Flow Chemistry: Recent Developments

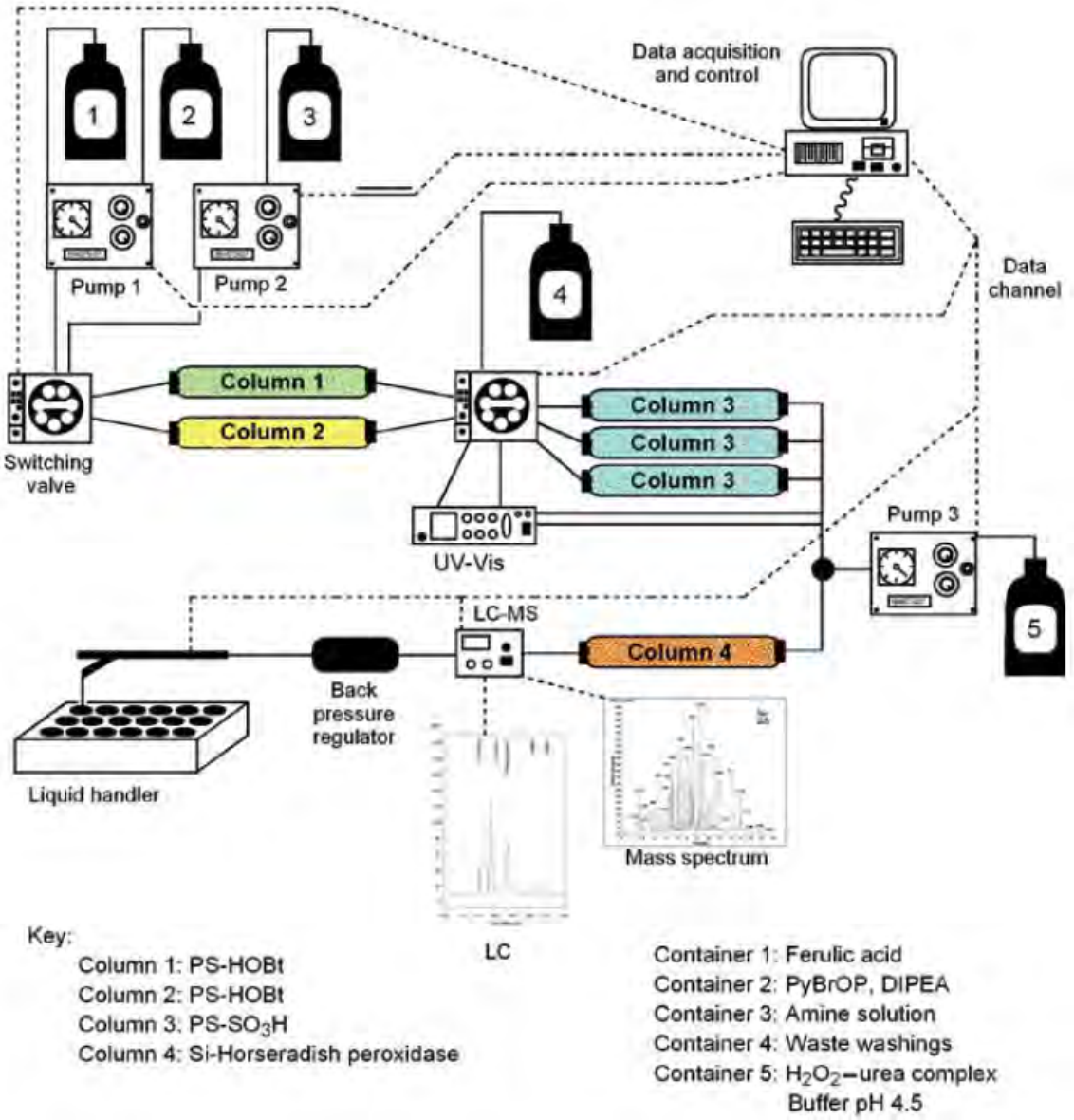
Steven V. Ley

Department of Chemistry, University of Cambridge

1st RSC/SCI Symposium on Continuous Processing and Flow Chemistry

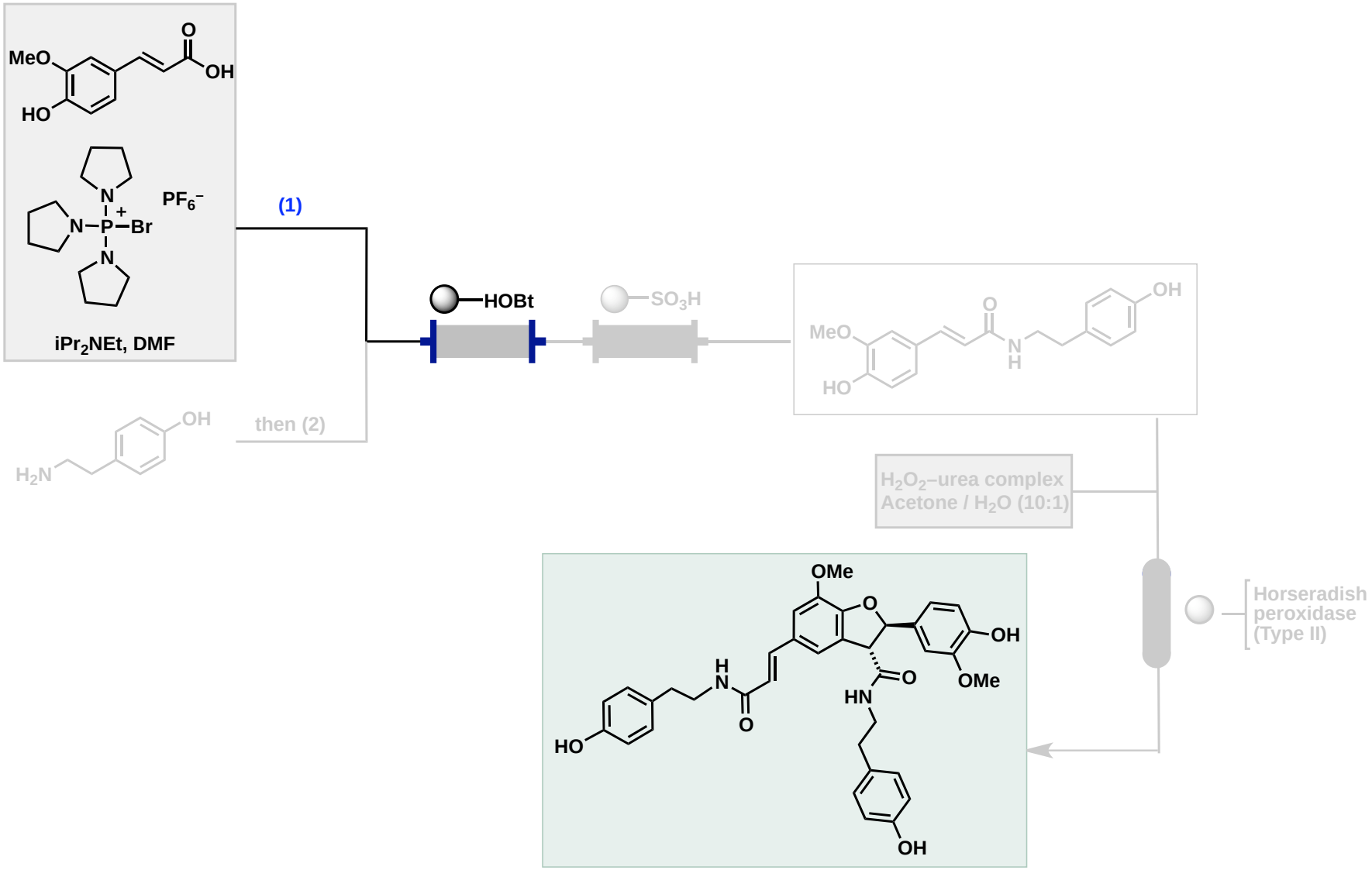
3rd - 4th November 2010

Flow Synthesis of Grossamide Using Immobilised Enzymes



I.R. Baxendale, C.M. Griffiths-Jones, S.V. Ley and G.K. Tranmer, *Synlett*, **2006**, 427-430

