Novel Applications of Flow Chemistry in Industry and Academia

Flow Chemistry India 2015

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Introduction

1. Introduction
2. Advantages and Current Limitations of Continuous Flow Chemistry
3. Generating Reactive Intermediates
4. Multistep Continuous Flow Chemistry
5. Continuous Flow Photochemistry
6. Novel Reaction Pathways

Advantages and Current Limitations of Continuous Flow Chemistry

Over the past 10 years the number of publications citing continuous flow reactors to perform synthesis has increased substantially.

The positive impact of flow chemistry on chemical processes is well studied

- improved heat and mass transfer
- greater reaction control
- the ability to heat solvents above their boiling points
- greater safety when dealing with hazardous and reactive intermediates
- the ease of automation and telescoping multistep reactions

The perceived limitations of flow are slowly being eliminated

- pumping regimes for handling slurries and suspensions are now available
- continuous pumping of moisture sensitive, pyrophoric reagents is possible
- pumping of strong acids and bases is possible

However there are still issues to overcome

- handling of solid product formation – both in reactors and through back pressure regulators
- scale limitations of packed bed reactors
- pumping of low solubility solutions
- EDUCATION

Generating Reactive Intermediates.

Generating Novel Intermediates

Continuous Synthesis of Organozinc Halides Coupled to Negishi Reactions.

Organoboranes (Suzuki) are the most common choice in C-C bond formation and a wide range are commercially available

Organozinc (Negishi) are commercially limited in range
- superior reaction rates
- can be used when organoboranes are too unreactive
- can facilitate the coupling of sp^3 carbons

However organozinc compounds can have issues with reproducibility and handling.

If we could generate these intermediates and react them in-situ then we can increase the scope of C-C cross coupling diversity.

Continuous Synthesis of Organozinc Halides Coupled to Negishi Reactions,
Nerea Alonso, L. Zane Miller, Juan de M. Munoz, Jesus Alcazar, Tyler McQuade,
Adv. Synth. Catal.,2014, 18, 3737-3741

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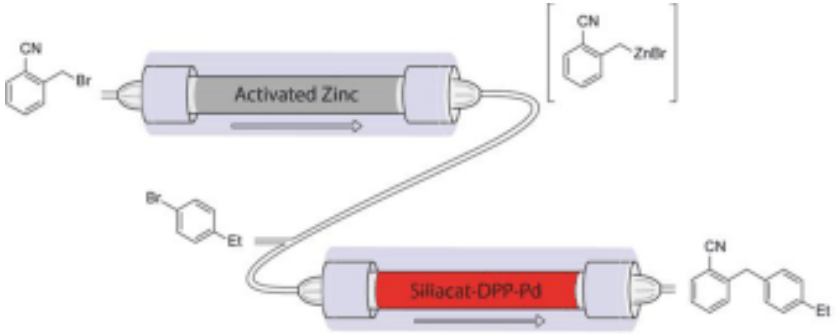
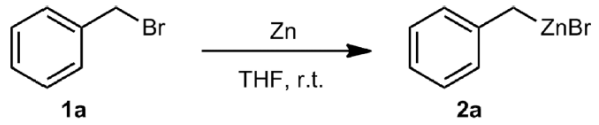
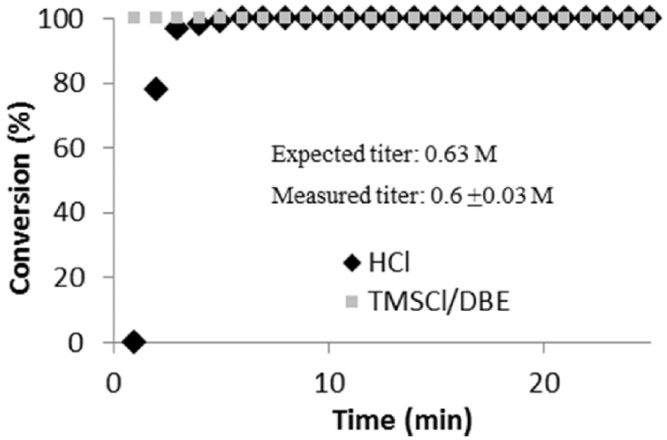
Generating Novel Intermediates

Continuous Synthesis of Organozinc Halides Coupled to Negishi Reactions.







When creating a packed bed column there are a few factors to be considered;

- particle size
- metal activation
- column packing
- column heating / cooling

Benzyl, allylic halides – 100% yield at r.t
Alkyl iodides – 100% yield at 30-60 ^{o}C
Aryl Halides – No reaction even up to 110^{o}C

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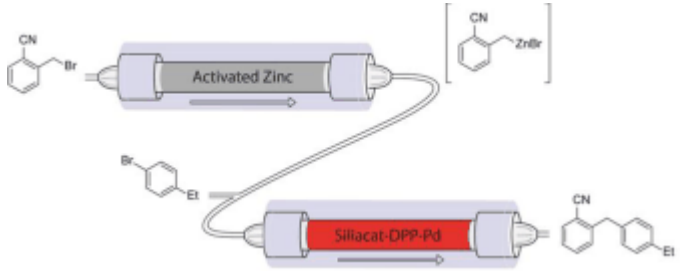

Aryl-X
0.2 M
0.2 mL/min

Alkyl-X
0.3 M
0.2 mL/min

Zn

Pd

Products

2 mL void vol.
t_R = 10 min

1 mL void vol.
t_R = 2.5 min

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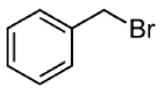
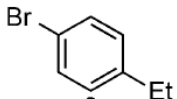
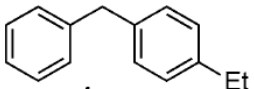
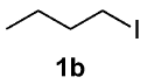
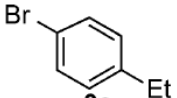
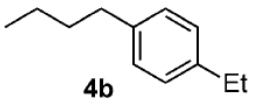
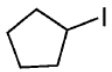
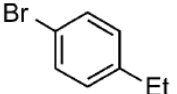
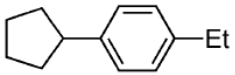
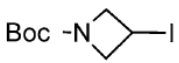
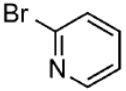
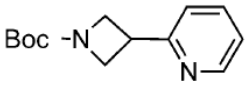
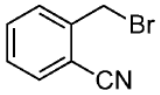
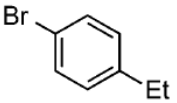
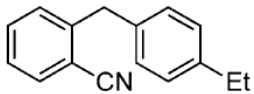
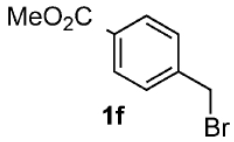
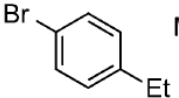
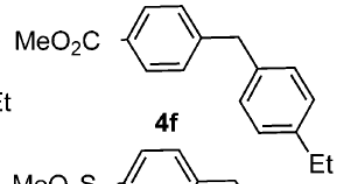
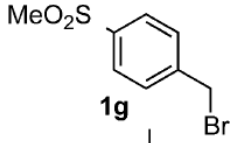
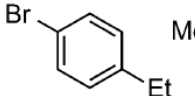
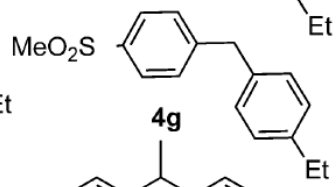
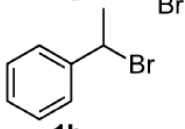
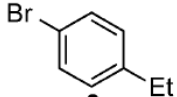
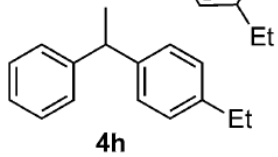
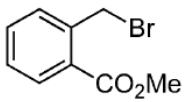
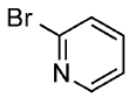
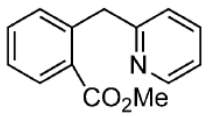
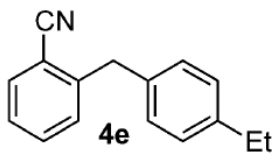
Generating Novel Intermediates

Entry	R-X	Aryl-X	Product	Yield [%]
1[a]	 **1a**	 **3a**	 **4a**	81
2[b]	 **1b**	 **3a**	 **4b**	74
3[c]	 **1c**	 **3a**	 **4c**	83
4[d]	 **1d**	 **3b**	 **4d**	71
5[a]	 **1e**	 **3a**	 **4e**	81

Entry	R-X	Aryl-X	Product	Yield [%]
6[a]	 **1f**	 **3a**	 **4f**	79
7[b]	 **1g**	 **3a**	 **4g**	82
8[b]	 **1h**	 **3a**	 **4h**	84
9[a]	 **1i**	 **3b**	 **4i**	86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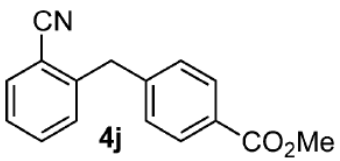
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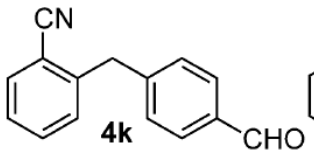
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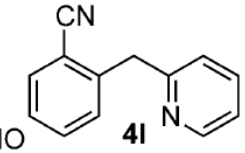
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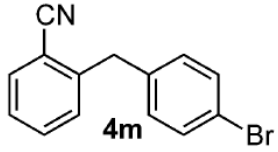
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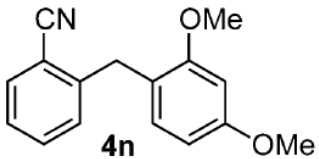
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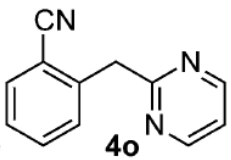
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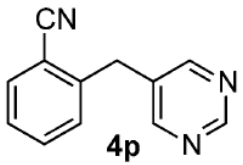
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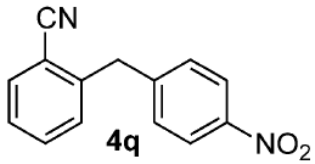
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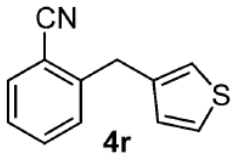
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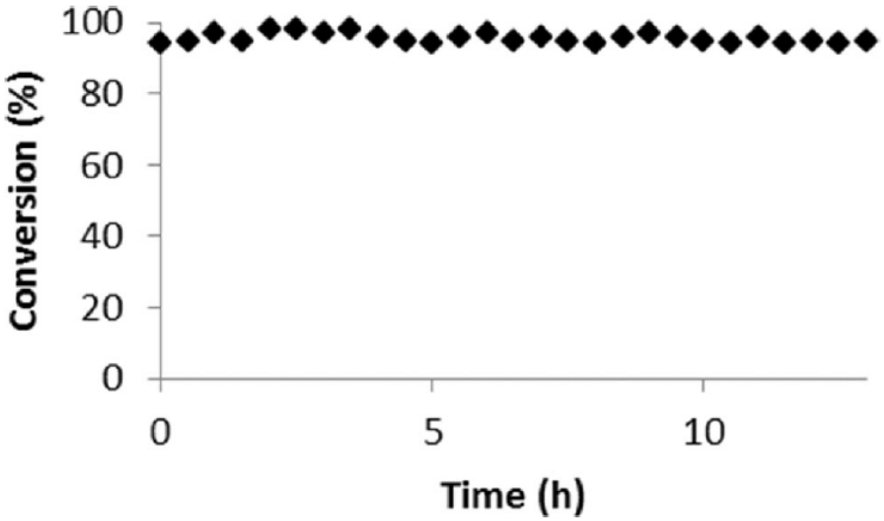
82%[b]

