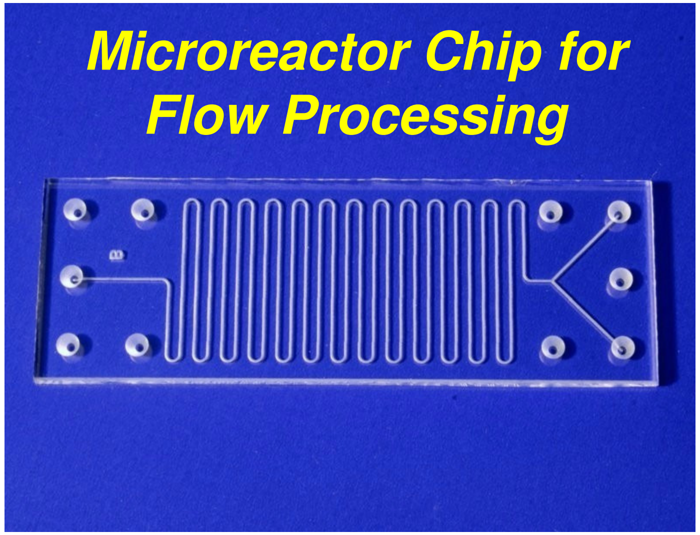
UK Flow Chemistry Seminar - Cambridge, 17th February 2009

Continuous Flow Processing Utilizing High Temperature/Pressure Conditions

Toma N. Glasnov, Ph.D
Christian Doppler Laboratory for Microwave Chemistry (CDLMC)
Institute of Chemistry, University of Graz
Heinrichstrasse 28, A-8010 Graz, Austria
toma.glasnov@uni-graz.at
www.maos.net

Advantages of Flow Chemistry

- Rapid heat transfer and temperature control of the reaction system
- Reaction temperature above the solvent's boiling point can be used
- Very efficient mixing of the reactants
- Automated reaction optimization – on the fly changes
- Multi step reactions in a continuous sequence
- Easy scale-up of a proven reaction by:
  - increase of time
  - reactor volume change
  - parallel processing
- Automated purification possible by:
  - Solid phase scavenging
  - Chromatographic separation
  - Liquid/liquid extraction



Flow Hydrogenations in H-Cube

Features

- A continuous flow of substrate is combined with hydrogen, generated in-situ from the electrolysis of water

- The hydrogen/substrate mixture can be heated and pressurized up to 100℃ and 100 bar respectively

- The mixture passes through a packed catalyst cartridge (CatCart®), where the reaction takes place

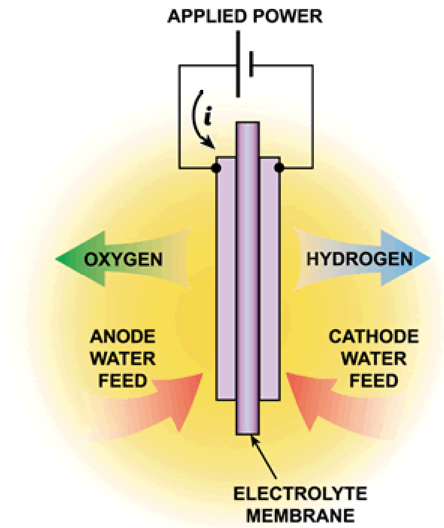
Advantages

Safer
- No gas cylinders or other external hydrogen source
- No catalyst filtration or direct catalyst handling
- Easy catalyst exchange

Efficient
- Analyze reaction results after 2 minutes
- Perform up to 50 different validation conditions in a day
- Higher reaction rates with increased phase mixing
- Easy to use, touch screen controlled