Flow Synthesis of Grossamide Using Immobilised Enzymes



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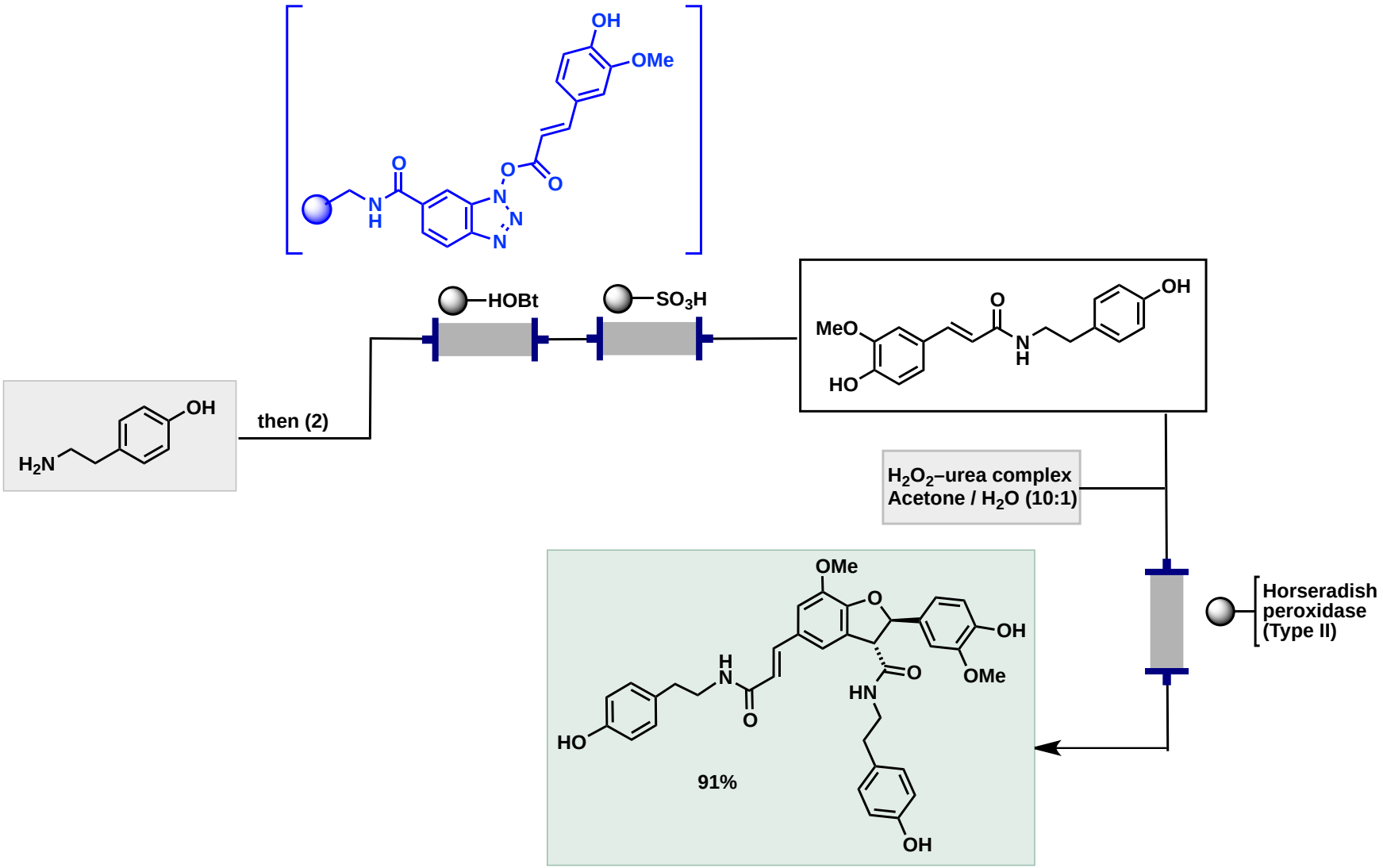
Flow Synthesis of Grossamide Using Immobilised Enzymes



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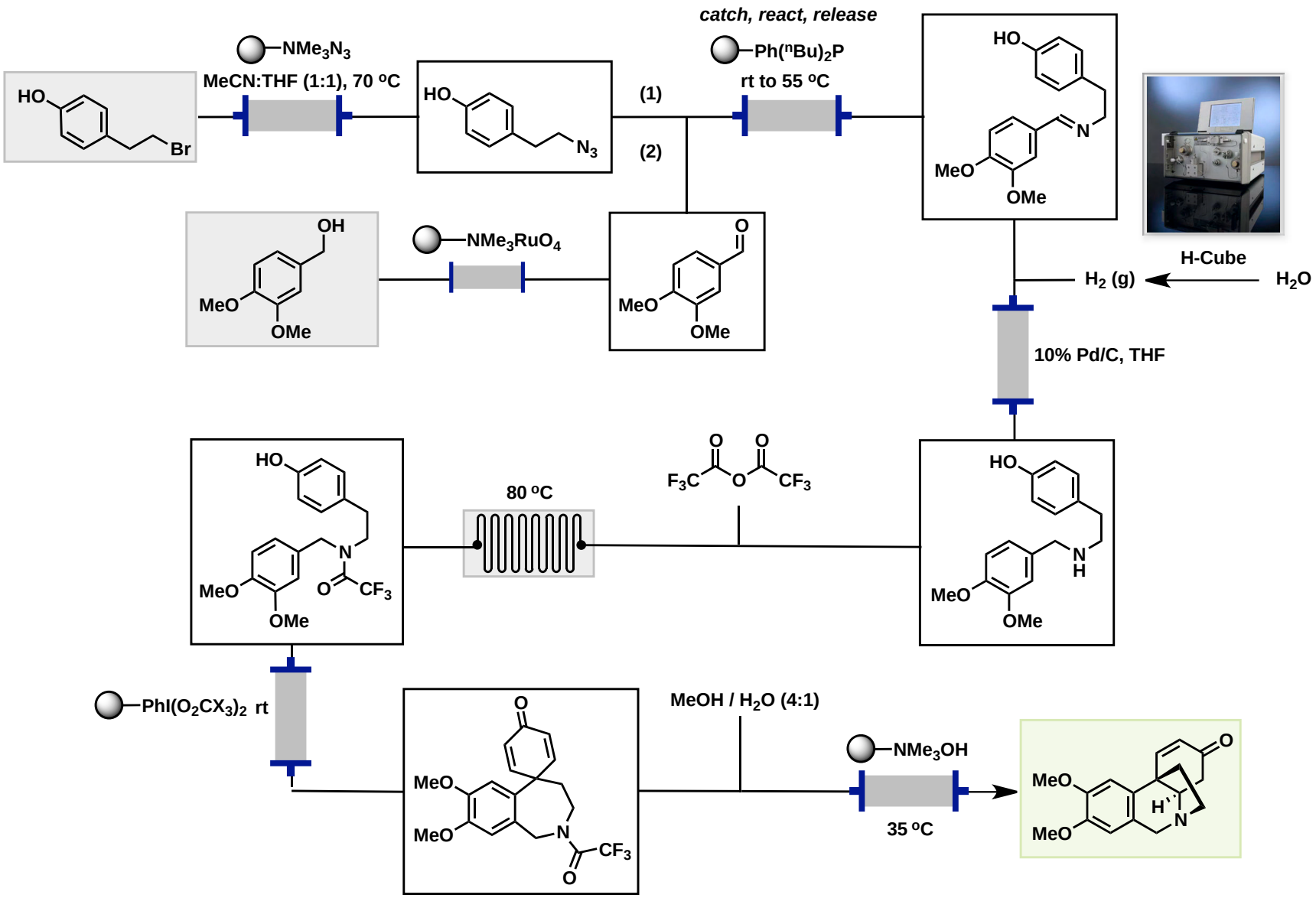
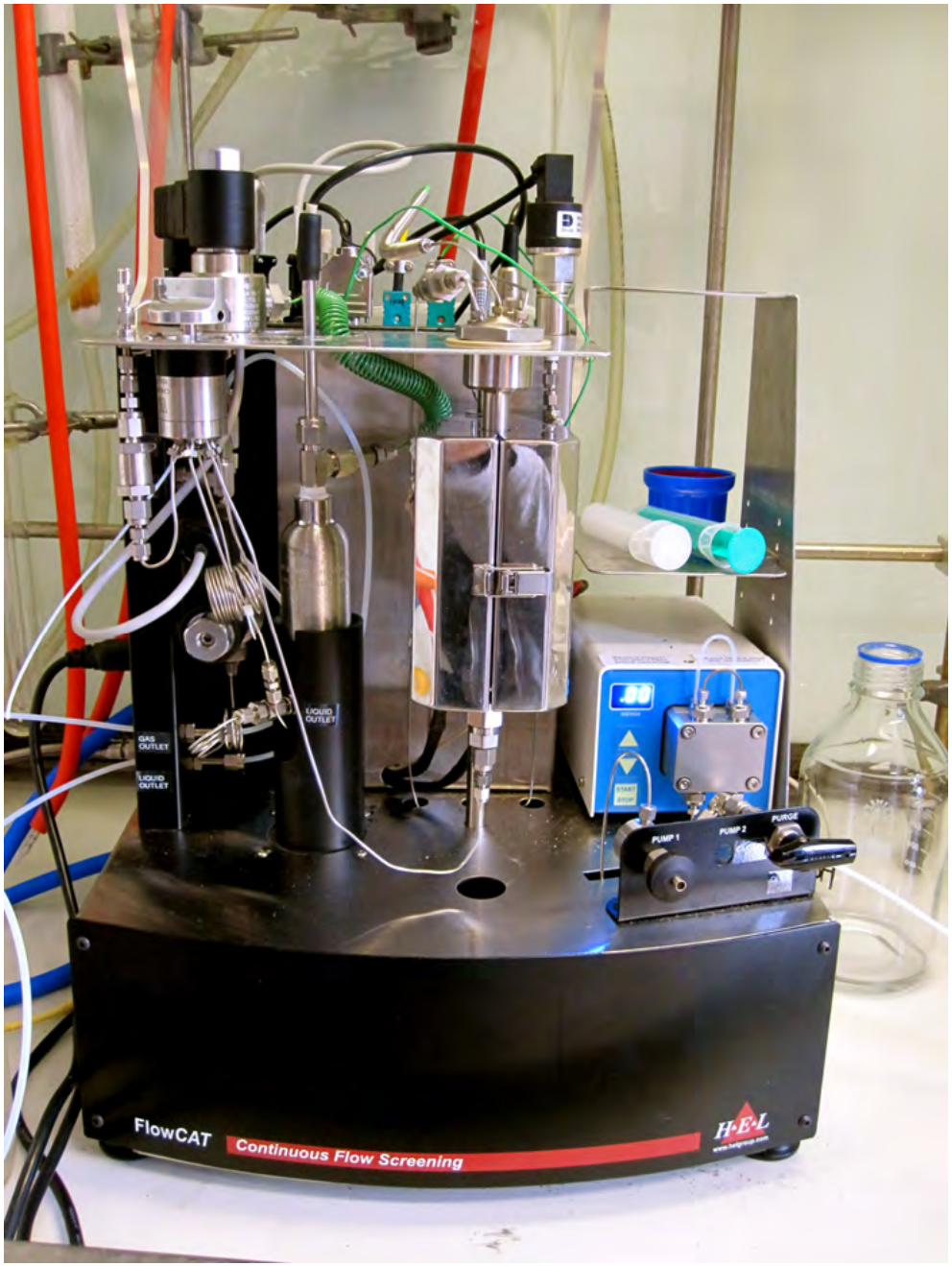
Convergent Flow Synthesis of Oxomaritidine

