Flow Chemistry

What is flow chemistry?

Flow chemistry is a process in which a reaction is run Continuously in a flowing stream rather than in batch production

Comparison between traditional chemistry and flow chemistry

Reaction Stoichiometry:

In traditional chemistry this is defined by the concentration of chemical reagents and their volumetric ratio. In flow chemistry this is defined by The concentration of the chemical reagents and the ratio of their flow rate

Residence time:

In traditional chemistry this is determined by how long a vessel is kept at given temperature. In flow the volumetric residence time is used given by the ratio of the volume of the reactor and the overall flow rate

What is residence time?

Residence time of a reagent is defined as the amount of time that the reaction is cooled or heated.

Residence time = reactor volume/flow rate

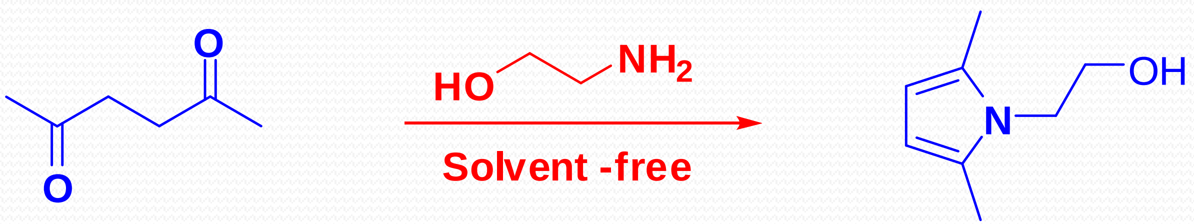
Continuous flow reactors: a perspective

Advantages:

1. Improved thermal management
2. Mixing control
3. Application of the extreme reaction conditions

Principles of green chemistry:

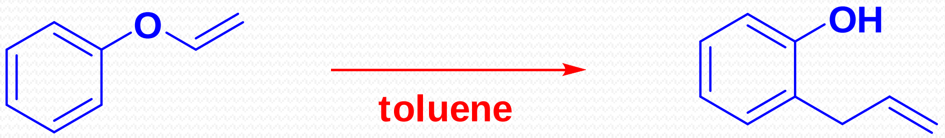
1. Prevention of waste



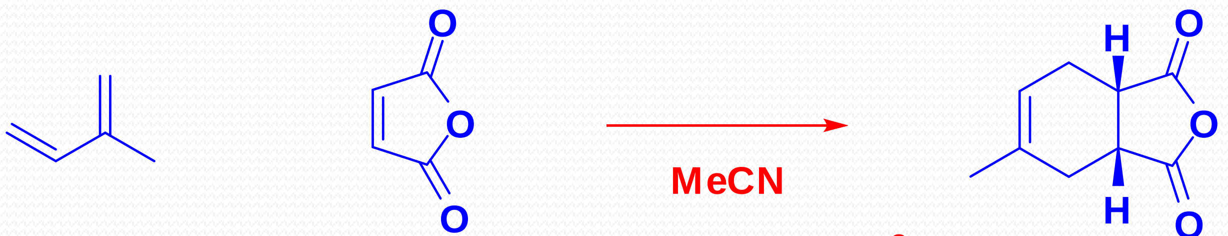
reaction temp : 65 ^{o}C
reaction time : 5.1 min
yield : 91%

Green chem., **2012**, *14*, 38-54

2. Atom economy

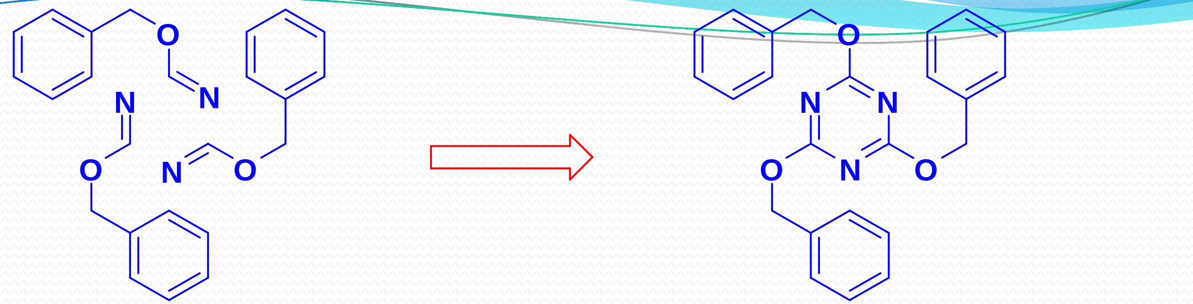


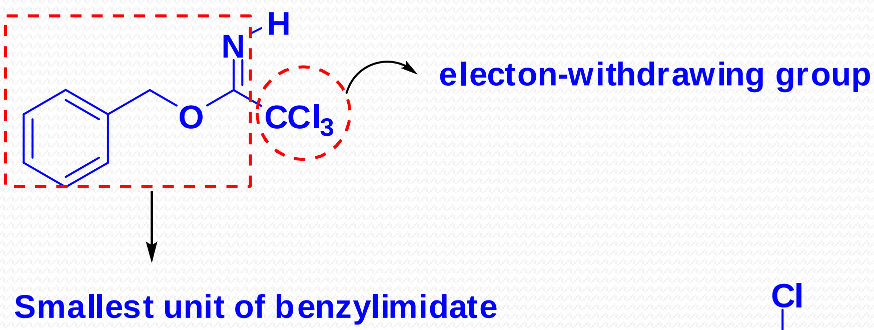
reaction temp : 240 ^{o}C
pressure : 100 bar
yield : 95%

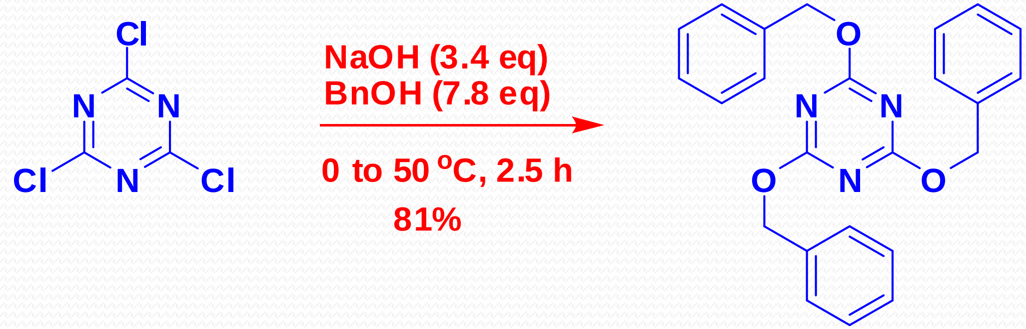


reaction temp : 60 ^{o}C

Green chem., **2012**, *14*, 38-54







Org. Lett., **2012**, *14*, 5026-5029

3. Less hazardous chemical synthesis

Synthetic methods should be designed to use and generate Substances that possess no toxicity to humans and to the environment as well