Convenient
- Compact size
- Can be coupled to standard liquid-handling robots

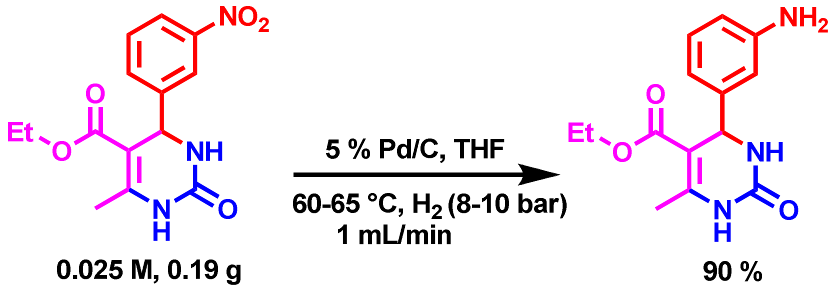
THALESNano



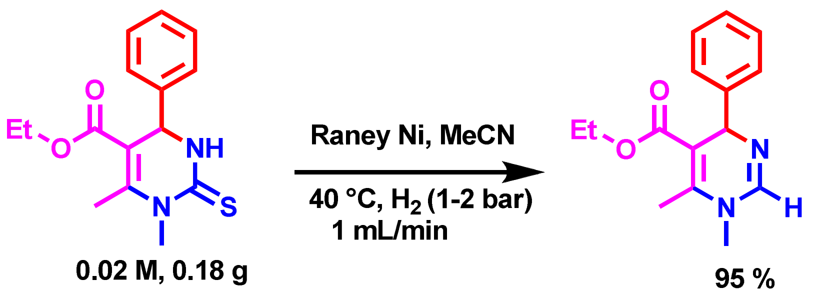
Continuous Flow Hydrogenations (H-Cube, 2005)