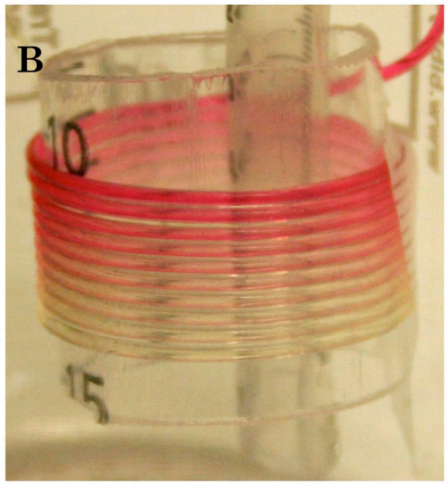


I.R. Baxendale, J. Deeley, C.M. Griffiths-Jones, S.V. Ley, S. Saaby and G. Tranmer, *J. Chem. Soc., Chem. Commun.*, 2006, 2566-2568

HEL FlowCAT for Flow Hydrogenation



Flow Ozonolysis using Teflon AF-2400



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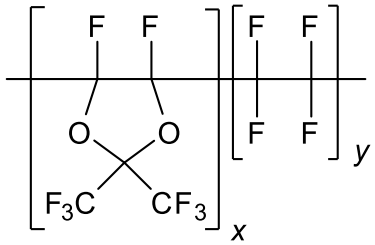
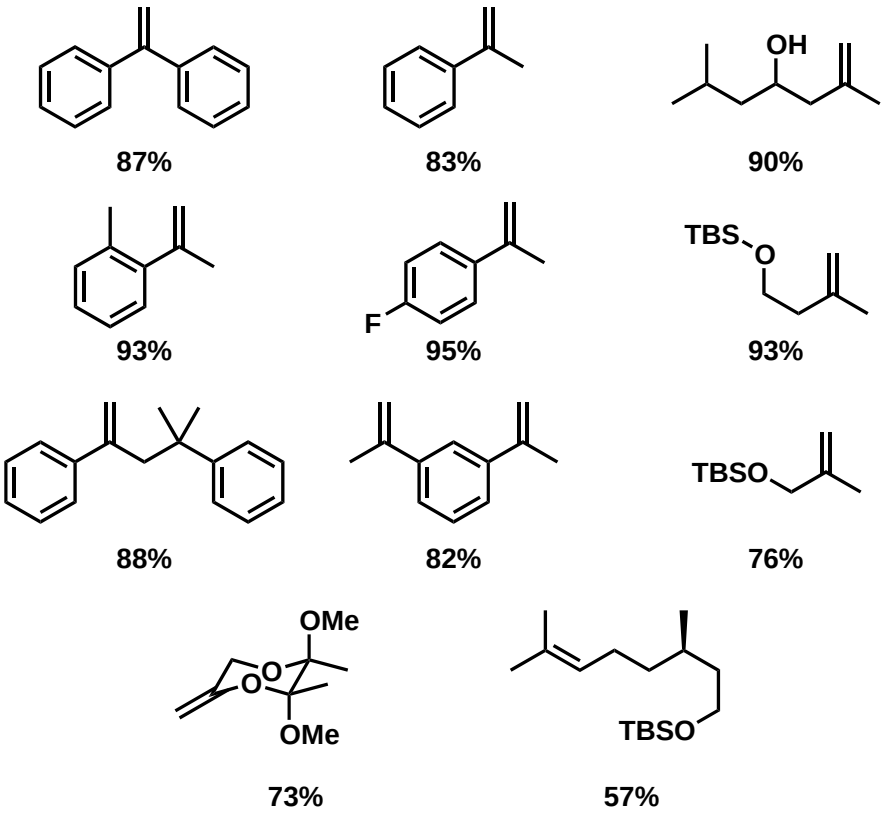