Generating Novel Intermediates



Long term stability assessment

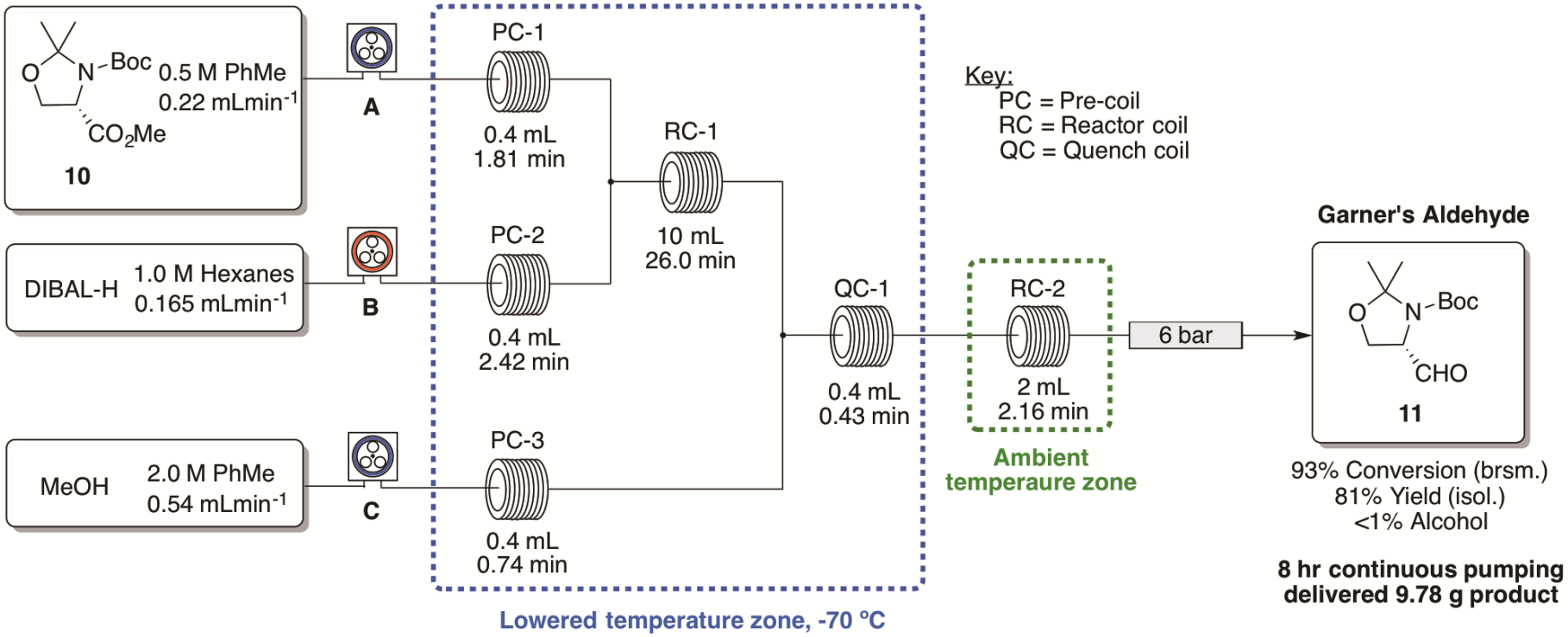
- Column filled 12g Zinc
- Initial trial used 5g Zinc – 150ml (0.5M) solution of benzyl zinc bromide (94%)
- Calculated turnover – 175
- Continuous output – 3.3. mmol h^{-1}

Approach is stable and robust enough to support larger scale chemistry

Generating Novel Intermediates

Continued DIBAL-H reduction of a methyl ester in flow.

Chiral starting material for natural product synthesis – used in over 100 natural product syntheses



Continuous Flow-Processing of Organometallic Reagents Using an Advanced Peristaltic Pumping System and the Telescoped Flow Synthesis of (*E/Z*)-Tamoxifen , Duncan Browne, Steven V. Ley. *OPRD. 2013,17, 1192-1208*

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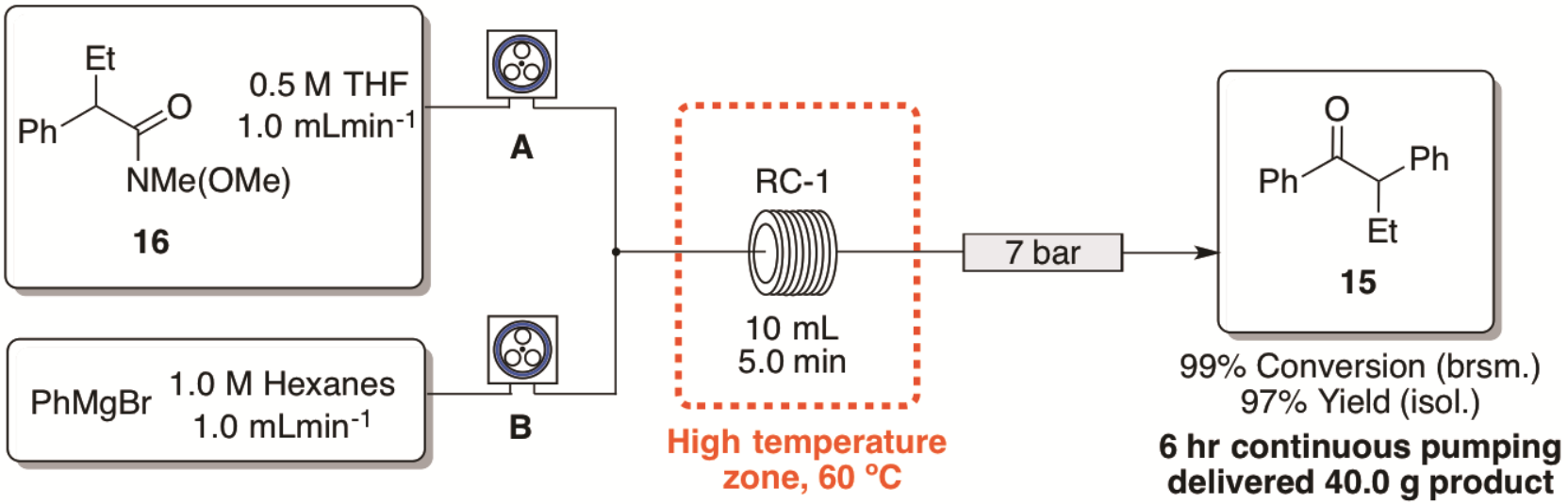
Generating Novel Intermediates

Continuous-flow ketone synthesis from Weinreb amide for the preparation of (*E/Z*)-Tamoxifen.



Only a very minor amount of the over addition product observed <1%

Continuous Flow-Processing of Organometallic Reagents Using an Advanced Peristaltic Pumping System and the Telescoped Flow Synthesis of (*E/Z*)-Tamoxifen , Duncan Browne, Steven V. Ley. *OPRD. 2013, 17, 1192-1208.*

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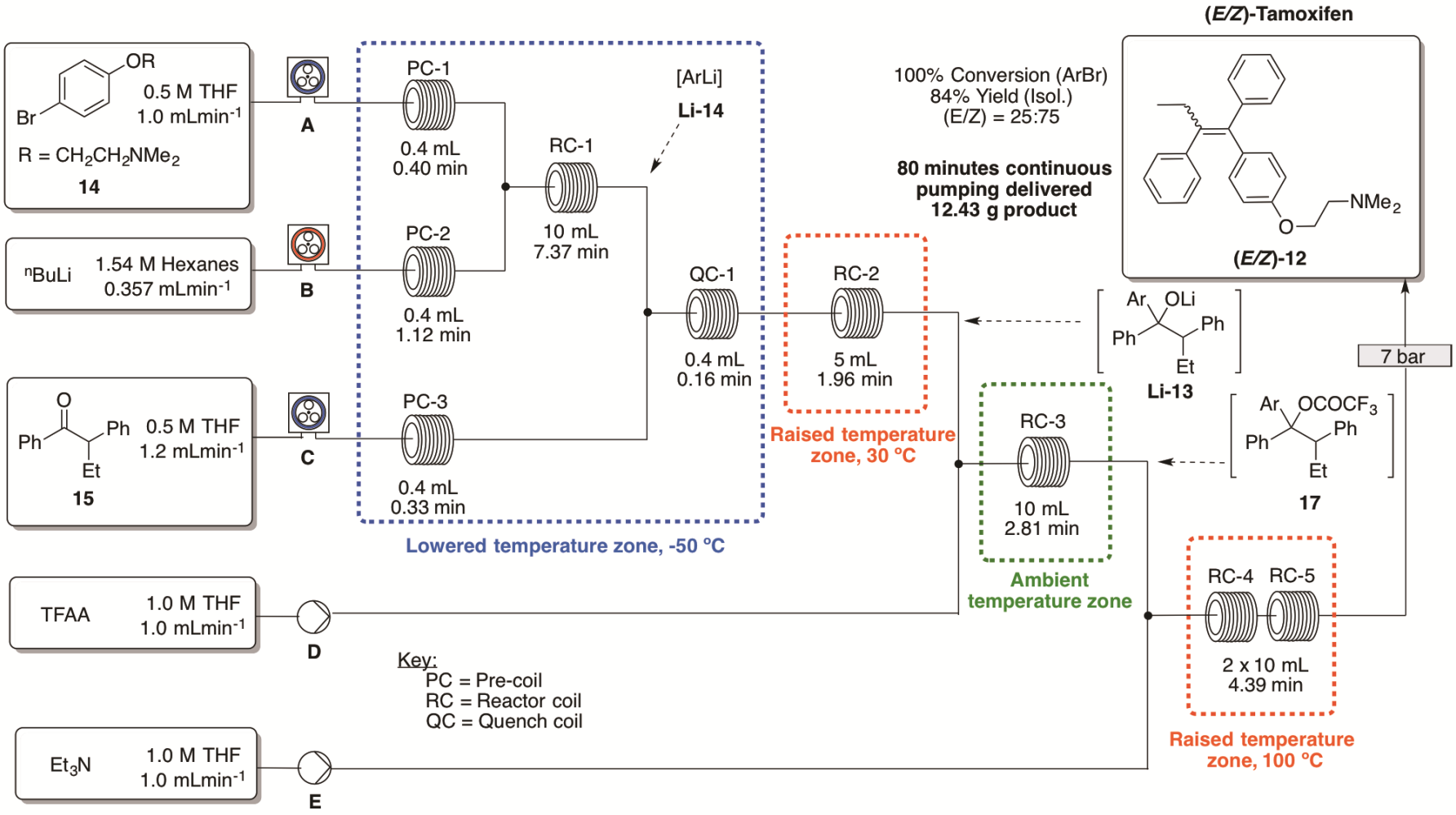
Generating Novel Intermediates

Continuous-flow telescoped synthesis of (E/Z)-Tamoxifen



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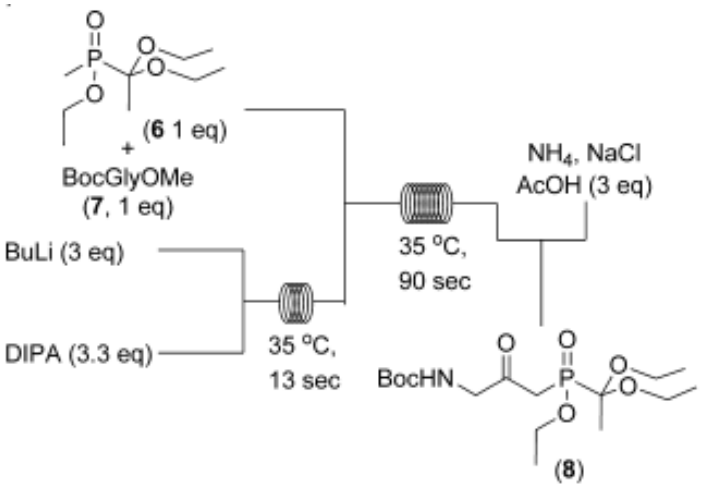
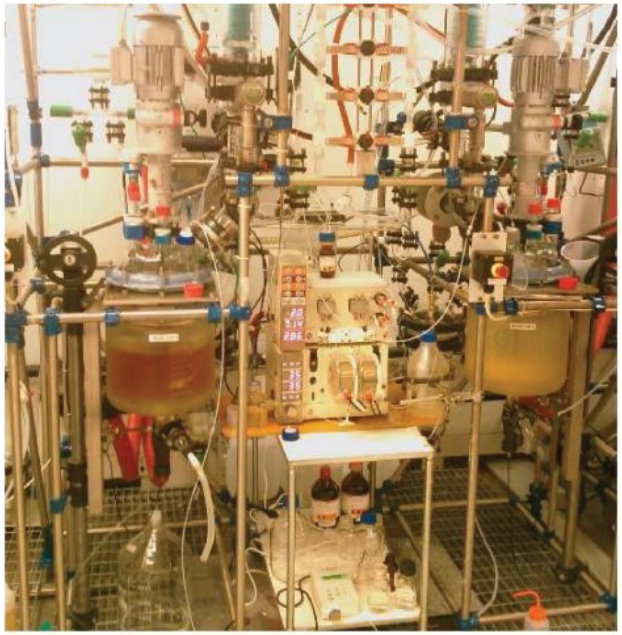
Generating Reactive Reagents

Continuous flow scale-up of Reflux inhibitor AZD6906

AZ identified possible problems to scaling compound – highly exothermic, required cryogenic conditions and slow addition of reagents





- LDA made in-situ - 13s res. time, 35°C, 2ml coil
- LDA mixed with substrate solution 1:1, 90s res. time, 35°C, 20ml coil
- Output continuously quenched: acetic acid, NaCl, NH4Cl at 10°C

Reaction generated 682g, 80% purity over 23 hours

LDA generation in-situ guaranteed quality of reagent, flow conditions avoided costly cryogenics, higher quality more stable product produced.