Debenzylation

Nitro Reduction

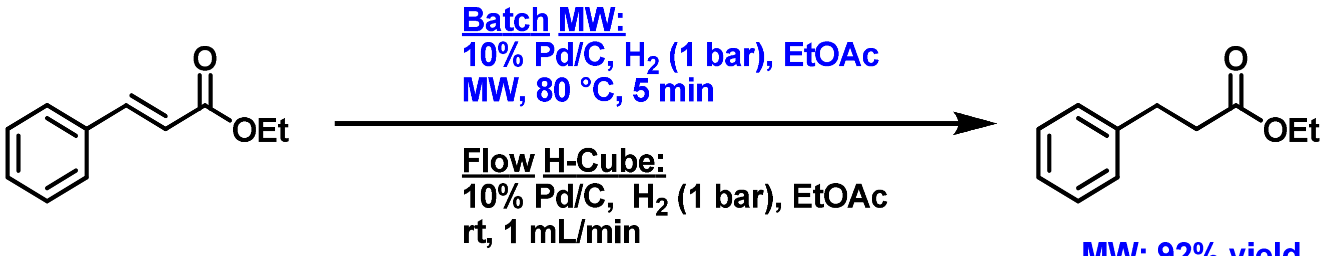


Desulfurization

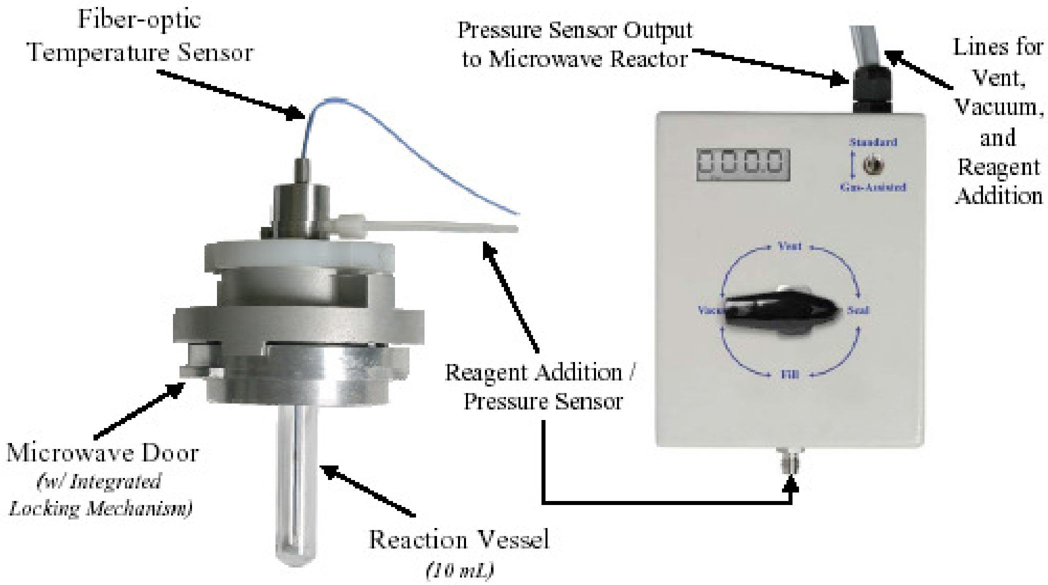


Desai, B.; Kappe, C. O. *J. Comb. Chem.* **2005**, *7*, 641

Hydrogenation of Ethyl Cinnamate



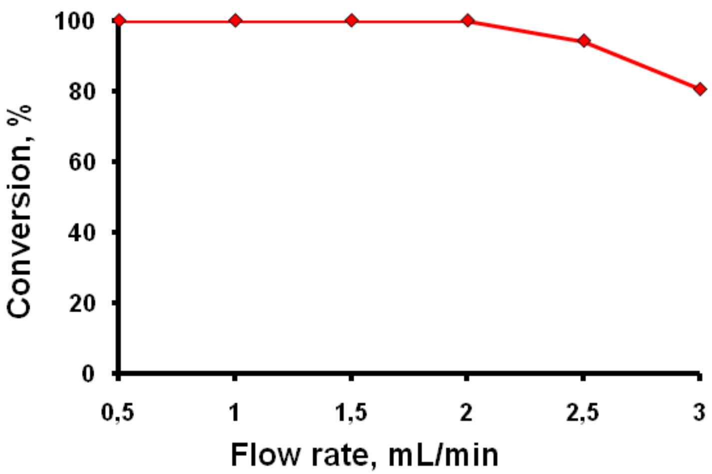
MW: 92% yield
H-Cube: 89% yield



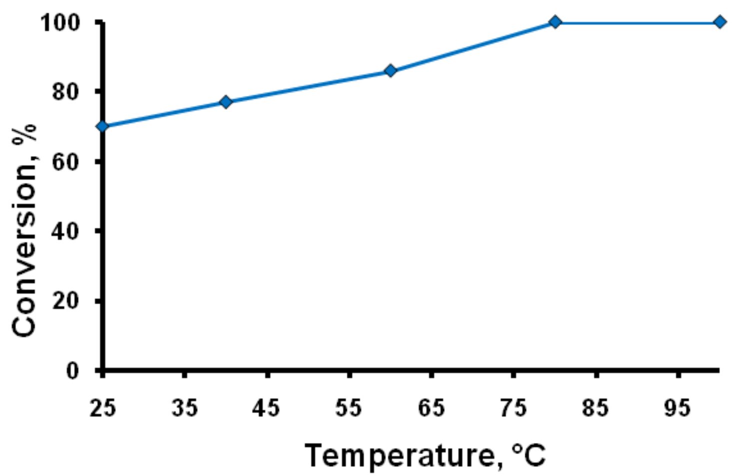
Vanier, G. S. *Synlett* **2007**, 131

Hydrogenation of Ethyl Cinnamate
Flow and Temperature Optimization

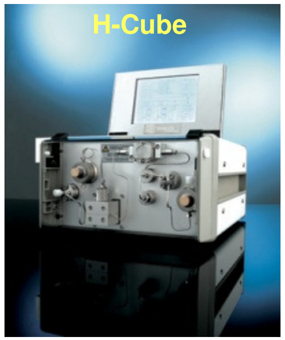
Flow Influence (0.1 M, rt)