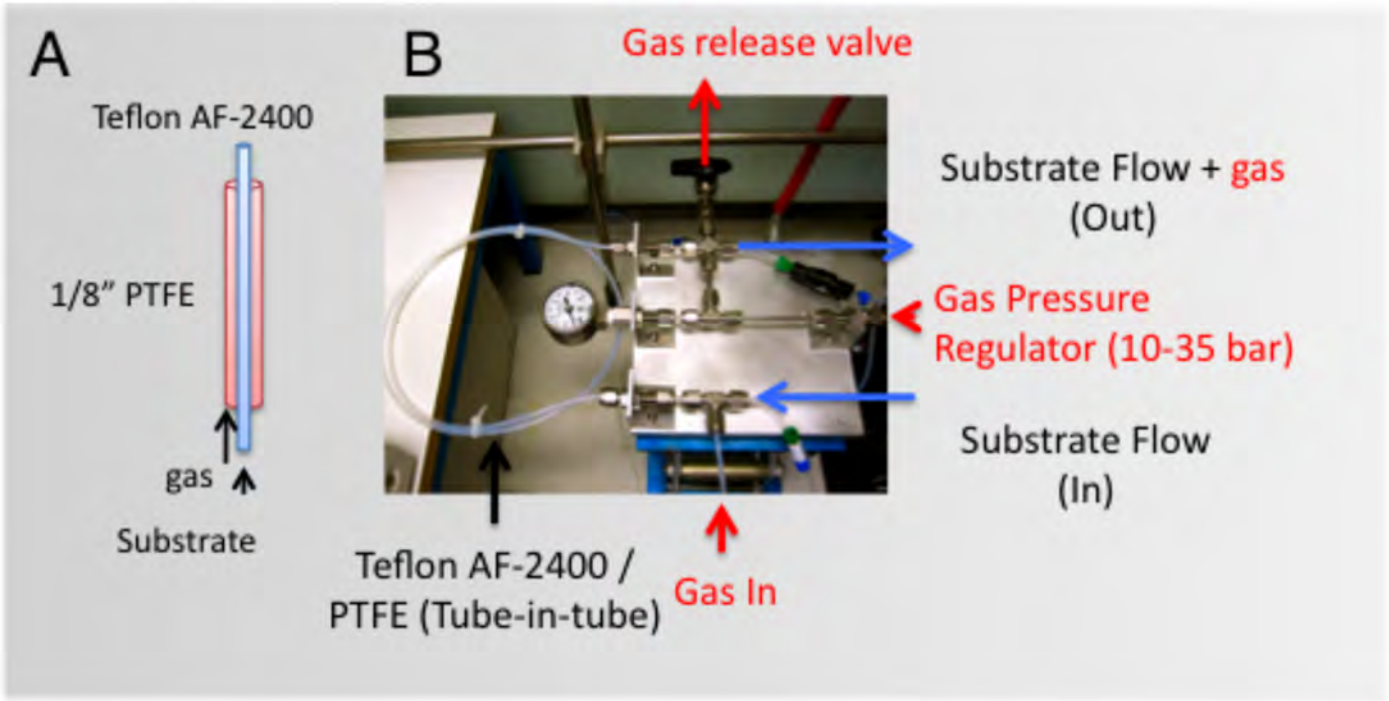
Teflon® AF-2400:
x:y = 83:17



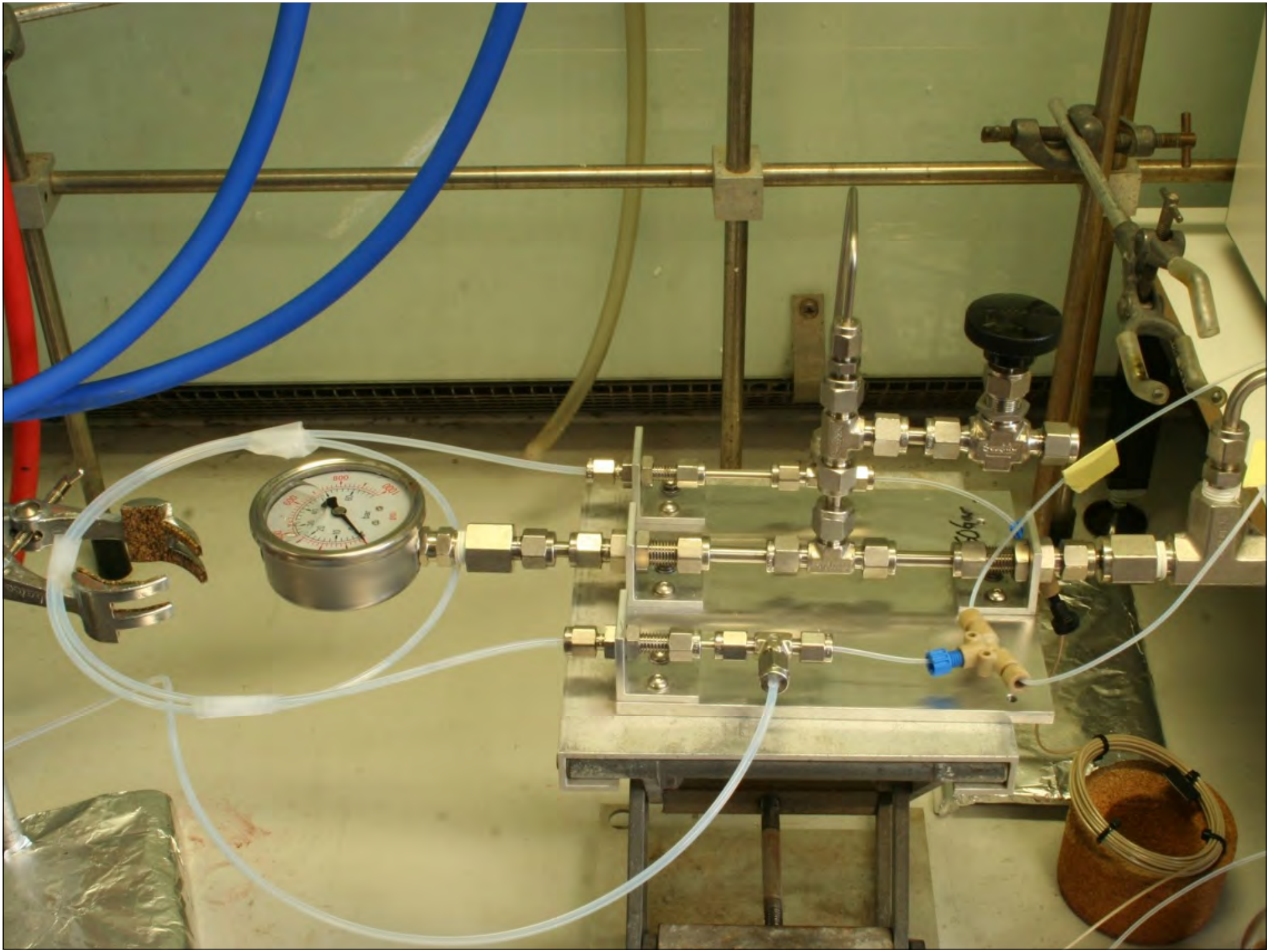
A. Flow ozonolysis apparatus (tubing filled with dye)
B. Bleaching of Sudan red 7B in flow, tubing coiled for clarity
C. Molecular formula of Teflon® AF-2400

M. O'Brien, I. R. Baxendale and S.V. Ley, *Org. Lett.* **2010**, *12*, 1596-1598.

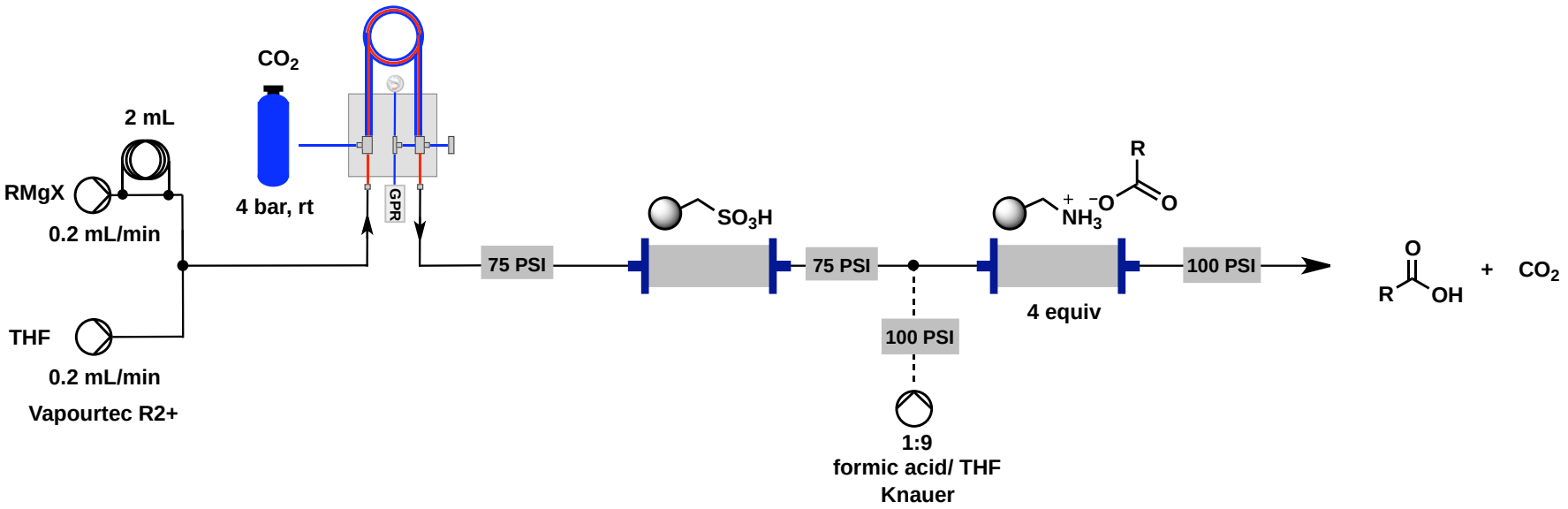
Tube-in-Tune Gas Flow Reactor

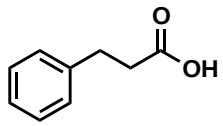


- reactor volume 0.28-0.56 mL (1-2.0 m Teflon AF-2400)
- gas pressure up to 35 bar
- small effective volume of gas input (safety)
- adaptable to commercial flow apparatus (heating / cooling)
- flow rates 0.1-10 mL/min



Carboxylation of Grignard Reagents (CO_2)