Development of a Continuous Flow Scale-UP Approach of Reflux Inhibitor AZD6906,
Tomas Gustafsson, Henrik Sorensen, Fritiof Ponten, *Org. Process Res. Dev*, 2012, 16, 925-929

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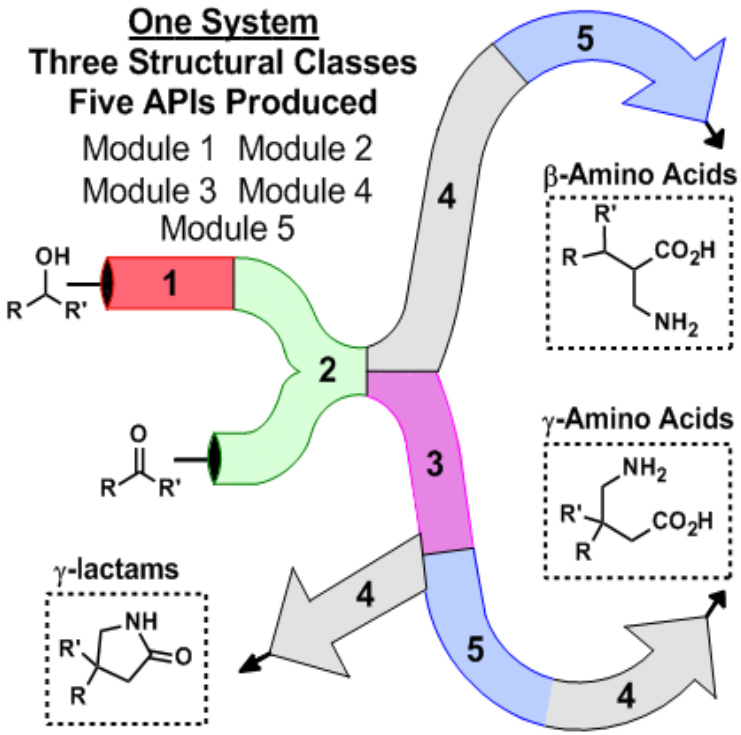
Multistep Continuous Flow Synthesis.

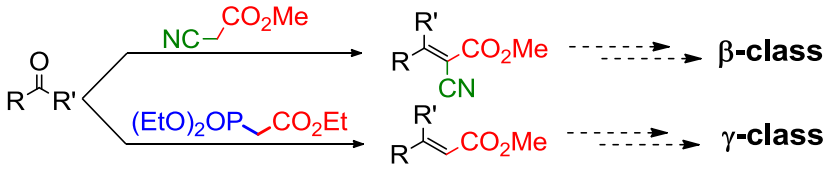
Multistep, Divergent Synthesis

Chemical Assembly Systems: Layered Control for Divergent, Continuous, Multistep Syntheses of Active Pharmaceutical Ingredients



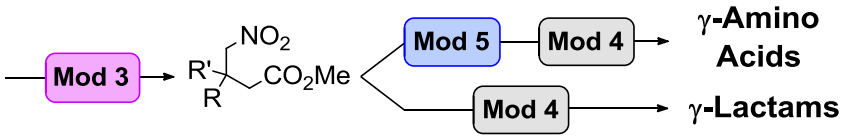
Reagent Choice

Change reagents within a module ⟶ access to different classes of compounds



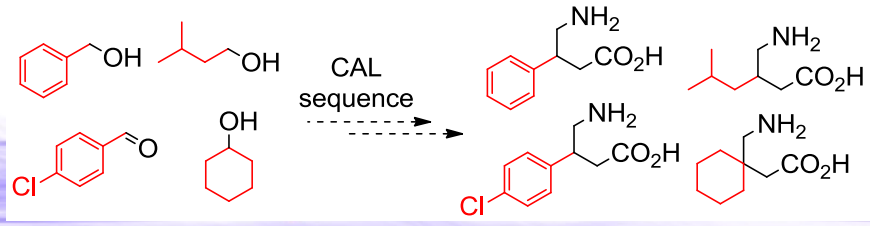
Order of Modules

Change order of modules ⟶ different families of structures



Starting Material

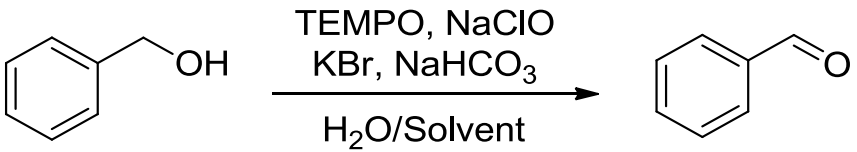
Change starting material ⟶ different products with the similar core structure



Chemical Assembly Systems: Layered Control for Divergent, Continuous, Multistep Syntheses of Active Pharmaceutical Ingredients, D. Ghislieri, K. Gilmore, P. H. Seeberger , Angew. Chemie. Int. Ed., 2014, 53, 1-6

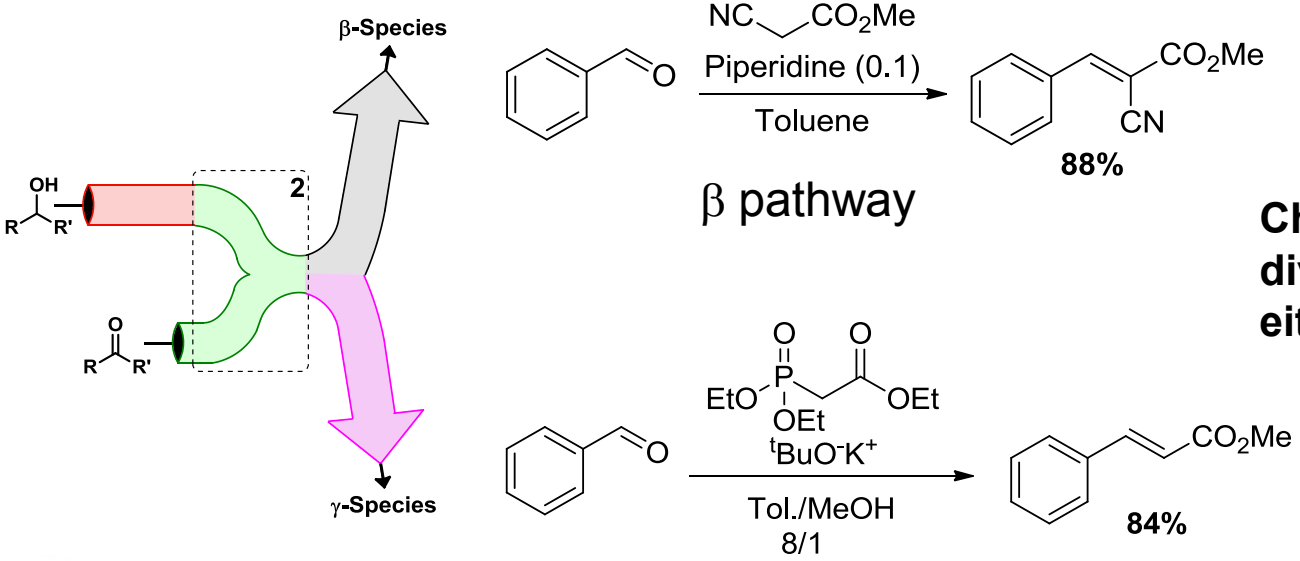
Multistep, Divergent Synthesis

Module 1 – Biphasic Bleach Tempo Oxidation



No Byproducts: Biphasic system, aqueous layer separated using modified Jensen extractor
Flexible: Multiple organic solvents tolerated
Selective: No over-oxidation detected

Module 2 – Olefination: Knoevenagel/HWE



Change in reagent diverts outcome to either β or γ pathway

Chemical Assembly Systems: Layered Control for Divergent, Continuous, Multistep Syntheses of Active Pharmaceutical Ingredients, D. Ghislieri, K. Gilmore, P. H. Seeberger , Angew. Chemie, Int. Ed., 2014, 53, 1-6

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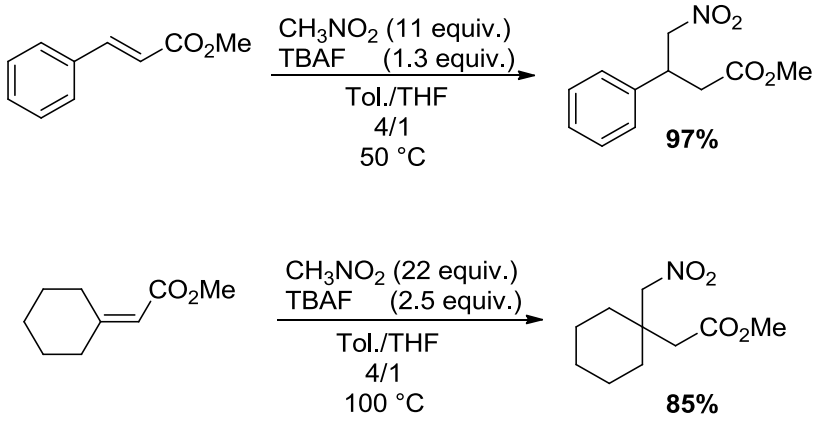
Multistep, Divergent Synthesis

Module 3 – Nitromethane Michael Addition

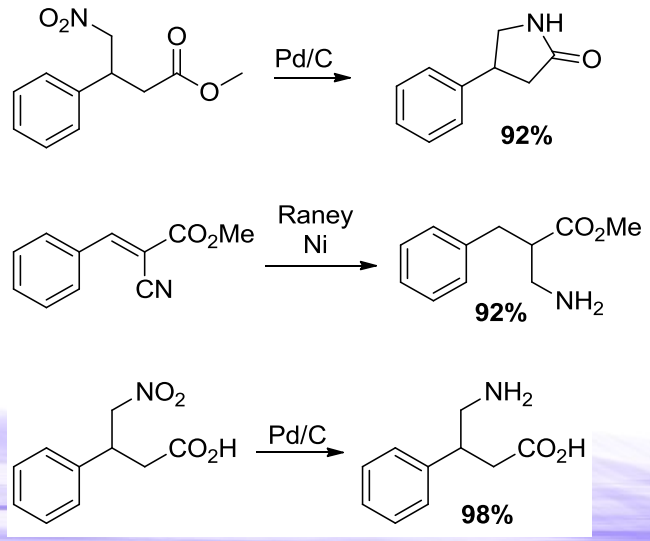


<u>Solvent for Assembly System Issue</u>:

Reason: Reaction fails in presence of methanol, which is added in module 2 to dissolve salts

Solution: Methanol efficiently removed by inline workup when toluene is organic solvent

Module 4 – Hydrogenation



Versatile: Commercial H-Cube® used with metal catalyst cartridges to effect nitro, nitrile, and olefin reductions.

