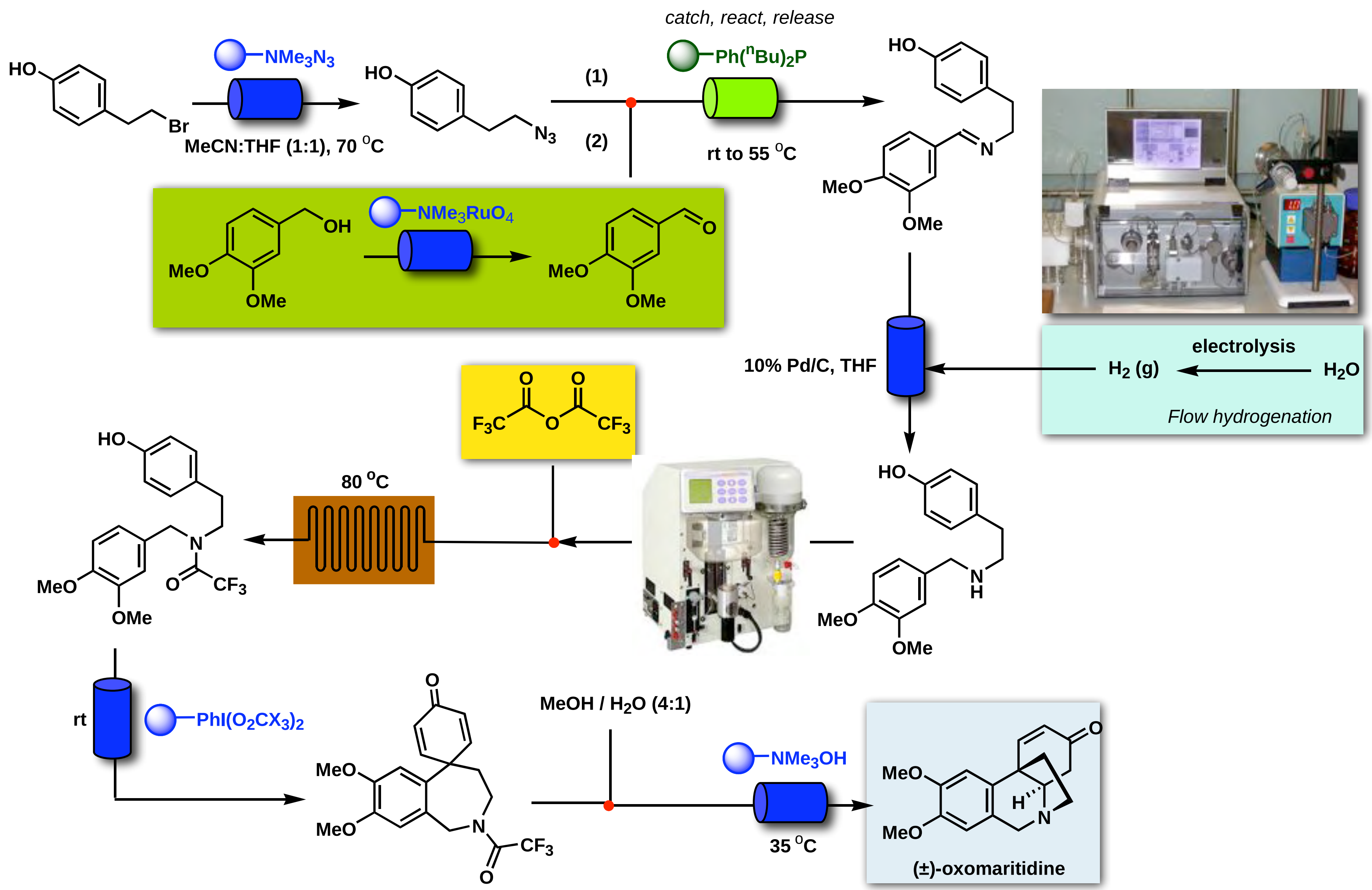
1 PS-HOBt
2 PS-HOBt
3 PS-SO_3H
4 Si-Horseradish peroxidase

Container

1 Ferulic acid
2 PyBrOP, DIPEA
3 Amine solution
4 Washings
5 H_2O_2 urea complex
Buffer pH 4.5

Preparation of the Neolignan Natural Product Grossamide by a Continuous Flow Process
I.R. Baxendale, C.M. Griffiths-Jones, S.V. Ley and G.K. Tranmer, *Synlett,* 2006, 427-430

Convergent Flow Synthesis of Oxomaritidine



A Flow Process for the Multi-Step Synthesis of the Alkaloid Natural Product Oxomaritidine: A New Paradigm for Molecular Assembly
I.R.Baxendale, J.Deeley, C.M.Grifiths-Jones, S.V. Ley, S.Saaby, G.K.Tranmer, *J. Chem. Soc.,Chem. Commun.* 2007, 2566-2568.

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