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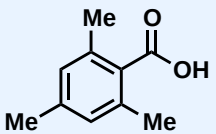
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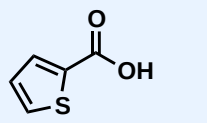
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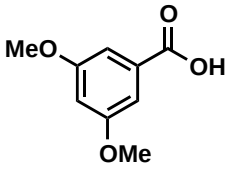
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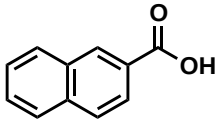
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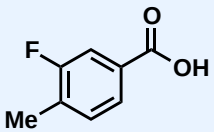
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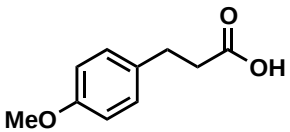
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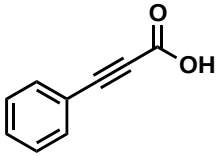
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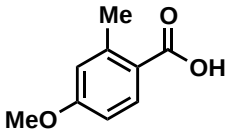
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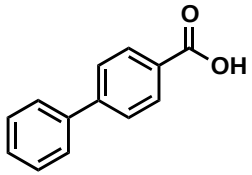
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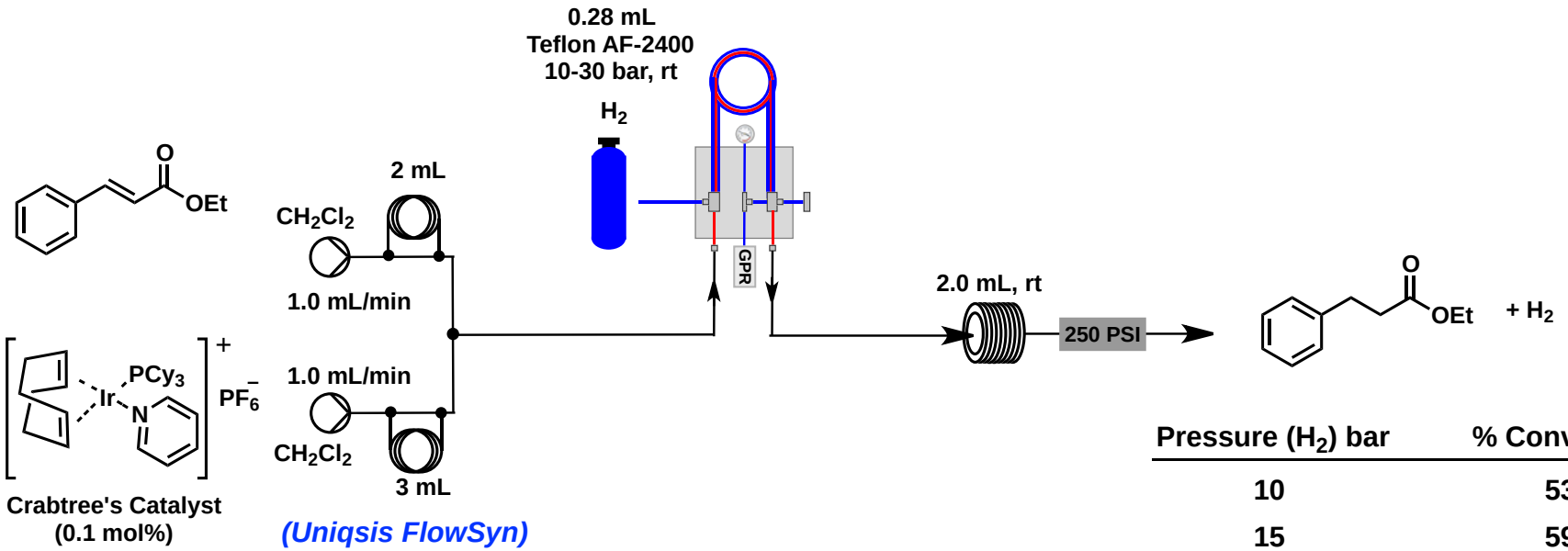
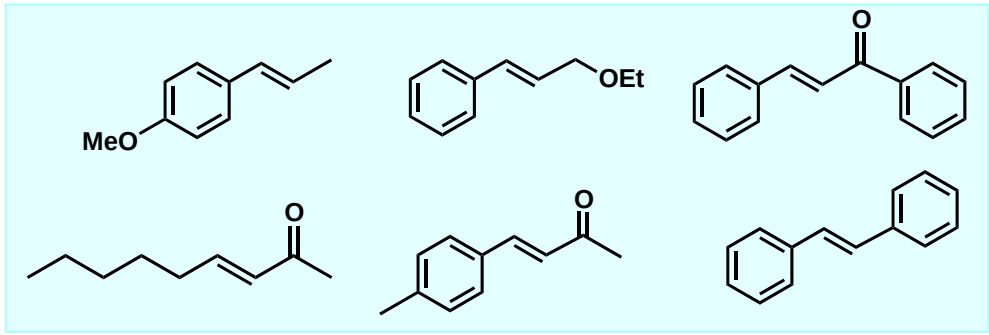
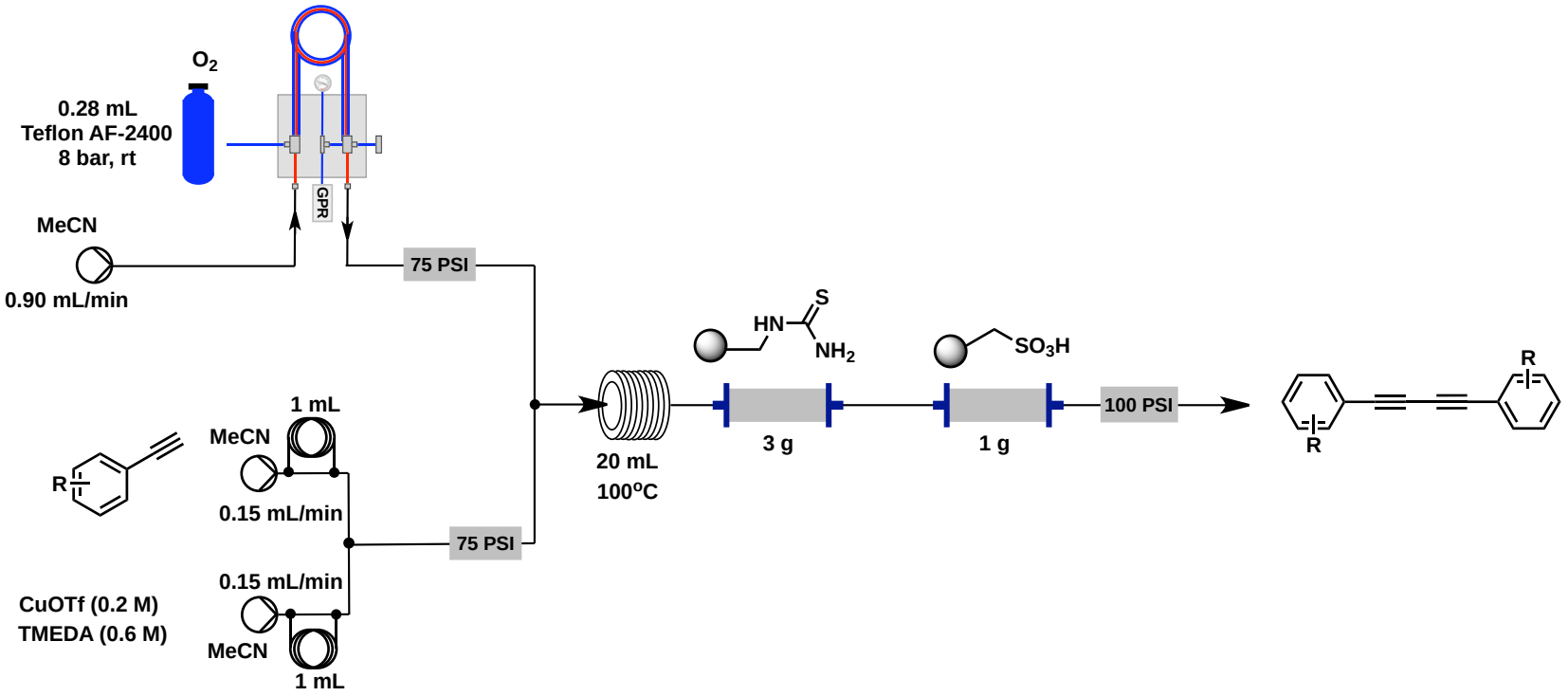
Hydrogenations (H_2)