4. Designing for safer chemicals

Chemical products should be designed to effect their desired function while minimizing their toxicity

5. Safer solvents and auxiliaries

The use of auxiliary substances should be avoided

6. Design for energy efficiency

Energy requirements of chemical process should be recognized for their environmental and economic impacts and should be minimized

7. Use of renewable feedstocks

A raw material should be renewable whenever technically and economically practical

8. Reduce derivatives

Unnecessary derivatisation must be avoided because such steps can generate waste

9. Catalysis

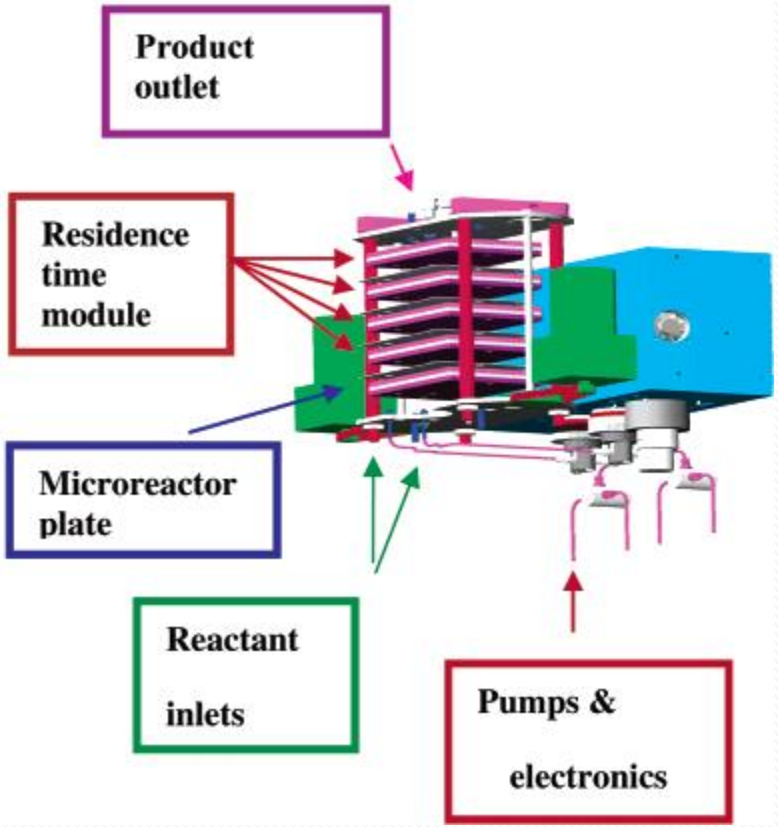
Catalytic processes are superior to stoichiometric reagents

10. Real-time analysis for pollution prevention

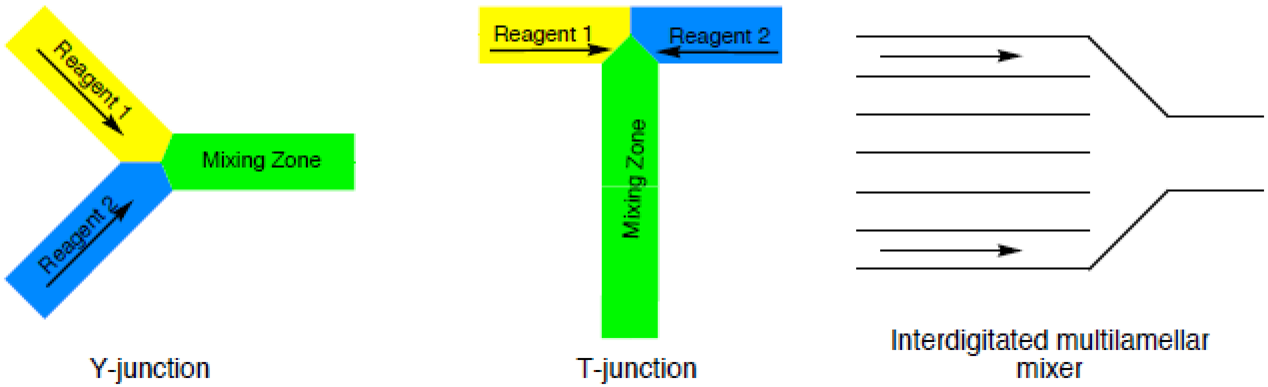
In- process monitoring and control to minimize the formation of hazardous substances

11. Inherently safer chemistry for accidental prevention

Substances used in a chemical process must be chosen to minimize The potential for chemical accidents