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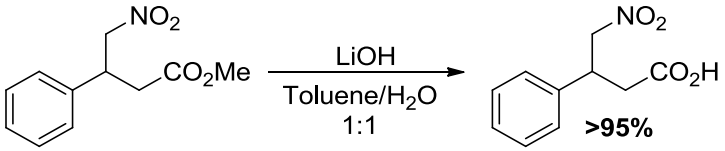
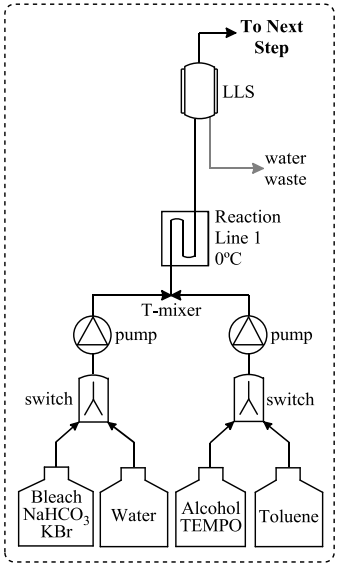
Multistep, Divergent Synthesis

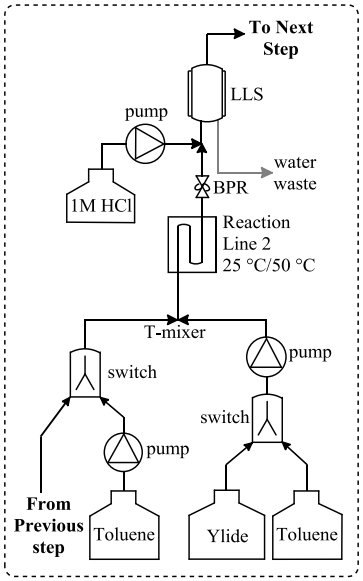
Module 5 – Hydrolysis



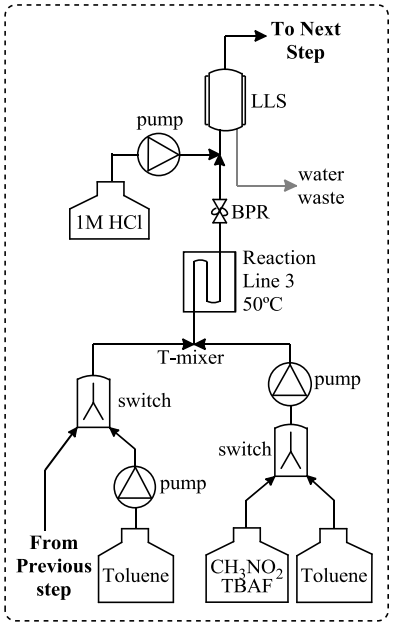
Clean: Upon hydrolysis, product in aqueous layer. All byproducts remain in the organic. Acidification and *inline* back-extraction provide product solution.



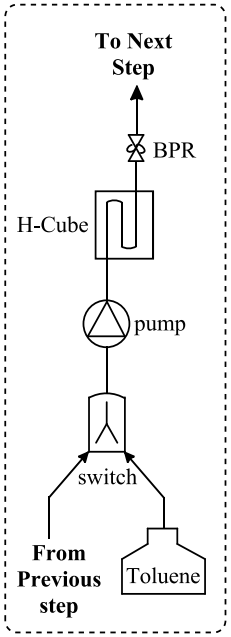
Module 1



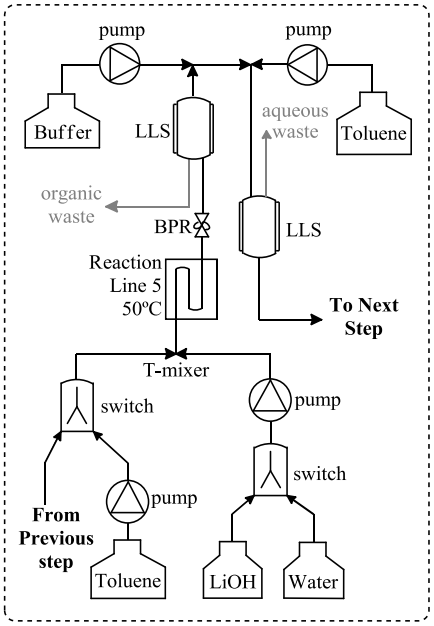
Module 2



Module 3



Module 4



Module 5

Chemical Assembly Systems: Layered Control for Divergent, Continuous, Multistep Syntheses of Active Pharmaceutical Ingredients, D. Ghislieri, K. Gilmore, P. H. Seeberger , Angew. Chemie, Int. Ed., 2014, 53, 1-6

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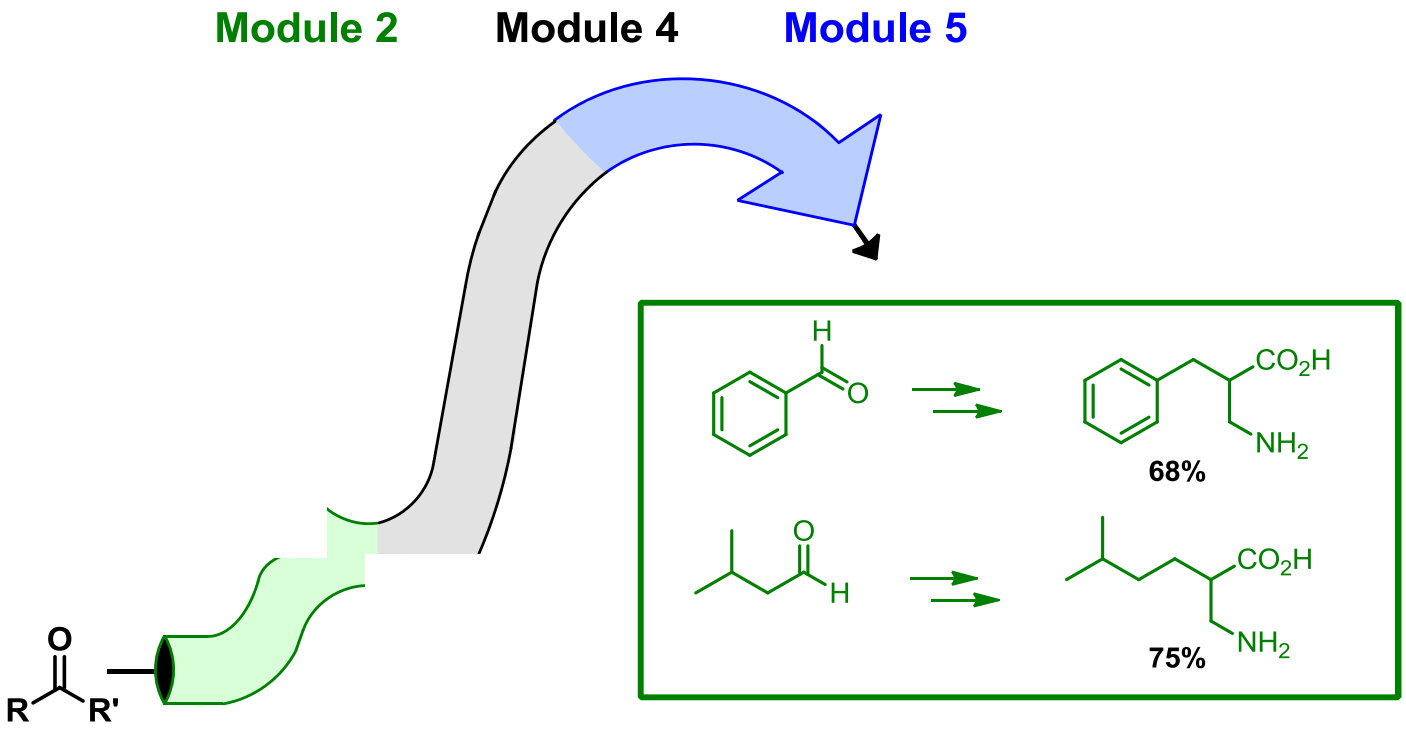
Multistep, Divergent Synthesis



Chemical Assembly Systems: Layered Control for Divergent, Continuous, Multistep Syntheses of Active Pharmaceutical Ingredients, D. Ghislieri, K. Gilmore, P. H. Seeberger , Angew. Chemie. Int. Ed., 2014, 53, 1-6

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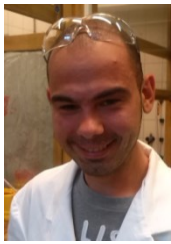
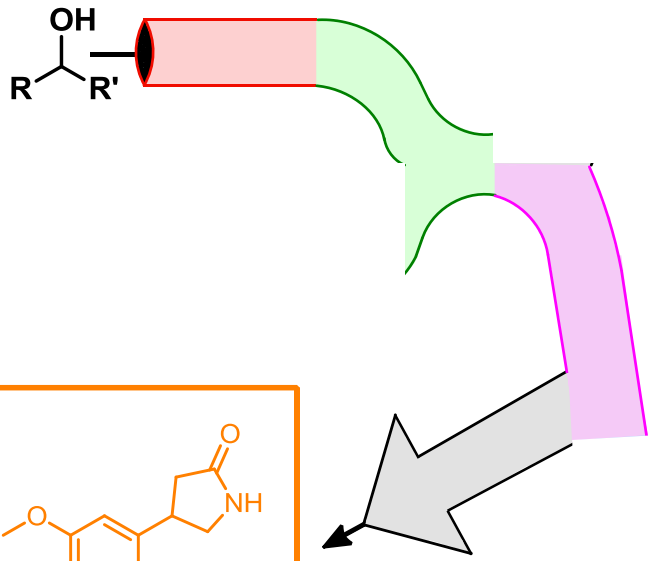
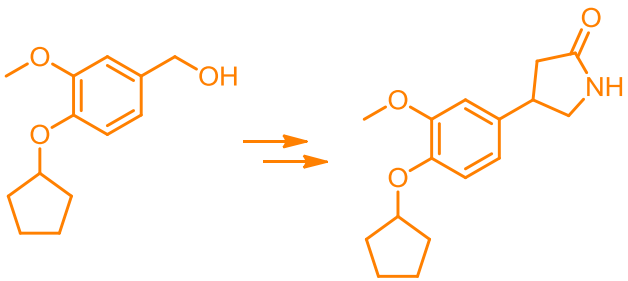
Multistep, Divergent Synthesis

Module 1 Module 2 Module 3 Module 4





Rolipram:
Anti-inflammatory



17 **18** (58%)

Rolipram (Modules 1, 2, 3, 4)

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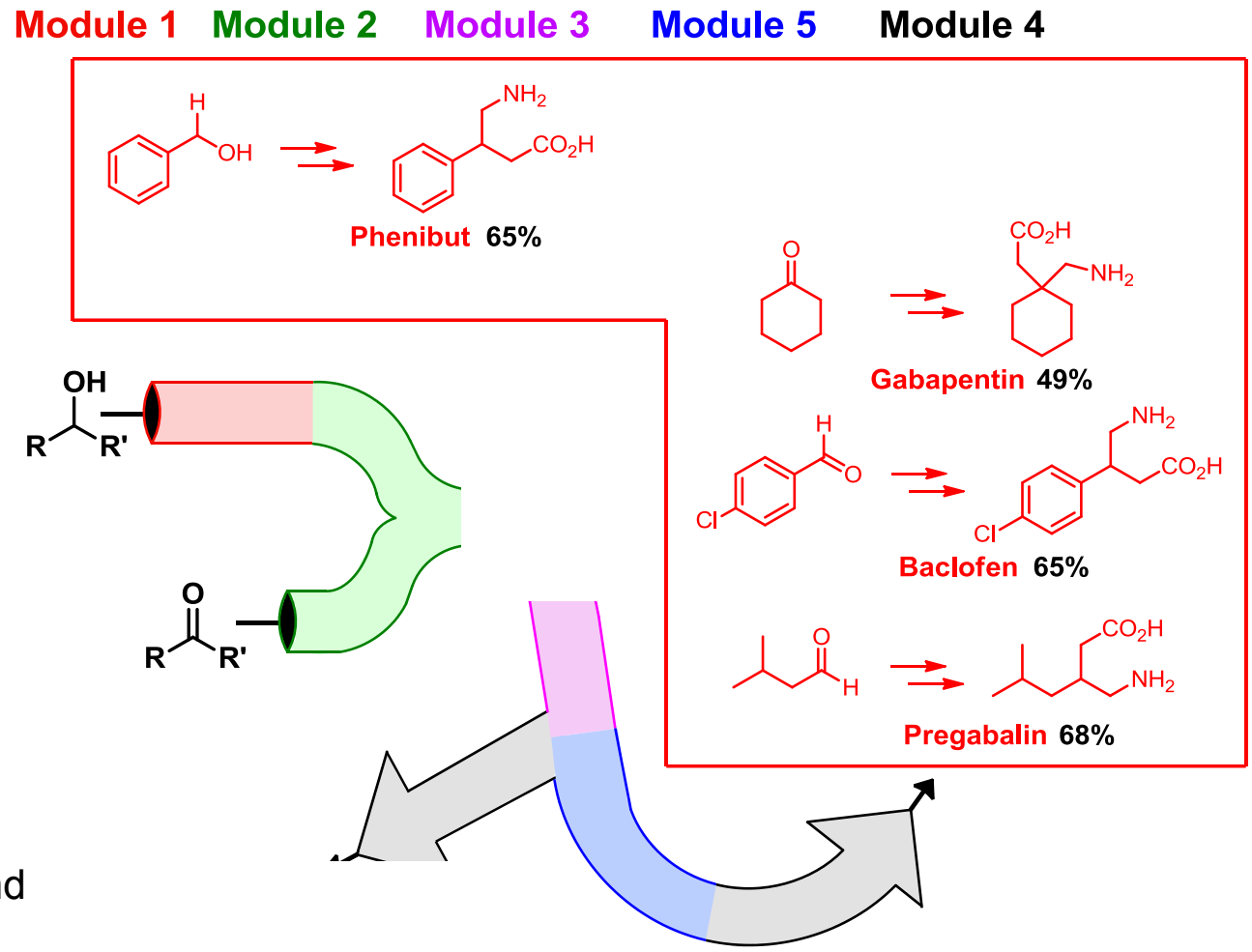
Multistep, Divergent Synthesis