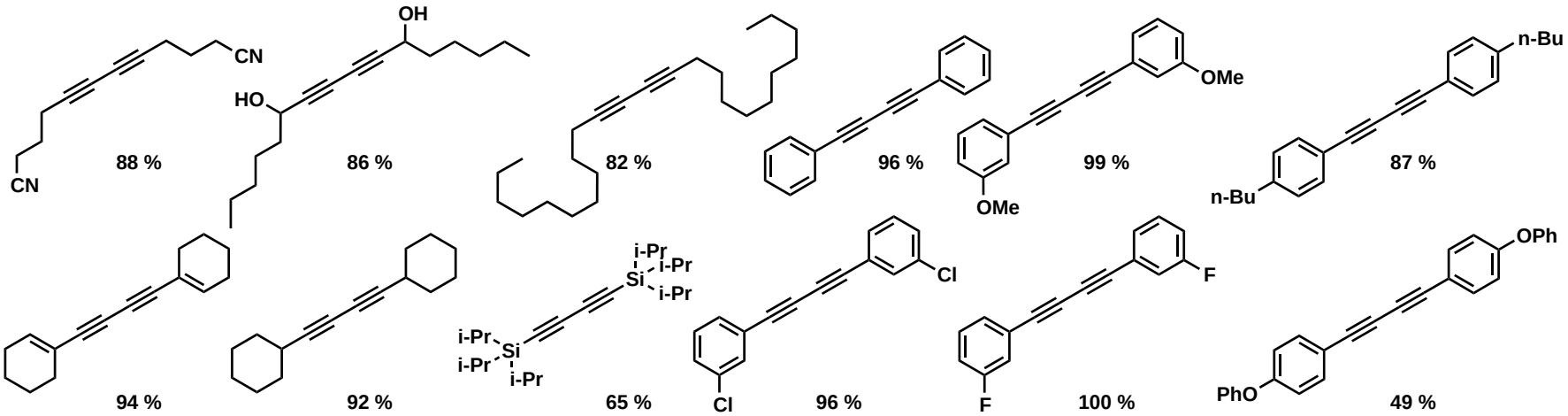


Pressure (H_2) bar	% Conversion
10	53
15	59
20	71
25	93
30	99

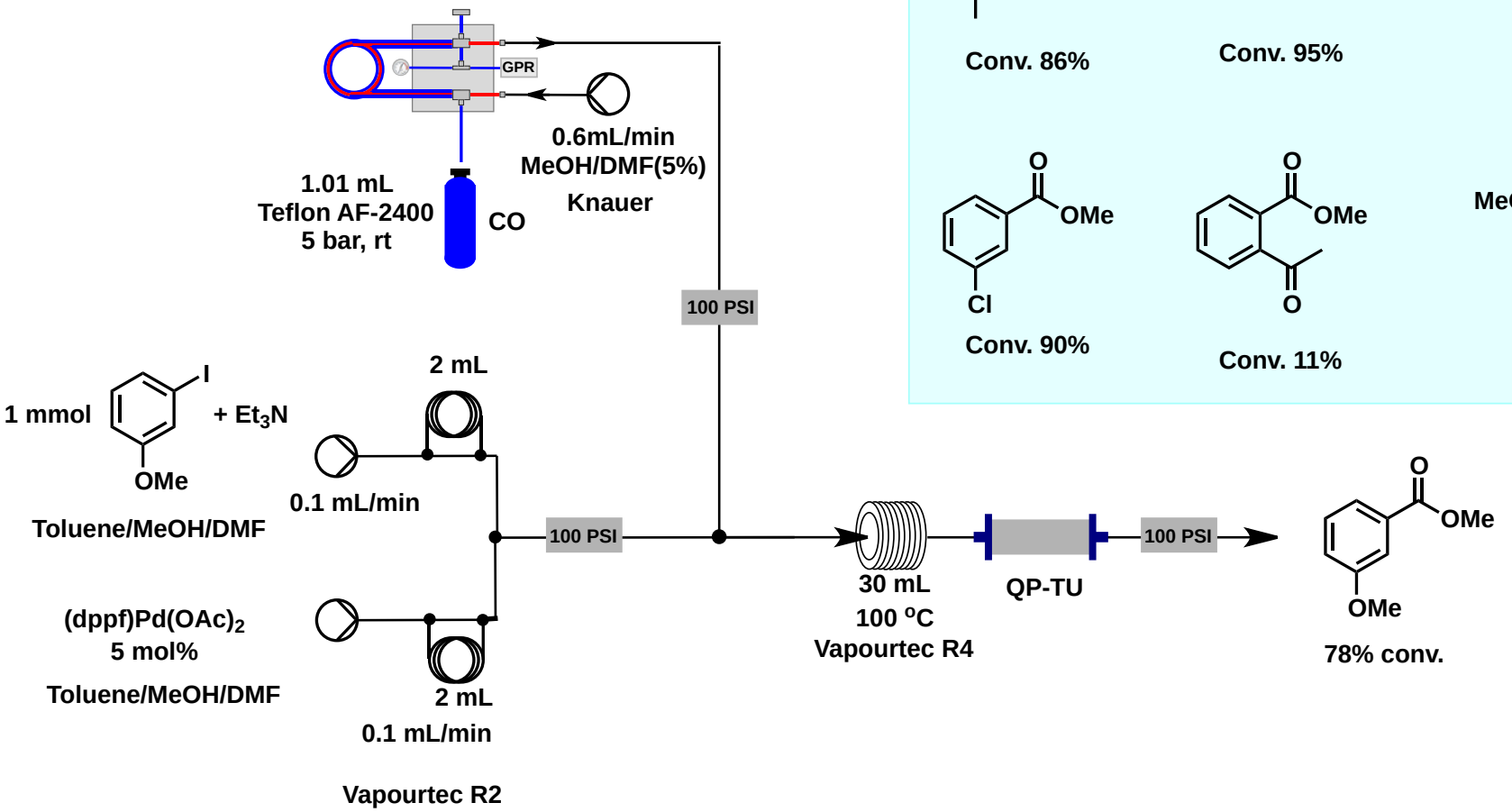


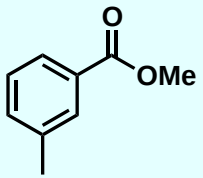
Glaser Couplings (O_2)



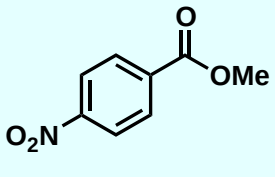


Carbonylations (CO)

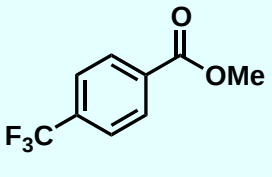




Conv. 86%



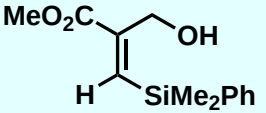
Conv. 95%



Conv. 95%

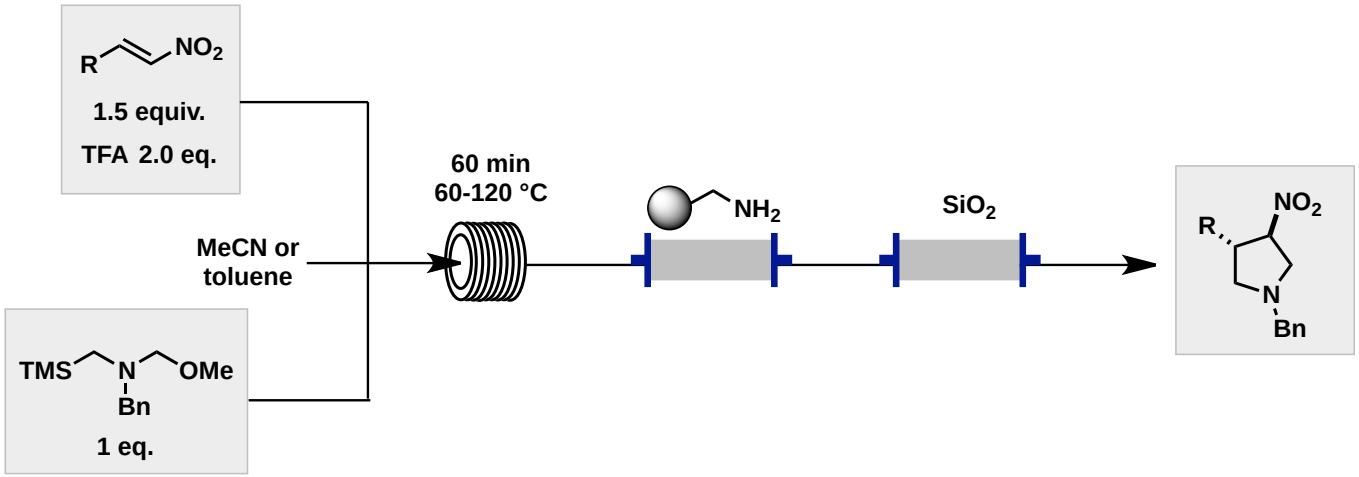
Conv. 90%

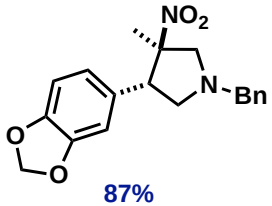
Conv. 11%



Conv. 100%

Pyrrolidines via [3+2] Cycloaddition





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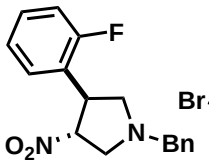

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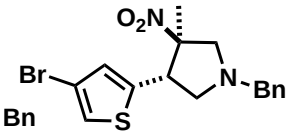

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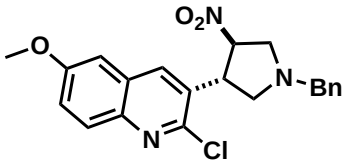

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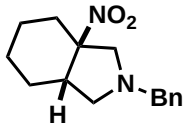

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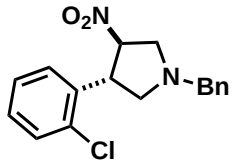

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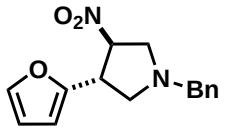

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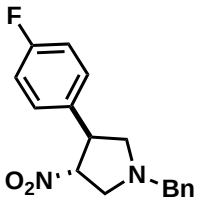

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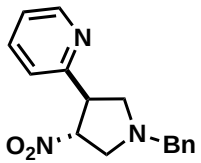

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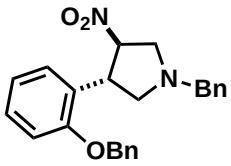

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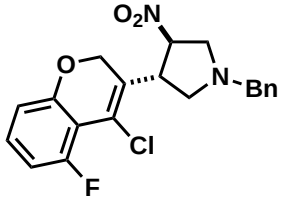

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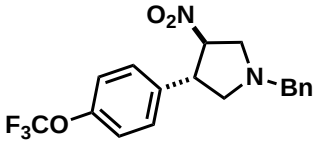

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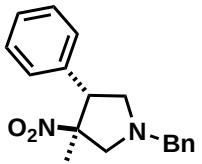

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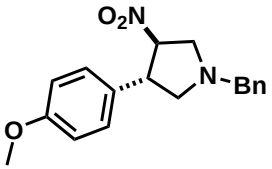
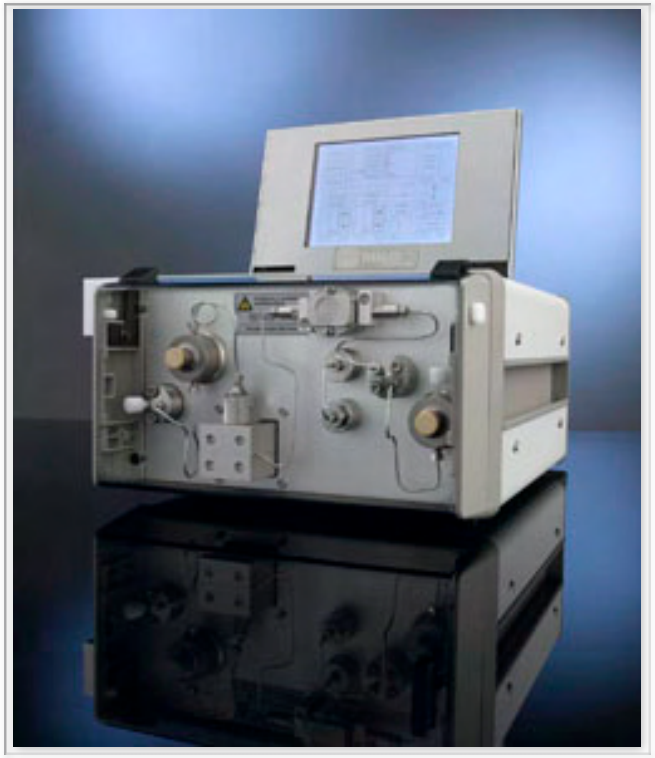