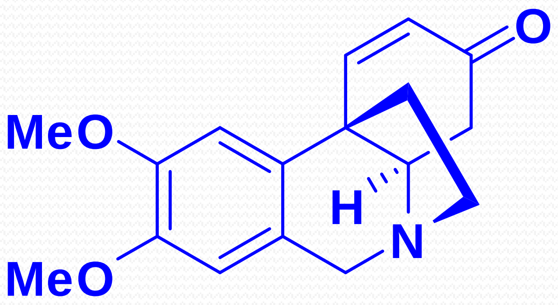


Org. process. Res. Dev. **2004**, *8*, 455



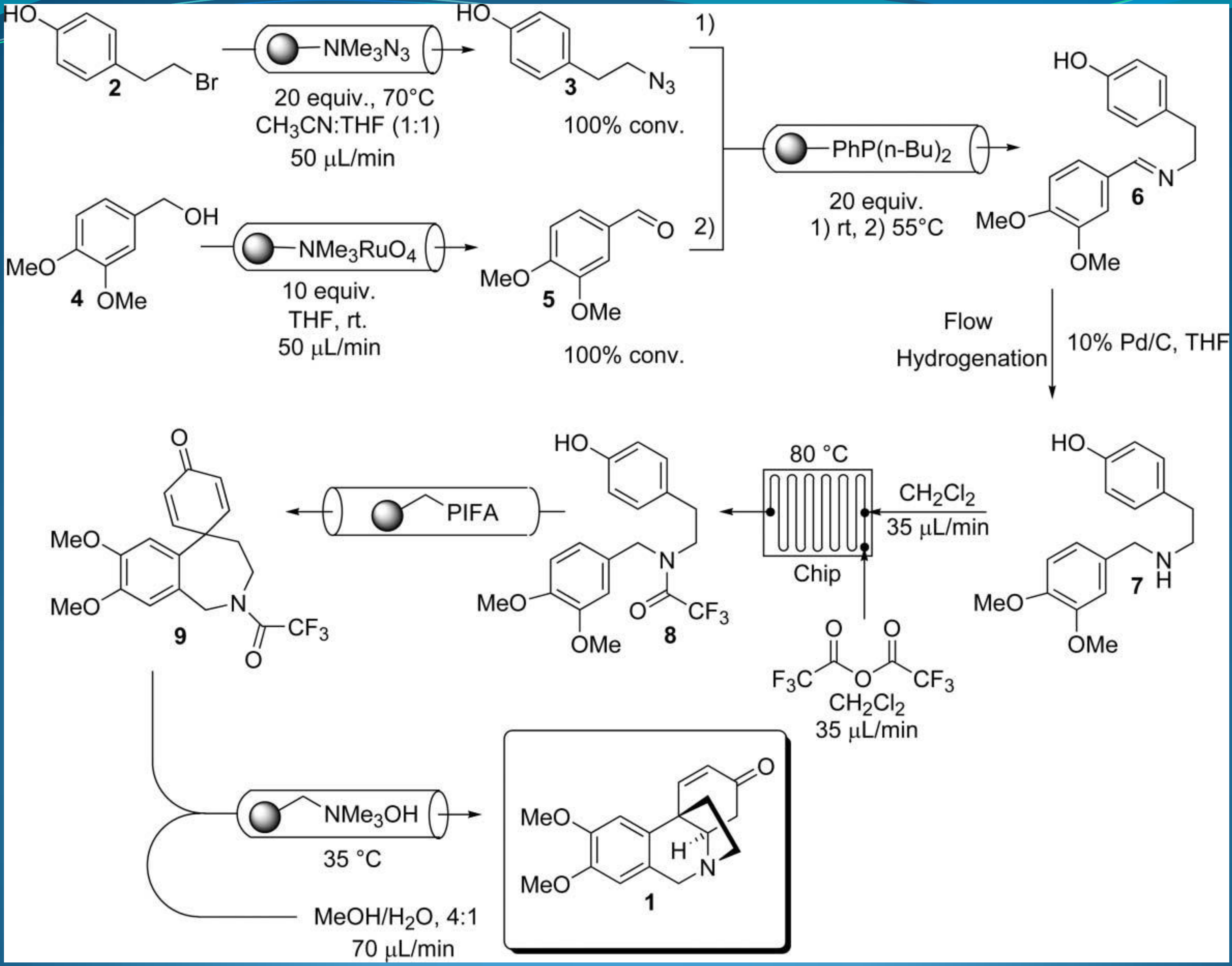
- Channel junctions can be simple Y or T-type junctions
- More complex configurations and channel shapes are possible
- Mixing times are usually on the microsecond time-scale

A flow process for the multi-step synthesis of the alkaloid natural product: Oxomaritidine



（±）-Oxomaritidine

Chem. commun., **2006**, 2566-2568



Chem. commun., **2006**, 2566-2568

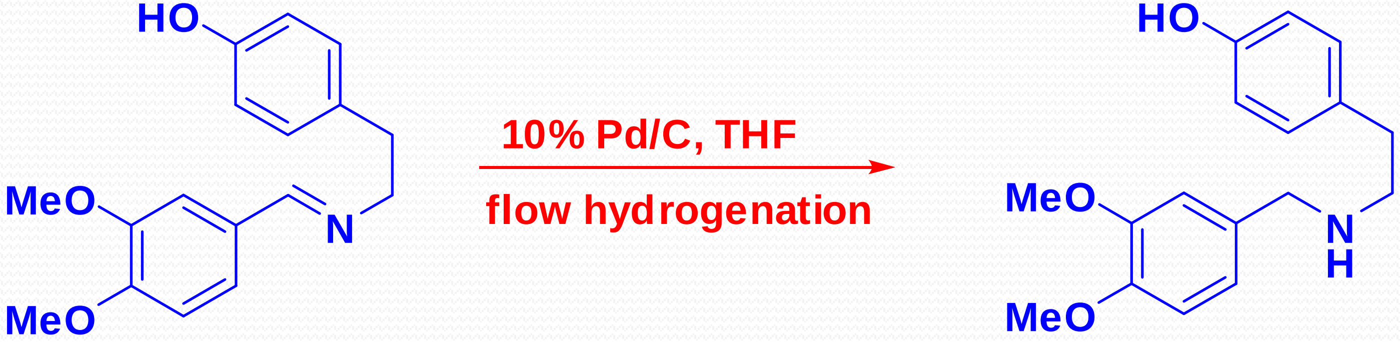
1. Product obtained with >90% purity by H NMR

2. 40% isolated yield overall (phenolic oxidation gave 50% yield

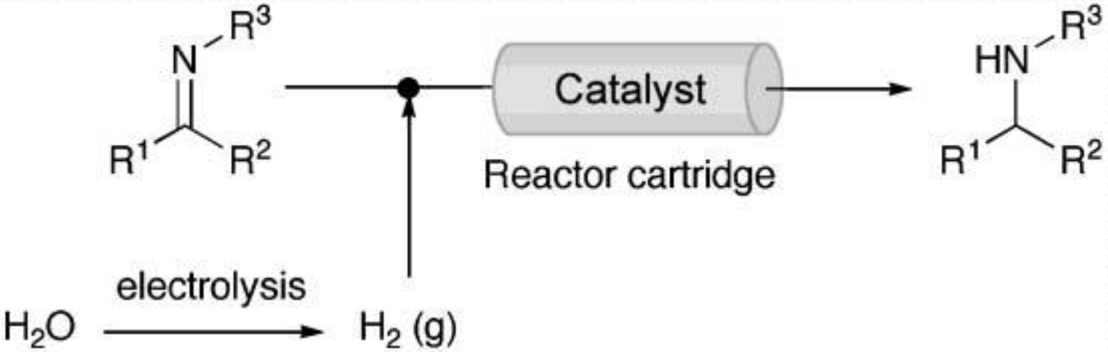
3. Natural product can be obtained in less than 1day