Phenibut:
Anxiolytic Effects

Gabapentin:
Epilepsy

Baclofen:
Spasticity

Pregabalin (Lyrica):
Anticonvulsant and general anxiety disorder

Chemical Assembly Systems: Layered Control for Divergent, Continuous, Multistep Syntheses of Active Pharmaceutical Ingredients, D. Ghislieri, K. Gilmore, P. H. Seeberger , Angew. Chemie. Int. Ed., 2014, 53, 1-6

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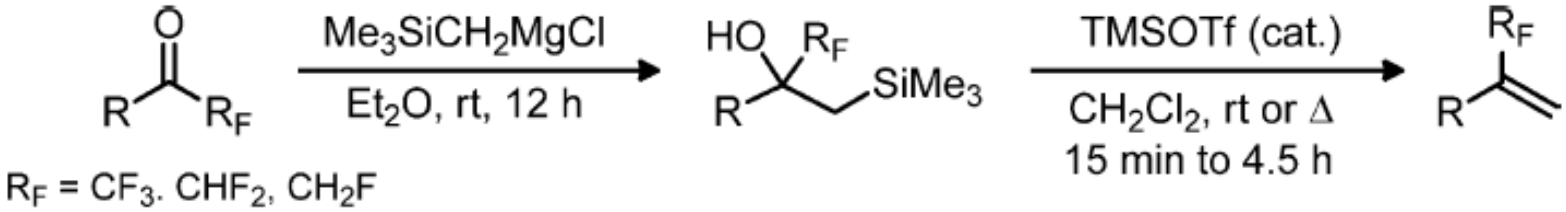
Multistep, In-line Extraction and Solvent Switching

A Continuous Flow Approach to 3,3,3-Trifluoromethylpropenes.

Synthetic approach involves Grignard addition followed by dehydrative desilylation.

- Reaction is compatible with a range of functionalities
- Alkene products obtained in excellant yield.



What are the limitations in converting this to a continuous process?

- the two-step process requires isolation of the intermediate
- the second step is carried out in a different solvent.

However both organometallic reagents and olefination processes have literature precedence.

A Continuous-Flow Approach to 3,3,3-Trifluoromethylpropenes: Bringing Together Grignard Addition, Peterson Elimination, Inline Extraction and Solvent Switching, Nicholas Leadbeater et al, *OPRD*, 2014, 18, 1253-1258

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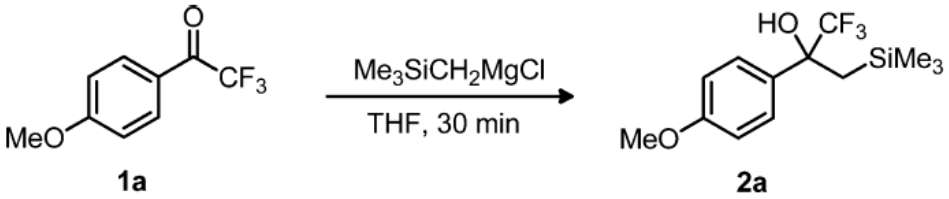
Multistep, In-line Extraction and Solvent Switching

Challenge 1: Need to remove THF and switch solvents
Challenge 2: Reduce reaction times and telescope reactions

Optimisation of the Grignard Reaction

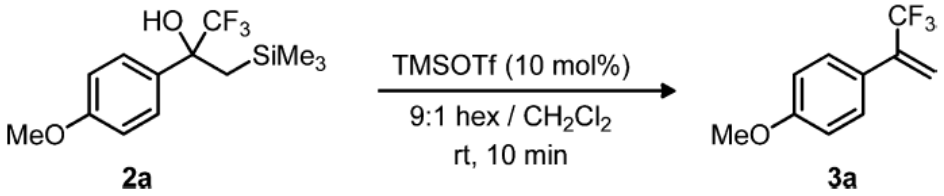


1a **2a**

entry	temperature (°C)	conversion (%)[b]
1	25	80
2	40	95
3	50	100

Zaiput Phase Separator

Optimised Condition for the Dehydrative Desilylation



2a **3a**

A Continuous-Flow Approach to 3,3,3-Trifluoromethylpropenes: Bringing Together Grignard Addition, Peterson Elimination, Inline Extraction and Solvent Switching, Nicholas Leadbeater et al, *OPRD*, 2014, 18, 1253-1258

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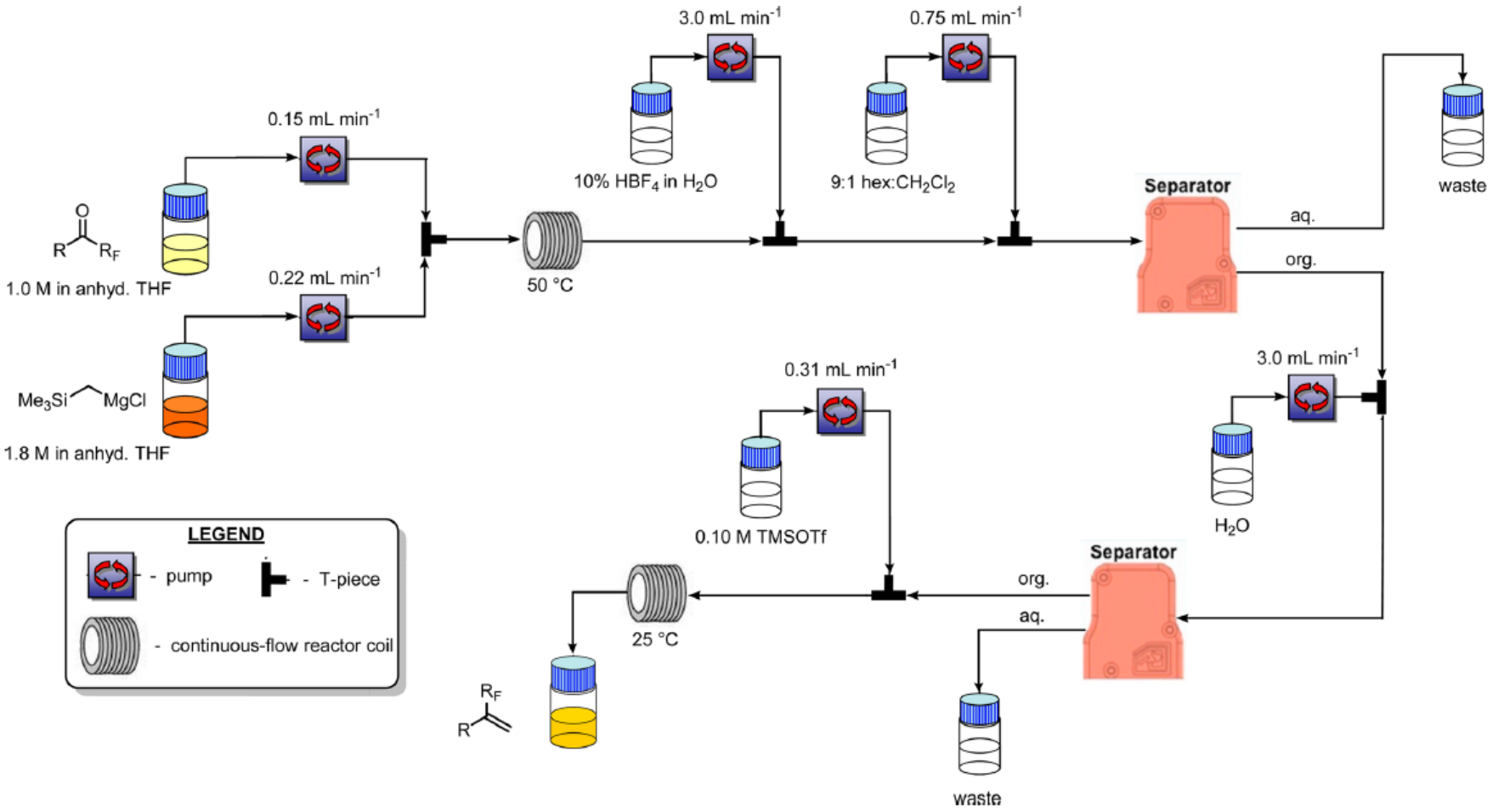
Multistep, In-line Extraction and Solvent Switching



A Continuous-Flow Approach to 3,3,3-Trifluoromethylpropenes: Bringing Together Grignard Addition, Peterson Elimination, Inline Extraction and Solvent Switching, Nicholas Leadbeater et al, *OPRD*, 2014, 18, 1253-1258

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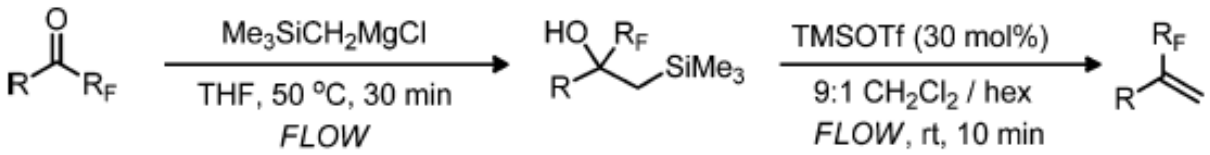
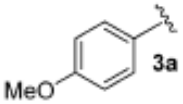
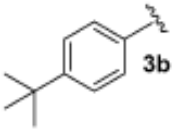
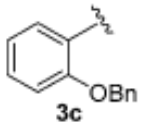
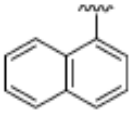
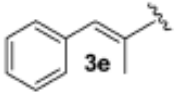
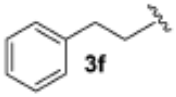
Multistep, In-line Extraction and Solvent Switching



entry	R	R_F	yield in flow (%)[b]	yield in batch (%)[c]
1	 **3a**	CF_3	84 (90)[d]	68
2	 **3b**	CF_3	90	65
3	 **3c**	CF_3	89	67
4	 **3d**	CF_3	92	72
5	 **3e**	CF_3	92	75
6	 **3f**	CF_2H	94	85

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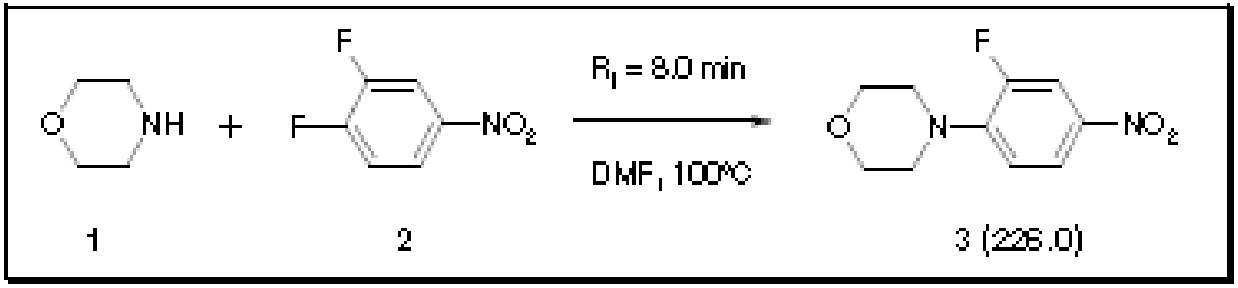
Solvent Free Flow Chemistry

Solvent Free Synthesis

Application Note 29 - Process Scale SNAr under Solvent Free Conditions

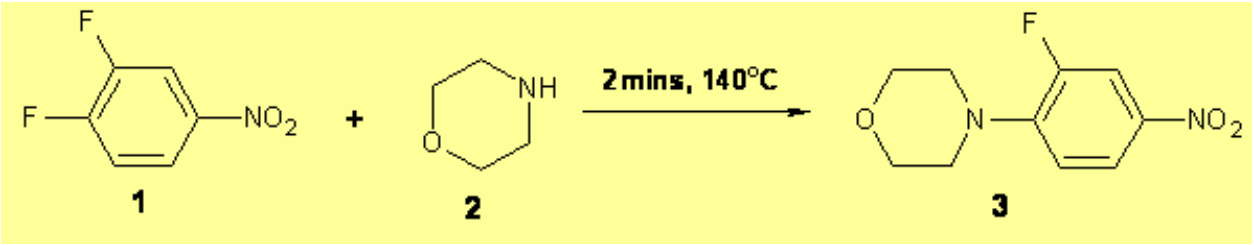


This expands on work previously carried out in showing the facility of placing four reactors in series.