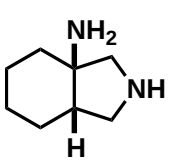
81%

M. Baumann, I.R. Baxendale, S.V. Ley, *Synlett*, **2010**, 749-752

H-Cube Reduction of Nitropyrrolidines



Debenzylation and nitro reduction in one go using 10% Pd/C cartridges



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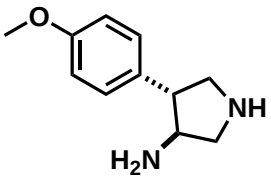

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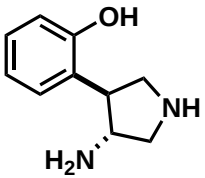

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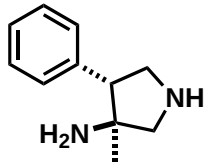
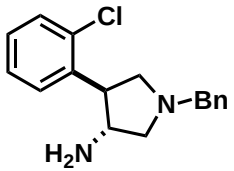


95%

Selective hydrogenation of nitro group using RaNi cartridges in the H-Cube



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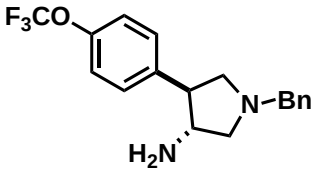

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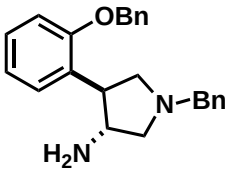

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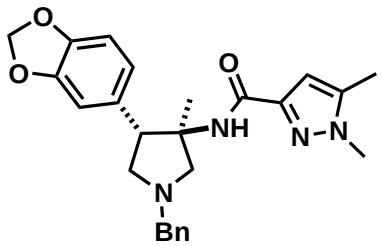
Pyrrolidines via [3+2] Cycloaddition



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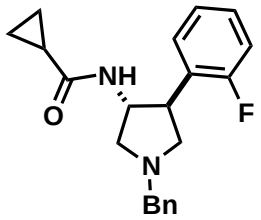

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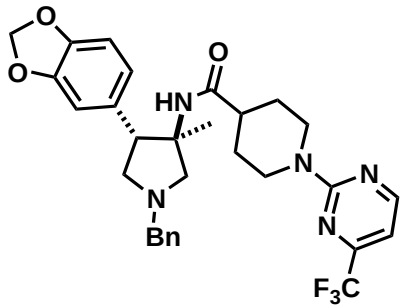

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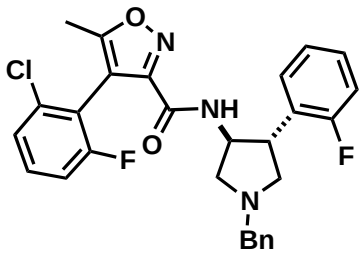

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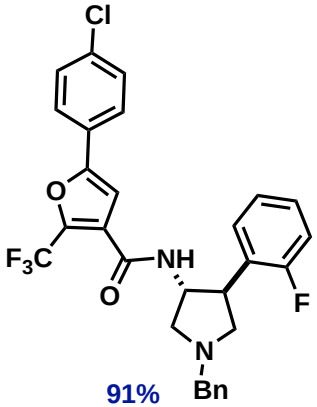

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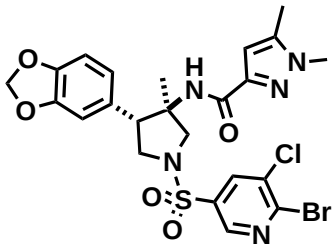

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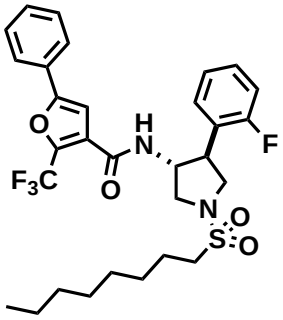

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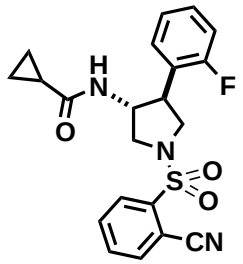

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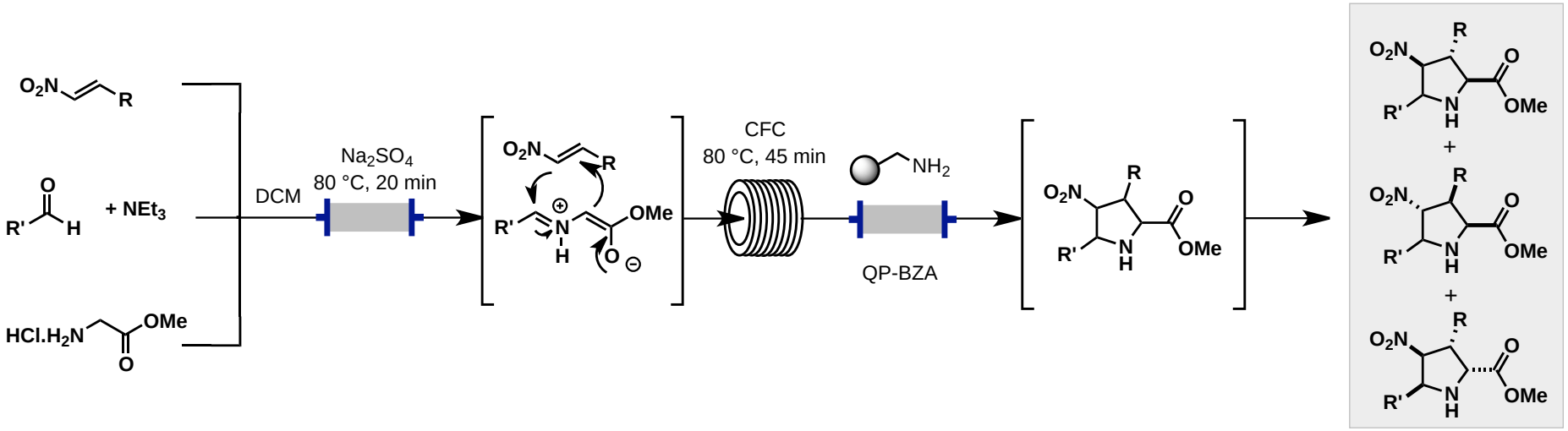
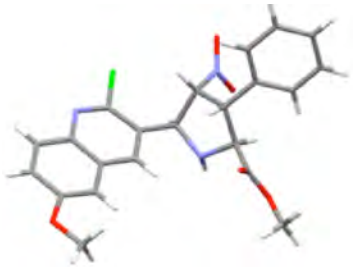
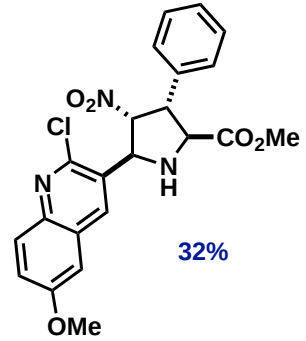
Introduction of Substituents and the 2- and 5- Position



Initial Results for Tri- and Tetra-Substituted Pyrrolidines

- Yields 70-80 %, in-line purification (QP-BZA) gives ~ 95% pure mixture of 3-4 diastereoisomers.
- When using L-proline-OMe only one pyrrolizidine diastereoisomer was obtained preferentially (up to *dr* 13:1:1) yields > 70%.





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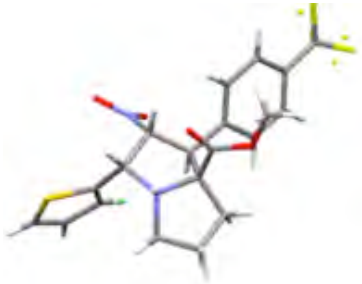

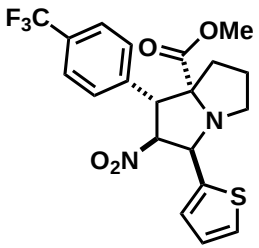

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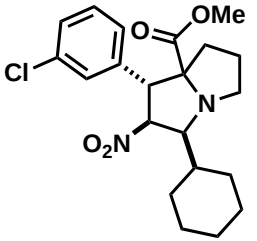

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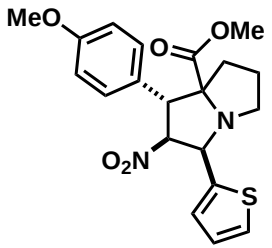

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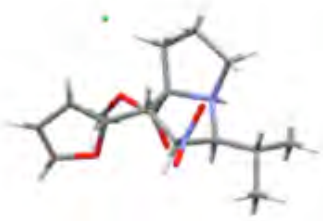

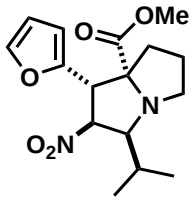

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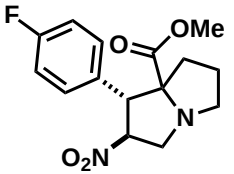