4. Only obtained 20 mg of (±)-oxomaritidine

Efficient reduction of imines to amines



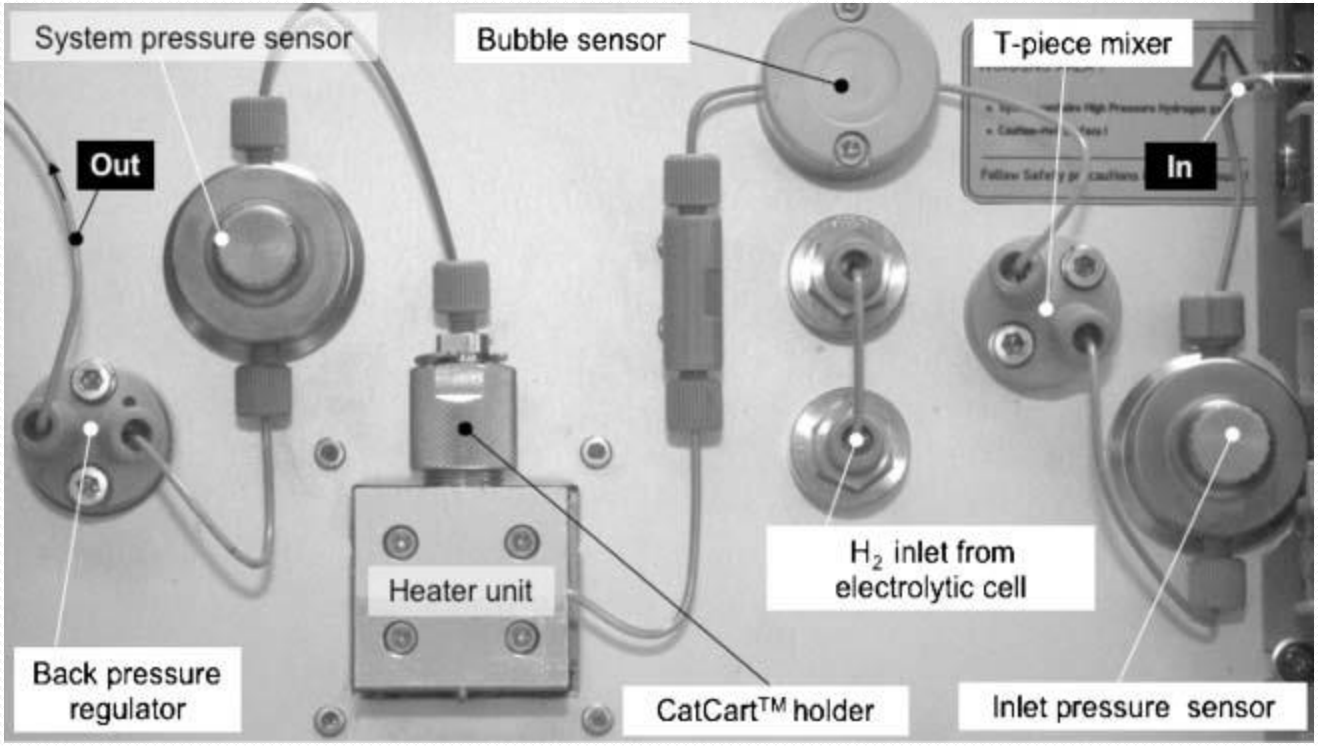
Continuous flow-through reduction of imines into amines



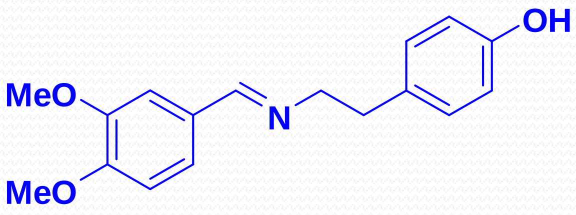
Continuous flow-through reduction of imines into amines

H-Cube flow hydrogenator

H-Cube Flow Hydrogenator front panel



Flow hydrogenation scope



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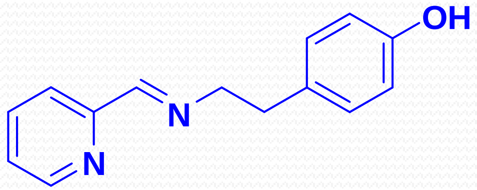

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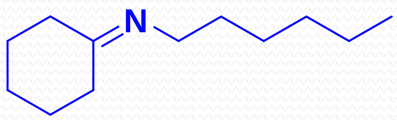

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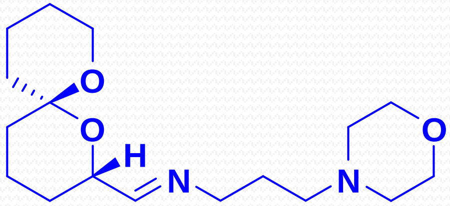
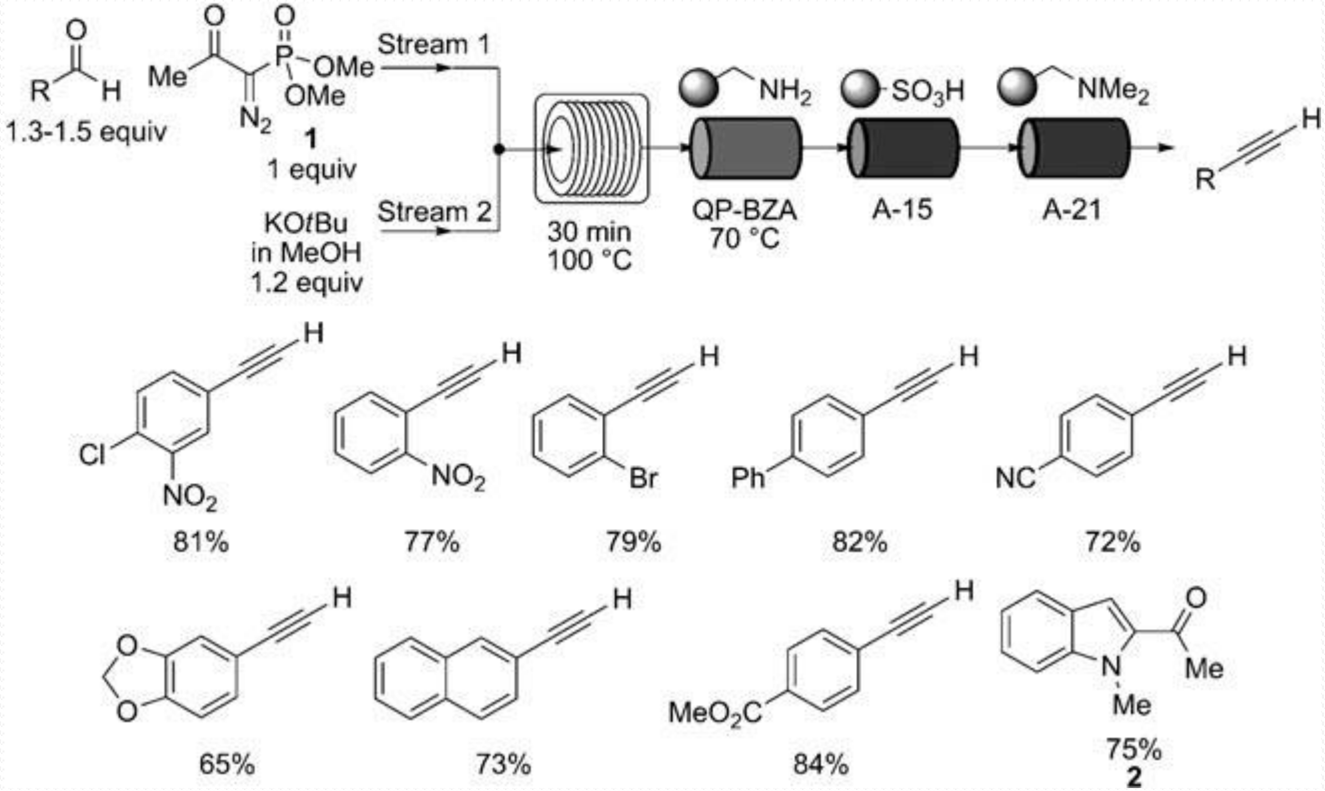