Reaction carried out at 2.0M in DMF – 68g/hr

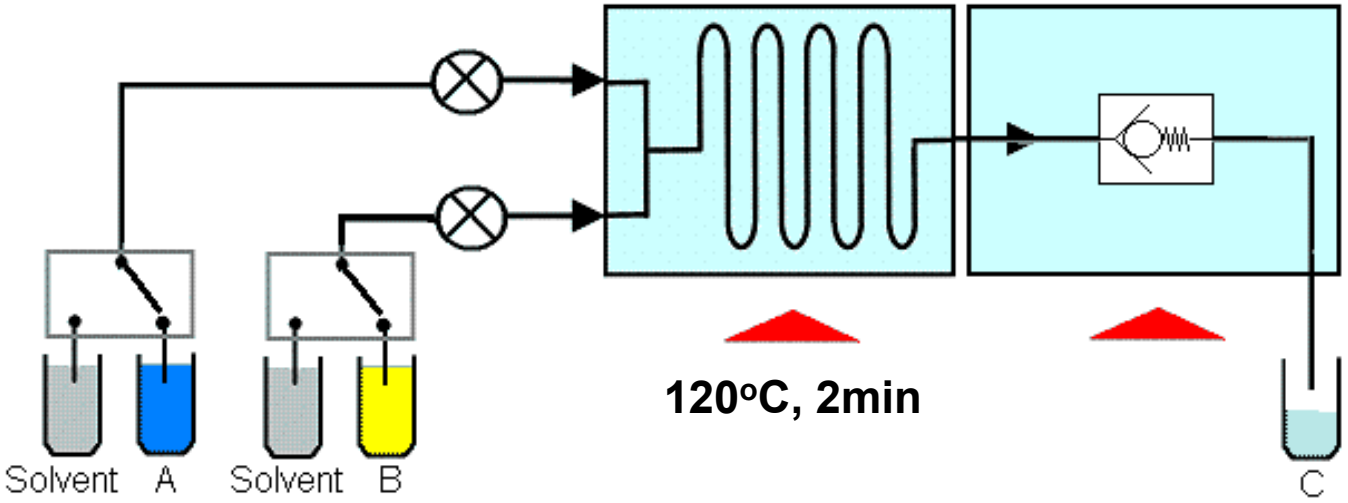
- 3,4-dinitrobenzene (density 1.437 g/cm3) and morpholine (density 1.007 g/cm3) - both liquid at room temperature.
- However, (4-(2-fluoro-4-nitrophenyl)morpholine) is a solid with a melting point of 112-113°C

Solvent Free Synthesis



Reaction performed neat

BPR and all exit pipework kept at 140°C



Collected into ice/water

Effective concentration 9M. Scale > 400g / hr

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Continuous Flow Photochemistry

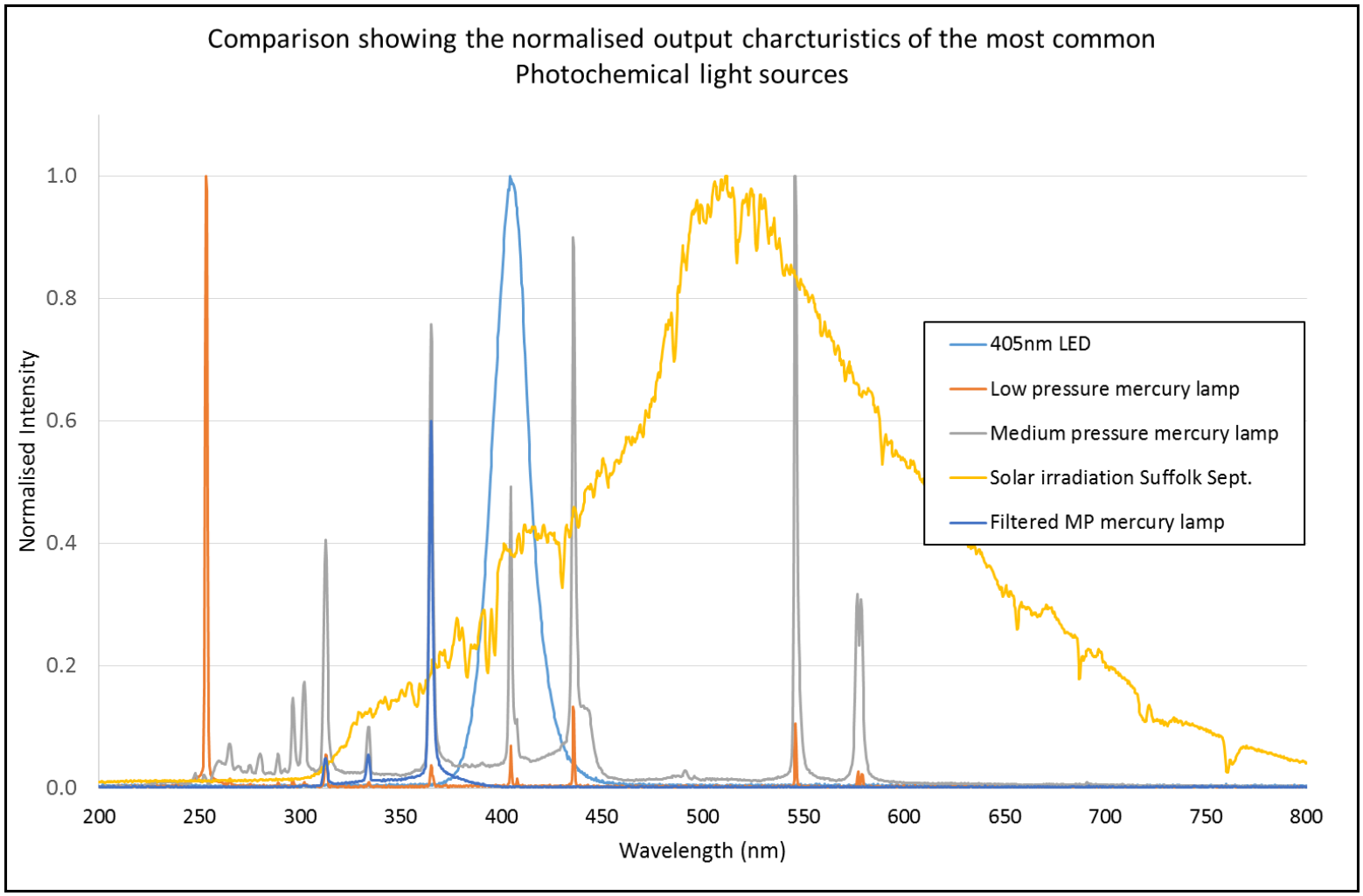
Continuous Flow Photochemistry

Photochemistry is a valuable but underused synthetic tool and offers potentially shorter and more efficient synthetic routes as well as access to new chemical space.

Recently there has been resurgence in interest in photochemistry due to its ability to provide novel structures and alternative, greener synthetic routes.

- Traditional batch photochemistry techniques have proven limitations, flow photochemistry provides improved control and safety profiles.
- Reaction products leave the reactor after exposure to the UV light source
- Reactive intermediates generated by UV exposure can be immediately fed into a second reaction step
- UV exposure times are precisely controlled and consistent
- UV penetration depth is not an issue as the thickness of the fluid being irradiated is typically 1.5mm
- The photochemical reaction can be scaled simply by running the process for longer
- The maximum volume of the reactor is typically smaller, the hazard of maintaining a large volume of solvent in close proximity to a high temperature lamp is significantly reduced

Light sources for photochemical reactors



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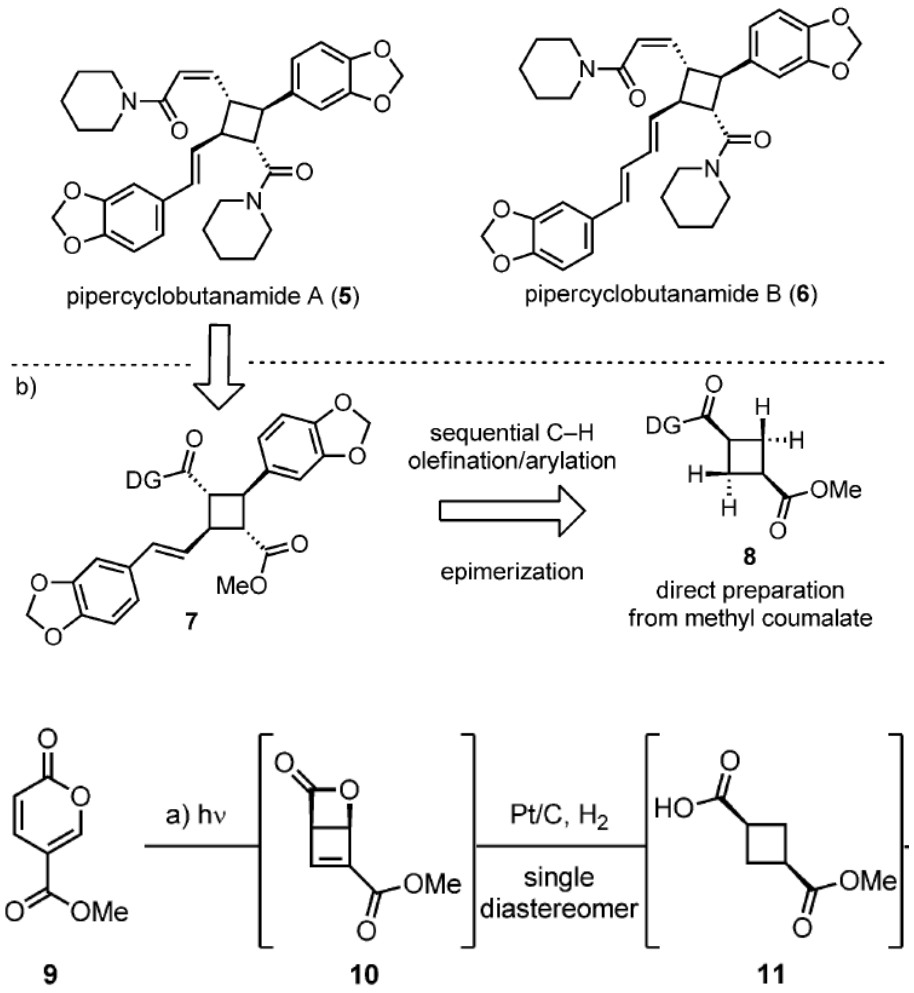
Photochemical Transformation of Methyl Coumalate



The photochemical transformation of methyl coumalate to the pyrone via 4π electrocyclisation has been shown in the total synthesis of a range of Piperarborenines by Prof. Phil Baran.