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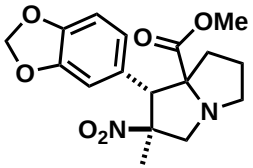
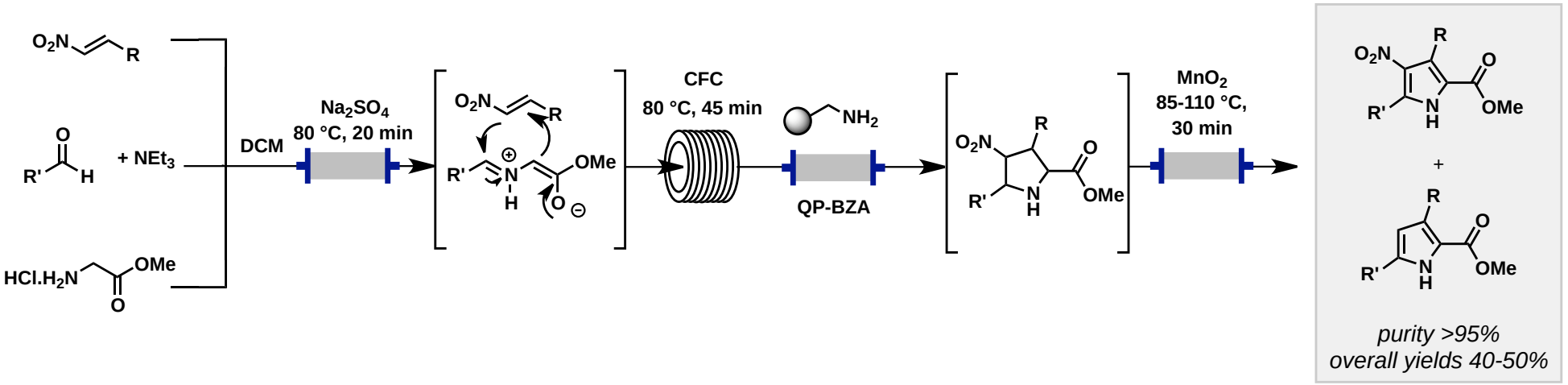
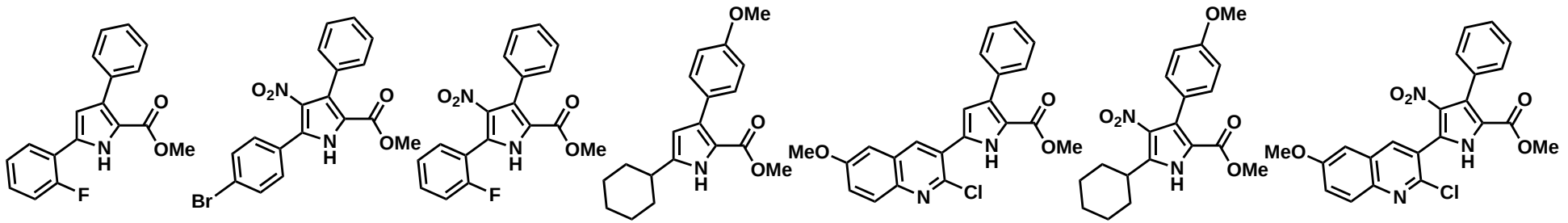


83%
dr 1:1

M. Baumann, I.R. Baxendale, J. Wegner, A. Kirschning, S.V. Ley, *Heterocycles*, **2010**, DOI: 10.3987/COM-10-S(E)77

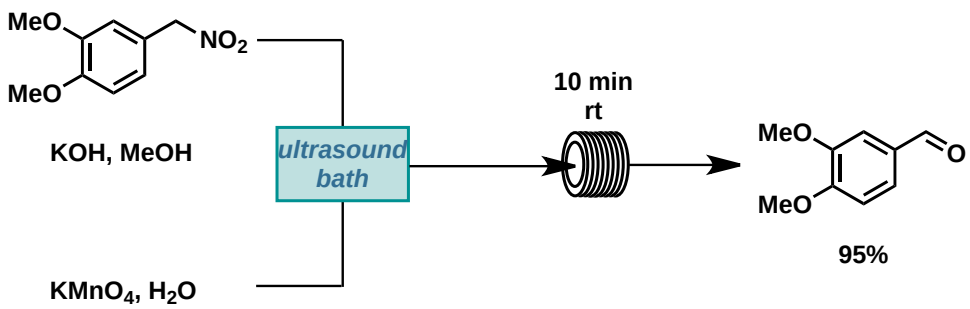
Flow Oxidation of Pyrrolidines to Pyrroles



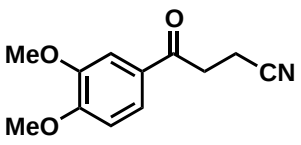


M. Baumann, I.R. Baxendale, J. Wegner, A. Kirschning, S.V. Ley, *Heterocycles*, **2010**, DOI: 10.3987/COM-10-S(E)77

Oxidative Transformations Using Nitro Compounds



Pulsed ultrasonication efficiently pumped MnO_2-slurry generated in the process without reactor fouling/blocking



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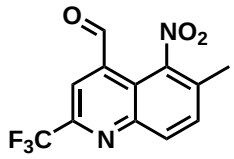

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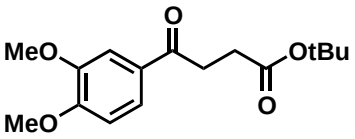

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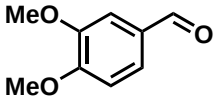

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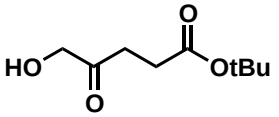

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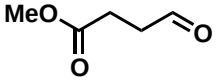

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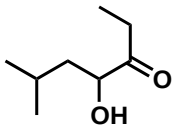

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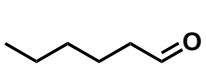

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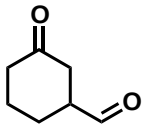

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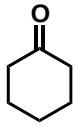

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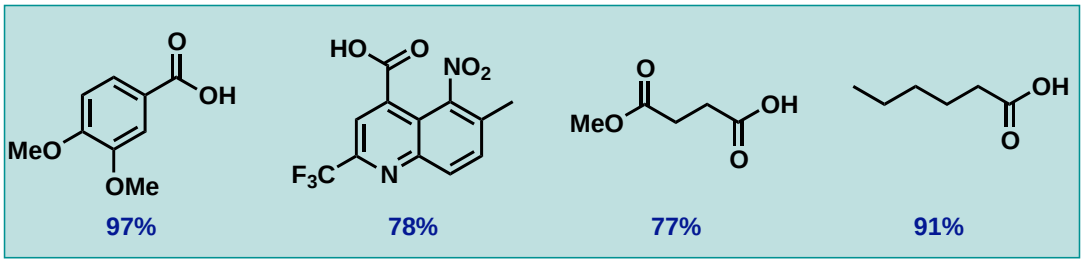
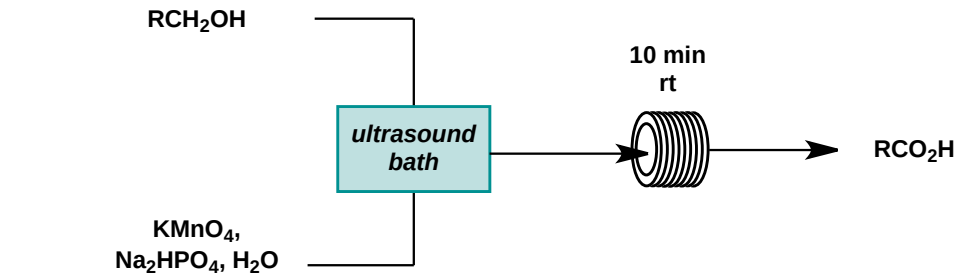
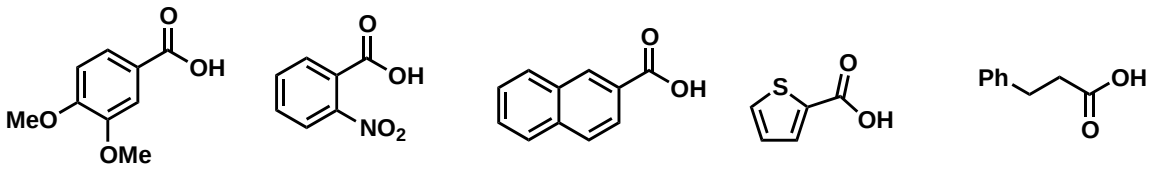


Oxidative Transformations Using Nitro Compounds





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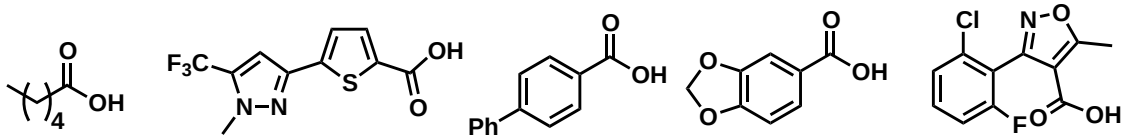
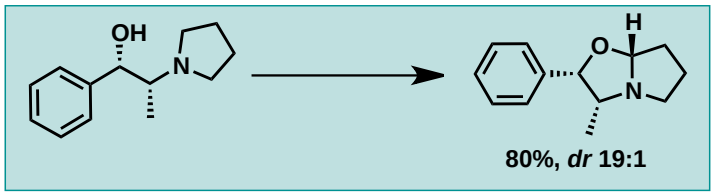


81% 83% 89% 79% 87%



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