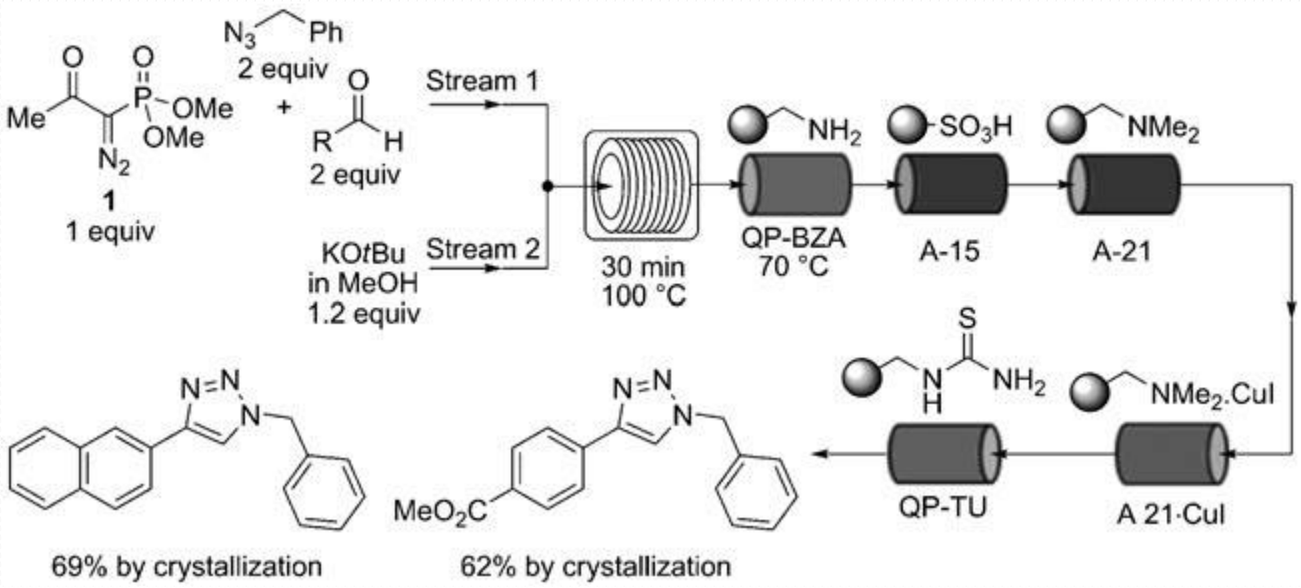
quant.

Bestmann-Ohira reagent for the formation of alkynes and triazoles

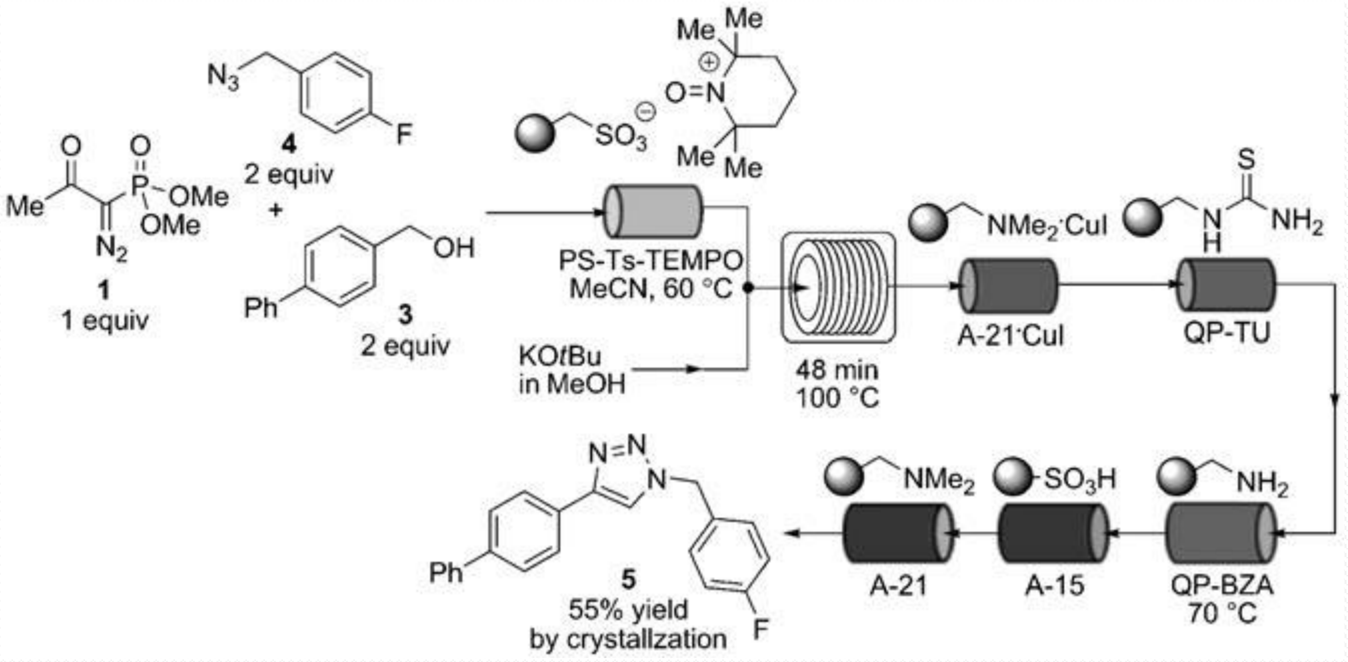
Flow synthesis of terminal alkynes:



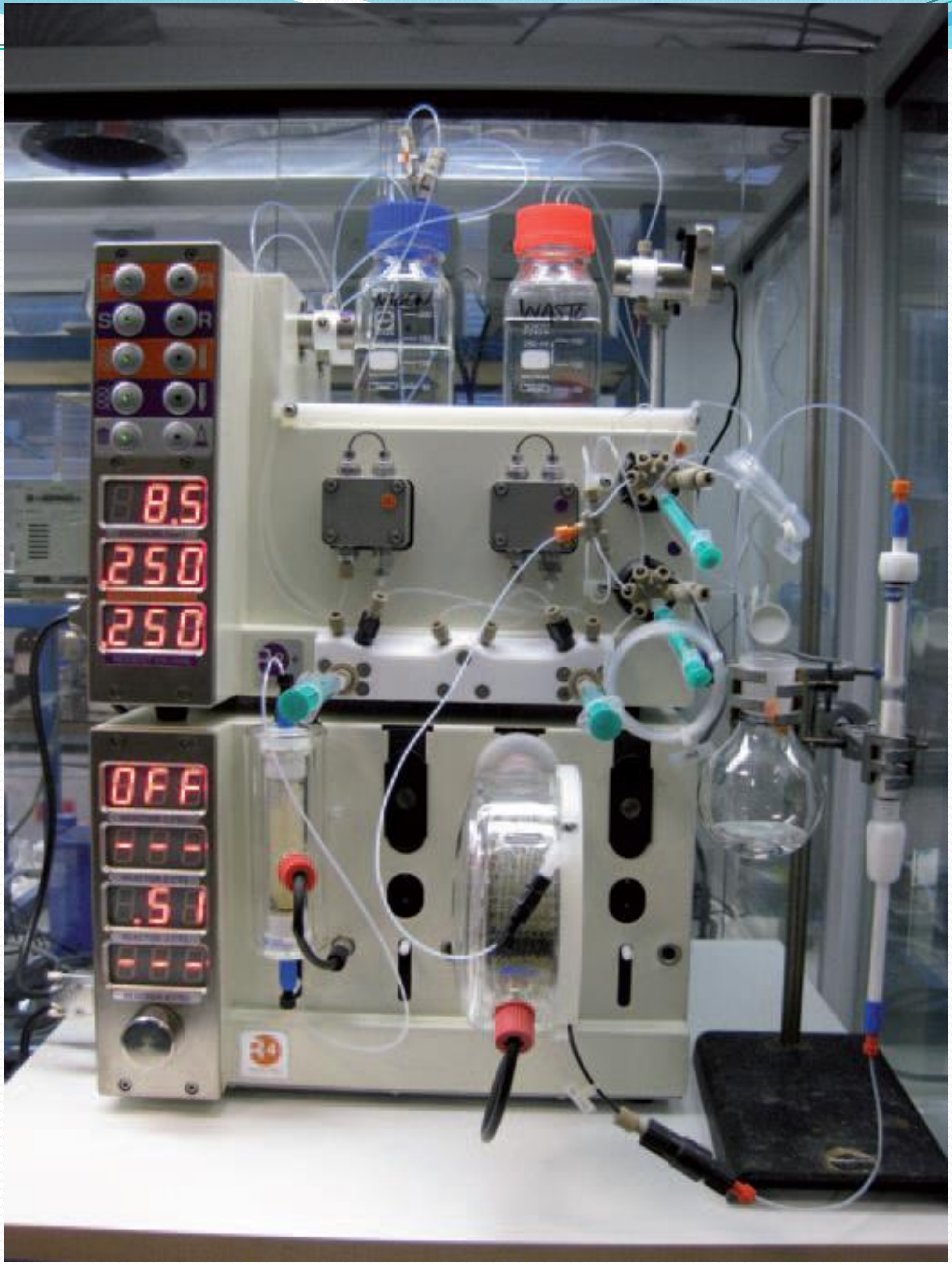
Two-step formation of triazoles from alkynes



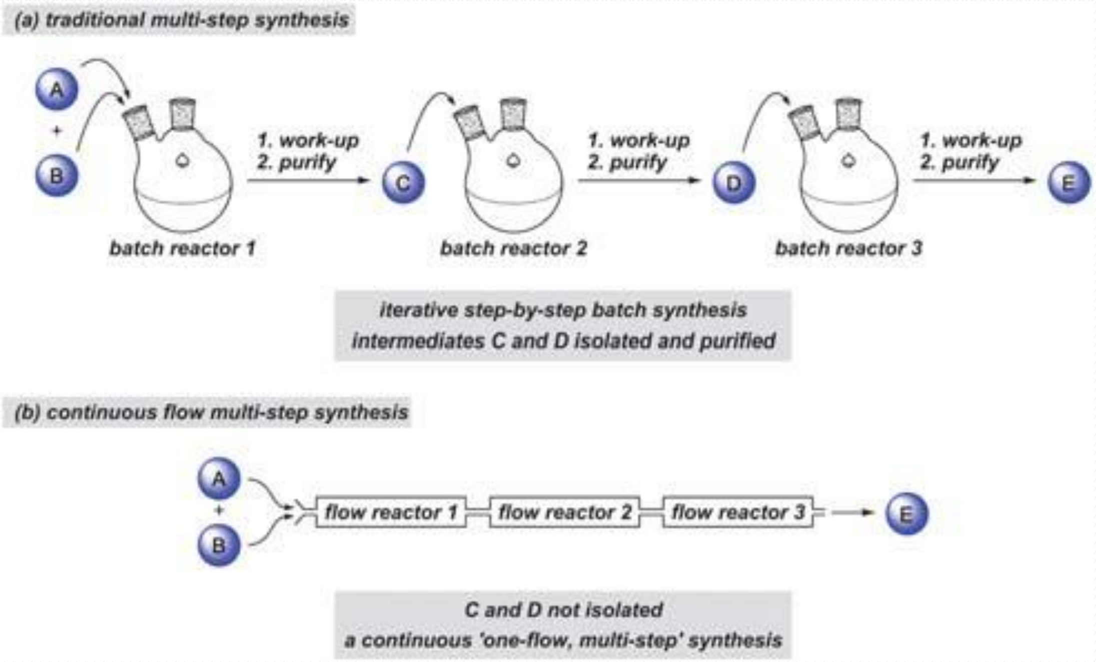
Three step synthesis of triazole 5 from alcohol 3