Vapourtec were keen to complete the synthesis in flow as a means to demonstrate:

1) The use of filters to improve selectivity in photolysis
2) The importance of temperature to control by-product formation
3) The dramatic increase in efficiency that flow photolysis can offer over its batch counterpart

Will R. Gutekunst, Ryan Gianatassia, Phil Baran, **Sequential C-H Arylation and Olefination: Total Synthesis of the Proposed Structure of Pipercyclobutanamide A,** Angewandte Chemie International Edition, 2012, 51, 7505 – 7510

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Photochemical Transformation of Methyl Coumalate

Batch Conditions (Baran et al):

450 Watt medium pressure Hg lamp

1g of starting material in 1000 mL DCM
(0.00649 M)

Irradiation 96 hours, Pyrex immersion well

Temperature 15°C

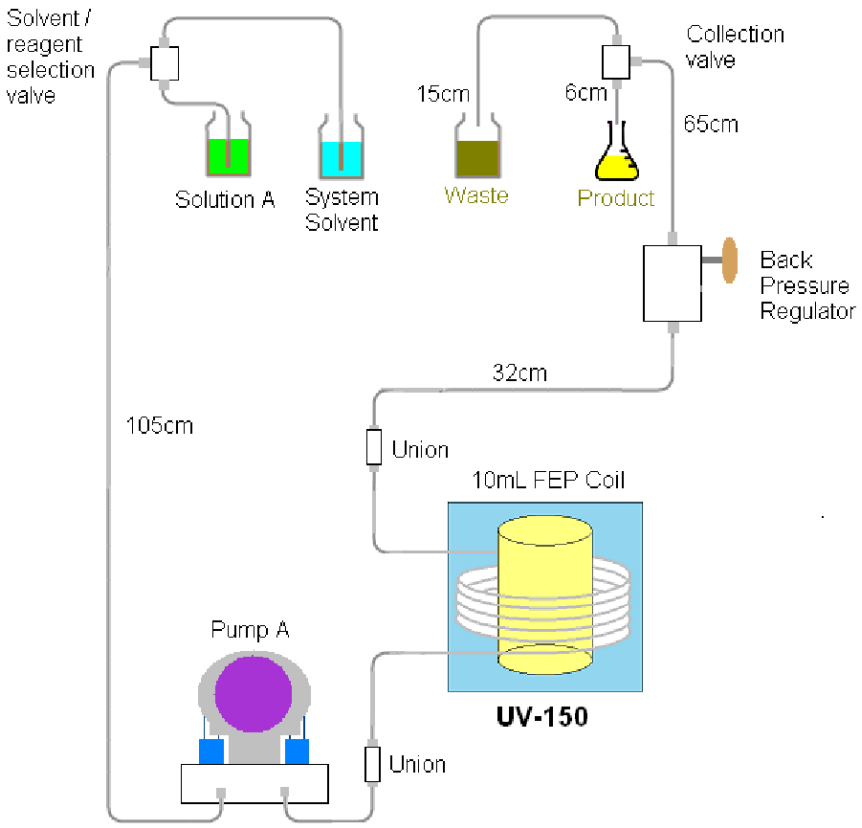
Optimised Flow Conditions:

120 Watt medium pressure Hg lamp

1g of SM in 130 mL Acetonitrile (0.05 M)

Irradiation 60 mins, Filter giving only > 290 nm

Temperature 0°C



Under the optimised conditions the reaction was run for just under 12 hours of continuous operation. Yield = 0.98g, 76% (purity by NMR)

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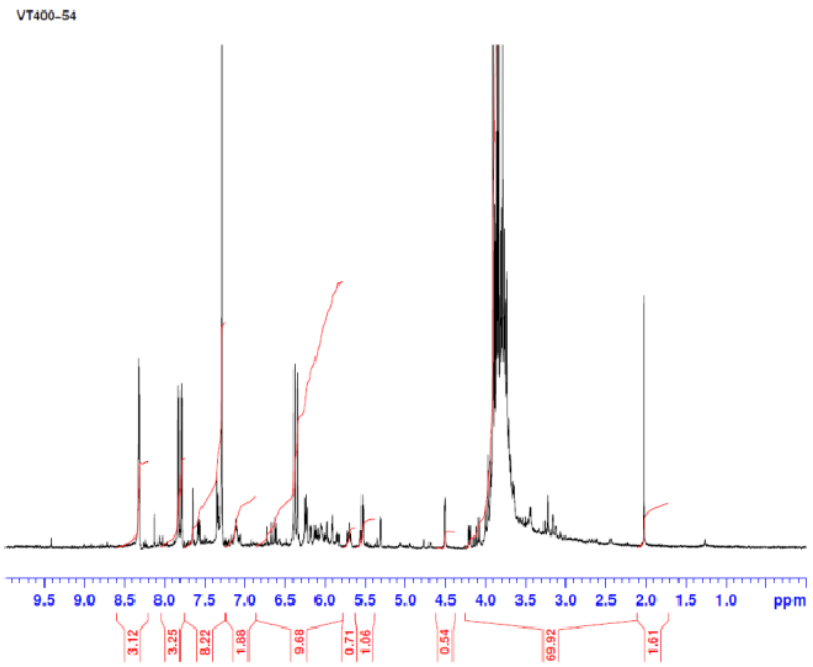
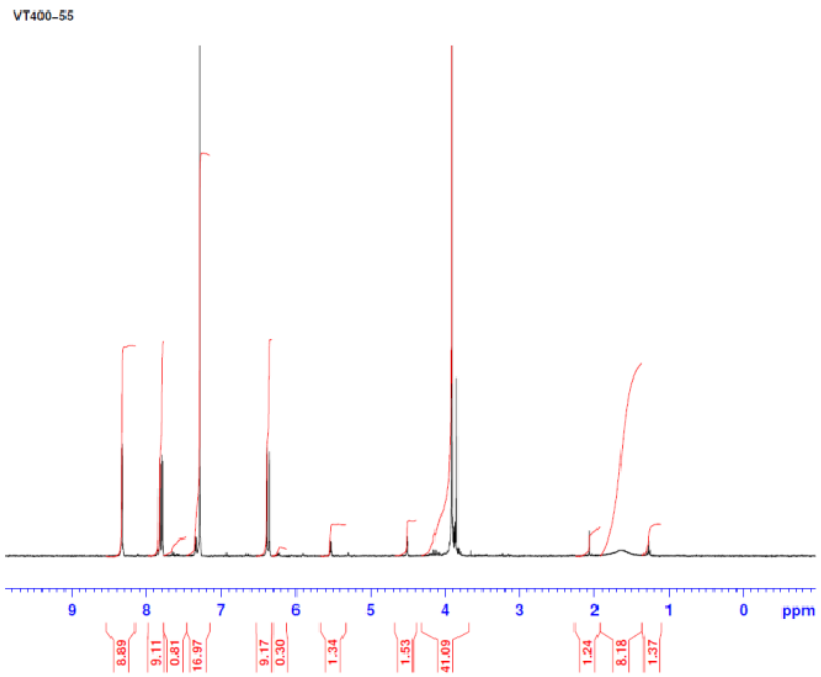
Photochemical Transformation of Methyl Coumalate

Effects of wavelength filtering

Reaction using filter 1



Reaction using filter 3



Other than the filter reaction conditions were identical

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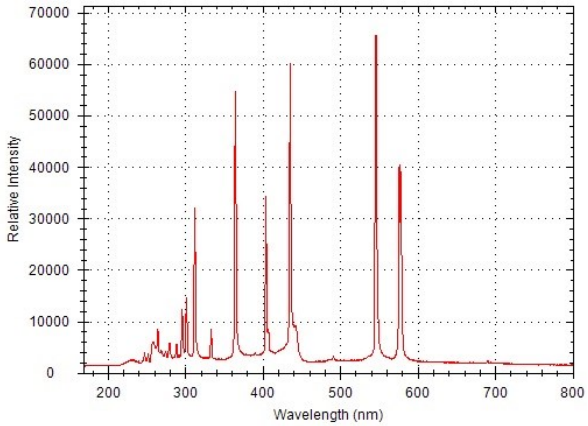
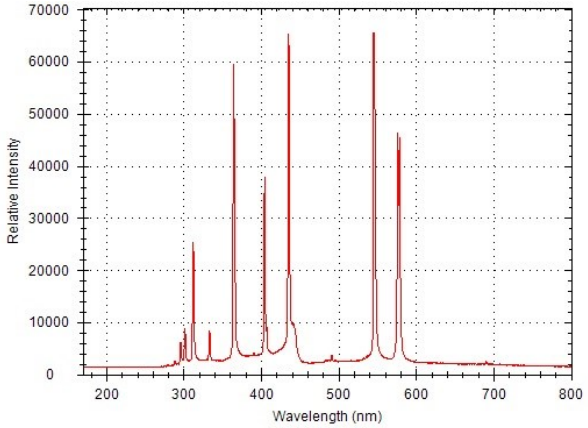
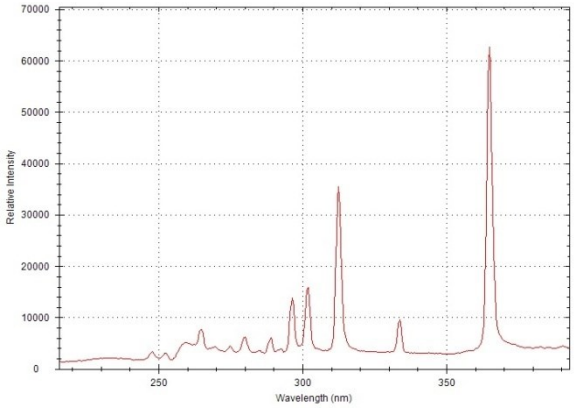
Photochemical Transformation of Methyl Coumalate



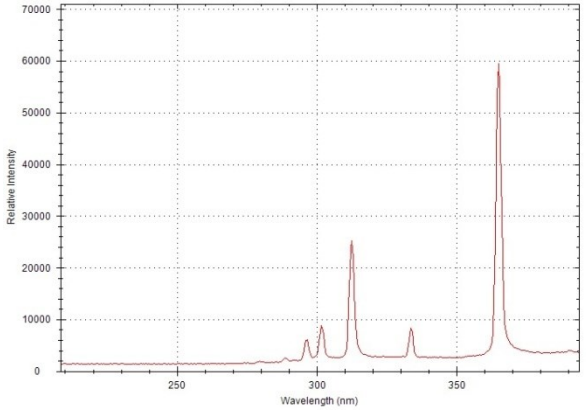
Transmission Spectra Type 1 Filter



Transmission Spectra Type 3 Filter



200 – 400nm Region View of Type 1 Filter

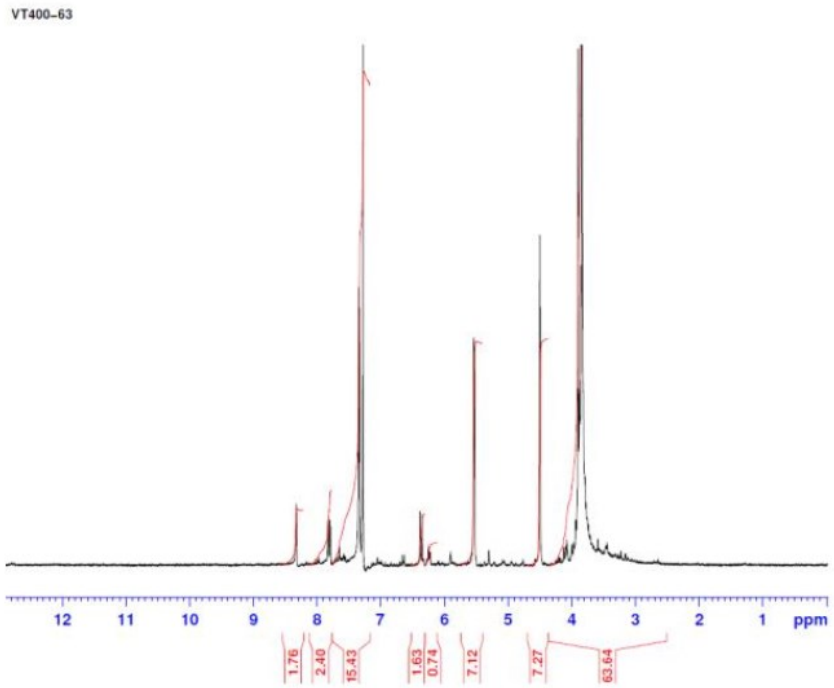


200 – 400nm Region View of Type 3 Filter

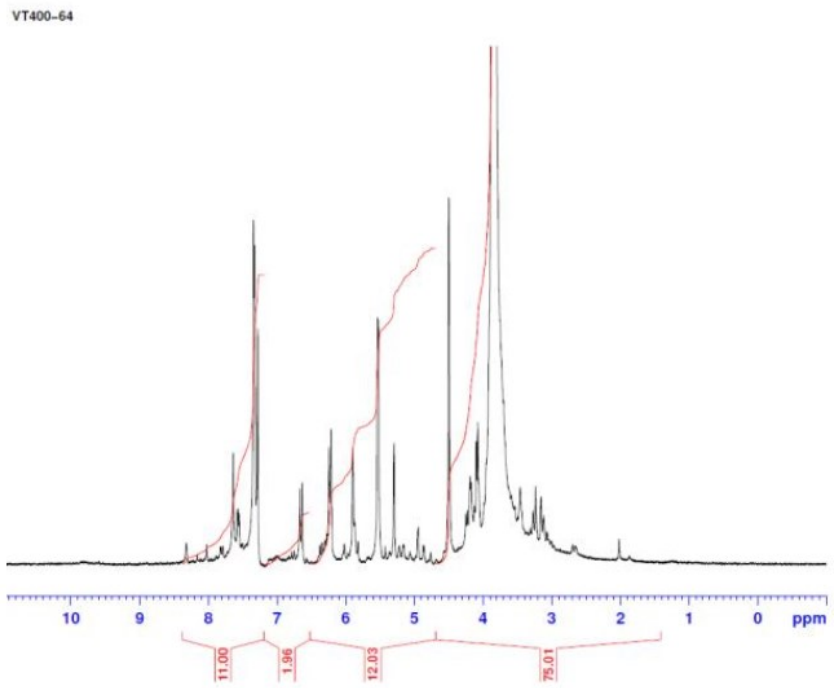
Photochemical Transformation of Methyl Coumalate

Effects of reaction temperature

Reaction at 0°C, 7.5% impurity



Reaction at 30°C, 18.7% impurity



Both conditions used filter 3 (>290 nm). Other than the temperature reaction conditions were identical

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Comparisons with the batch process

- 8 fold decrease in the total reaction time for 1 gram
- 8 fold decrease in solvent used
- 30 fold decrease in the Kwh consumed for 1 gram
- A switch in greener solvent from DCM to Acetonitrile

Vapourtec wishes to thank members of The Ley group for their contribution to this work.