Vapourtec R2+/R4 flow system

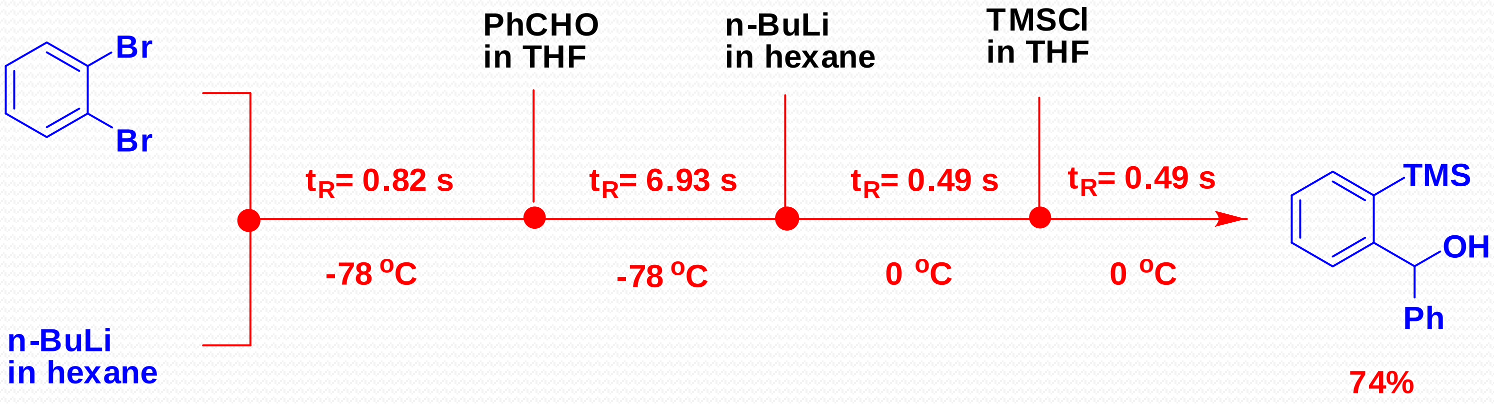


Multi-step synthesis strategies



Chem.sci., **2010**, *1*, 675-680

Generation and reaction of *o*-bromophenyllithium

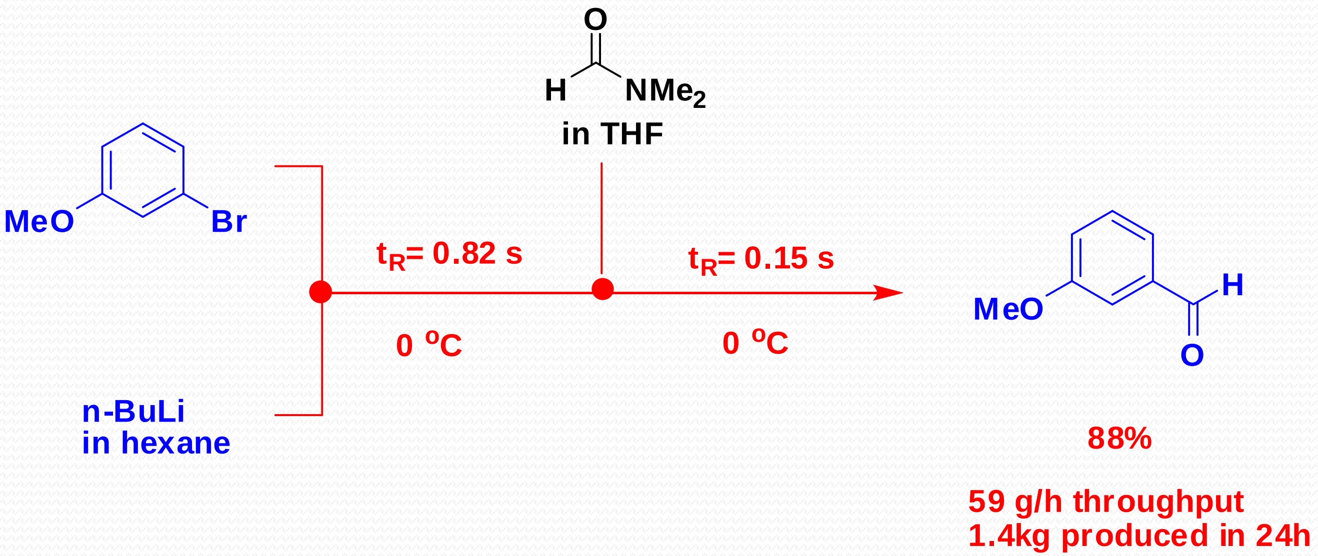


● = the introduction of an input stream to the reactor network

t_R= residence time in the reactor

J. Am. Chem. Soc. **2007**, *129*, 3046

Generation of kilogram quantities of 3-methoxybenzaldehyde

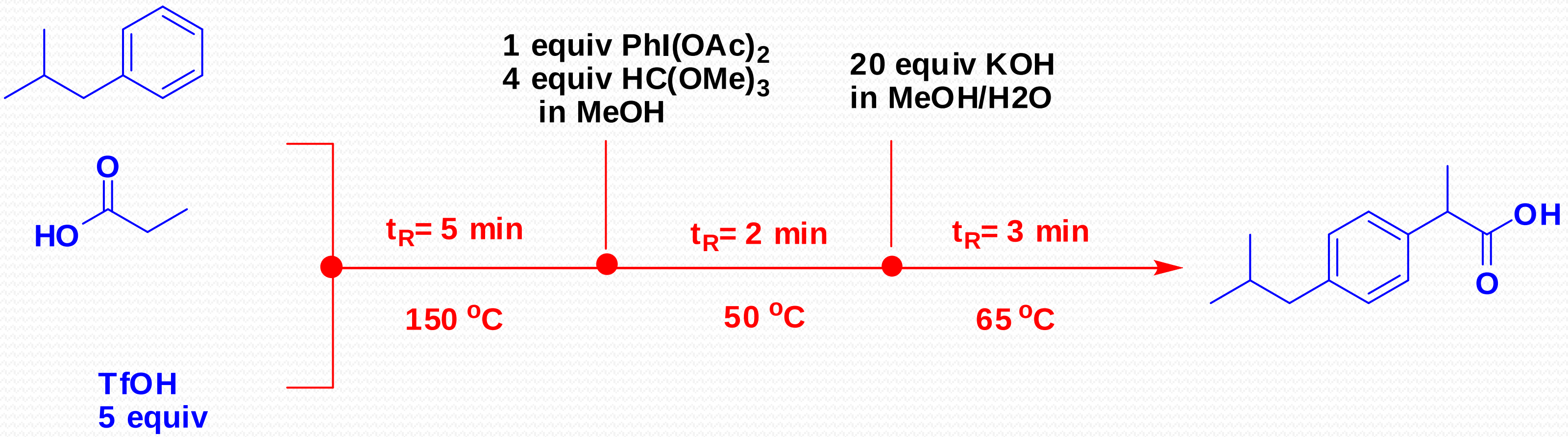


● = the introduction of an input stream to the reactor network

t_R = residence time in the reactor

Difficult to reproduce on kilogram scales using batch methods (24% yield, -40 oC)