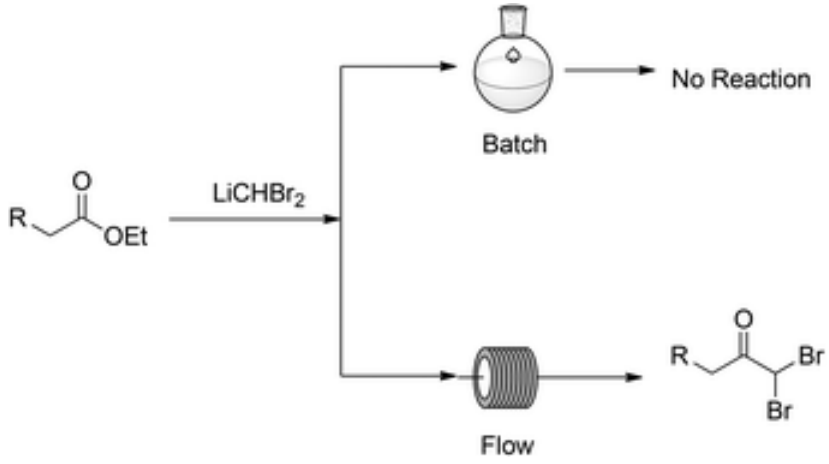
Novel Reaction Pathways

Flow Chemistry: A Discovery Tool for New Chemical Patterns

Continuous flow chemistry as a process intensification tool is well known.

However it's ability to perform reactions **not available** in batch is less well studied.

Formation of a-Bromoketones Previously Unavailable Under Batch Conditions



α-Dibromoketones are useful intermediates in the formation of pyrazines, triazines, imidazoles and alkynol ethers.

Researchers required the intermediate for the formation of a-keto esters via oxidative esterification.

Continuous flow chemistry: a discovery tool for new chemical reactivity patterns, Jan Hartwig, Jan Metternich, Nikzad Nikbin, Andrea Kirschning and Steve V. Ley, Organic and Biomeolecular Chemistry, 2014, 12, 3611

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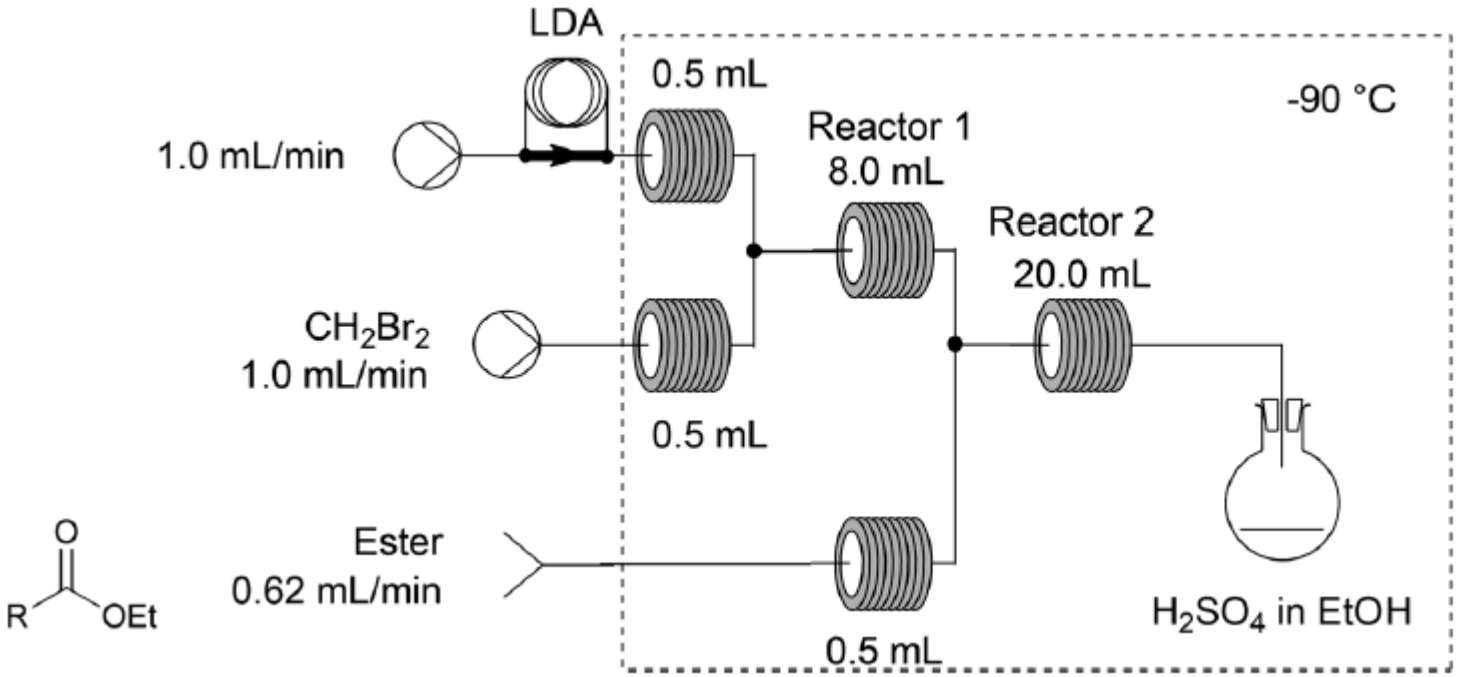
Flow Chemistry: A Discovery Tool for New Chemical Patterns



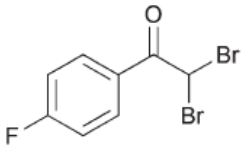
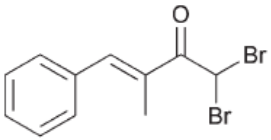
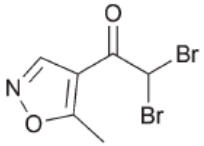
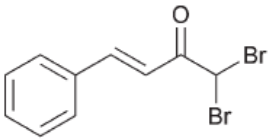
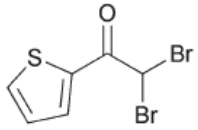
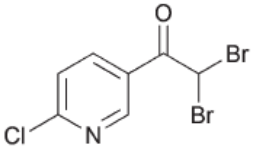
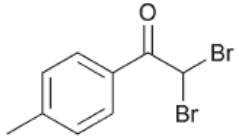
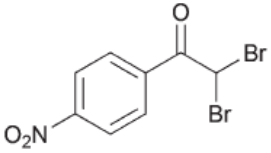
Deprotonated dibromomethane species formed in Reactor 1 (Rt = 4min)

Unstable even at -90oC

Ester in substoichiometric amounts so dispersion matching wasn't an issue

Flow Chemistry: A Discovery Tool for New Chemical Patterns

Table 1 Formation of α-dibromoketone from esters with aromatic or sp^2-hybridized carbon-substituents as R[a]

Entry	Product	Yield batch	Yield flow	Entry	Product	Yield batch	Yield flow
1		80%	95%	5		70%	87%
2		—	72%	6		—	80%
3		58%	62%	7		—	50%
4		66%	38%	8		—	50%

[a] 1.05 mmol scale, $c(\mathrm{LDA}) = c(\mathrm{CH_2Br_2}) = 0.81$ M, $c(\mathrm{ester}) = 0.58$ M, total residence time for flow was nearly 12 minutes while batch reaction time was 15 minutes. LDA and CH_2Br_2 were used in excess (2.2 eq.). Both reaction modes were performed at −90 °C.

With general improvements in flow optimised the researchers focused on reactivity patterns *not possible in batch*.

Continuous flow chemistry: adiscovery tool for new chemical reactivity patterns, Jan Hartwig, Jan Metternich, Nikzad Nikbin, Andrea Kirschning and Steve V. Ley, Organic and Biomeolecular Chemistry, 2014, 12, 3611

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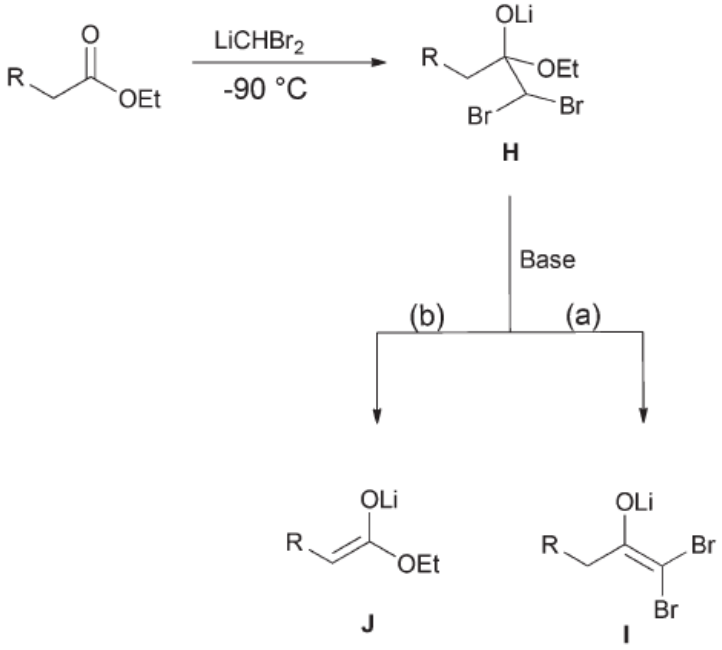
Flow Chemistry: A Discovery Tool for New Chemical Patterns

Compounds with acidic protons in α positions are not possible in batch.



It was reasoned that accelerated mixing and suppression of back mixing may stop the 2nd equivalent of base reacting with intermediate H
Further the increased temperature control may help stabilise the unstable intermediate.

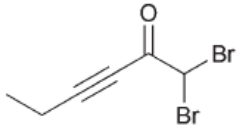
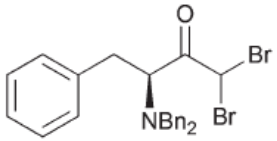
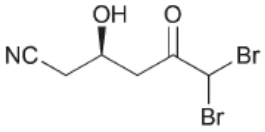
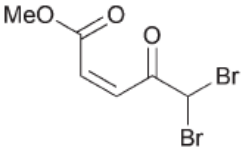
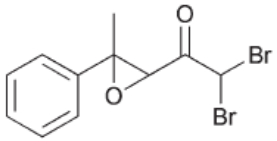
Flow Chemistry: A Discovery Tool for New Chemical Patterns

1 2

Entry	Mode	Eq. $LiCHBr_2$	Yield (%)	Rsm (%)
1[a]	Batch	2.2	10	—
2[a]	Flow	2.2	49	43
3[b]	Flow	4.4	95	0

Method tolerated chemoselectivity in the presence of various functional groups – triple bonds (53%) and nitriles (22%)

Scale-up:
α-Methyl cinnamyl ester
1.74g in 25mins in 87% yield

Entry	Product	Yield batch	Yield flow
1		10%	53%
2		0%	54%
3		0%	22%
4		0%	17%
5		0%	25%[a]

Continuous flow chemistry: adiscovery tool for new chemical reactivity patterns, Jan Hartwig, Jan Metternich, Nikzad Nikbin, Andrea Kirschning and Steve V. Ley, Organic and Biomeolecular Chemistry, 2014, 12, 3611

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Acknowledgements

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Philip R. D. Murray, Duncan L. Browne, Julio C. Pastre and Steven V. Ley

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