Continuous flow synthesis of ibuprofen

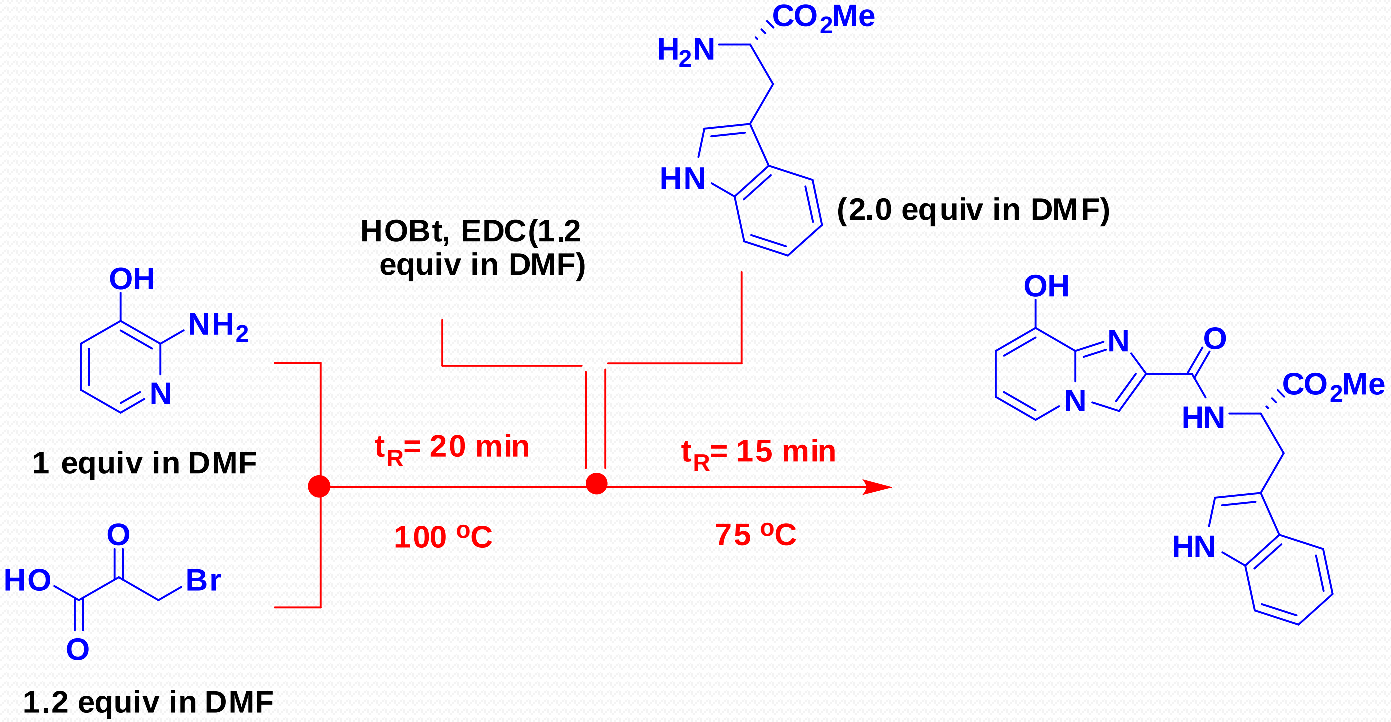


● = the introduction of an input stream to the reactor network

t_R = residence time in the reactor

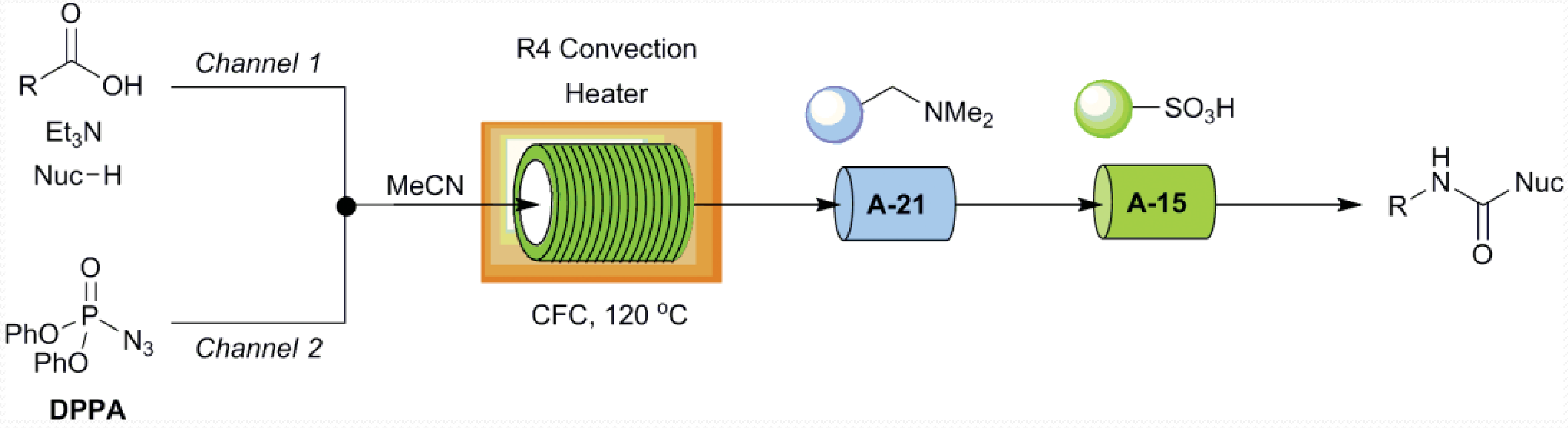
Angew. Chem. Int. Ed. **2009**, *48*, 8547

Synthesis of a Mur ligase inhibitor



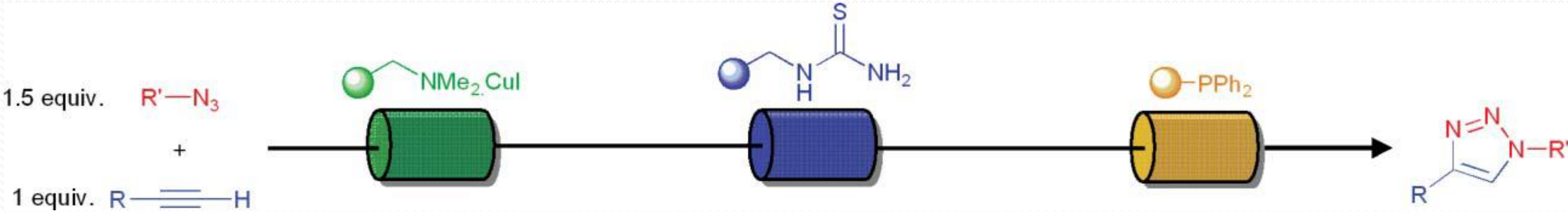
Org. Lett., **2010**, *12*, 412

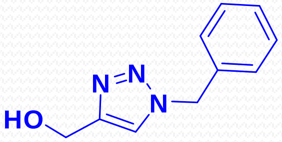
Curtious rearrangement of Carboxylic acids



Org. Biomol. chem., **2007**, *5*, 1559-1561

3+2 cycloaddition of actylenes with azides





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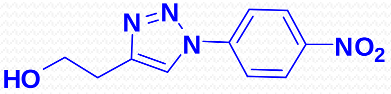

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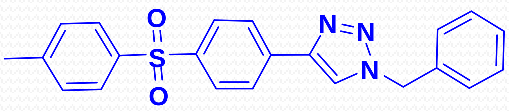

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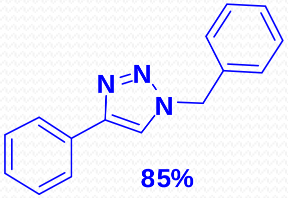

85%

Conclusions

large quantities of synthetically use intermediates can be accessed through flow chemistry

Multiple reactors in tandem can be used to build molecular complexity

Micro reactors have the potential to increase reaction efficiency

It is better to prevent waste than cleanup after creation!!!

Thanks for your attention