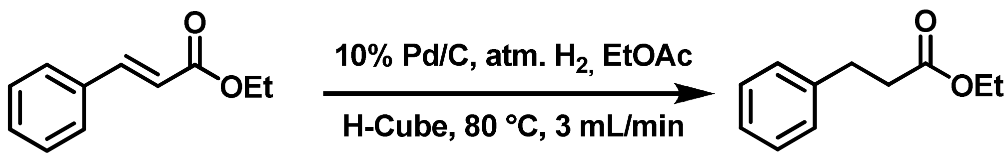


Temperature Influence (0.2 M, 3 mL/min)



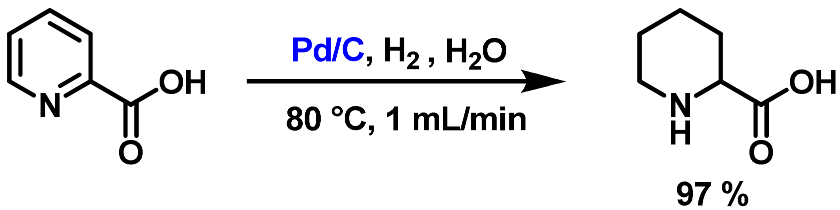
Scale-Up Run – 10 mmol (0.2 M)





~ 2 g; ~90% yield

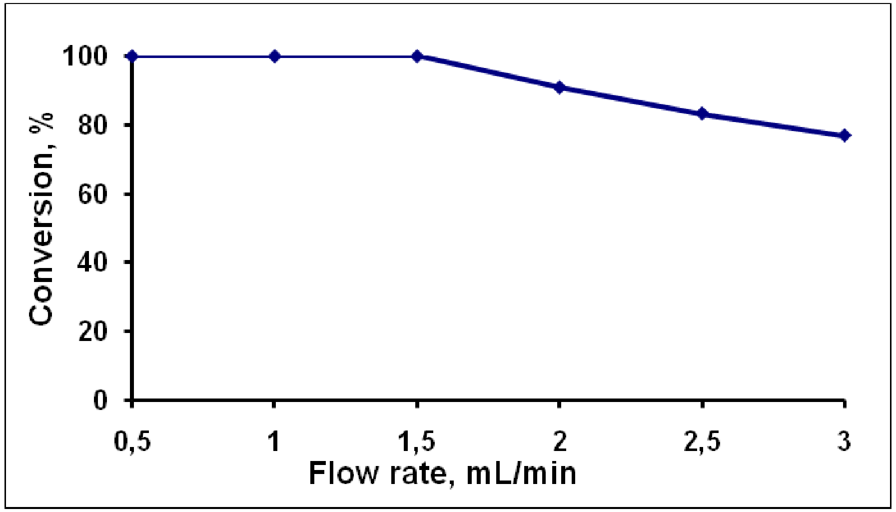
Hydrogenation of Picolinic Acid (H-Cube)



Optimization:

Temperature:	rt – 80 °C
Concentration:	0.01 – 0.1 M
Pressure:	atm – 10 bar
Solvent:	EtOAc, EtOH, H_2O
Flow Rate:	0.5 – 1 mL/min

Kinetic Profile in Water (80 °C, 0.1 M)

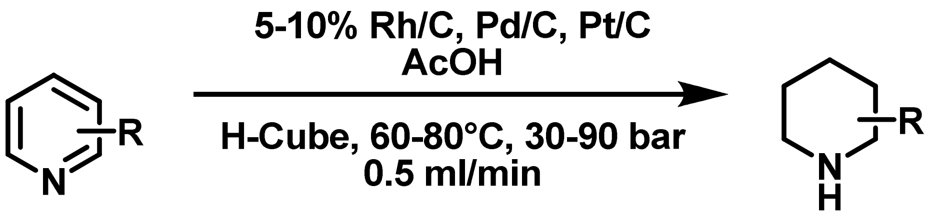


Best Conditions (Full Conversion, 0.1 M):

EtOH, 80 °C, H_2 (1 bar), 0.5 mL/min,100% conv

H_2O, H_2 (1 bar), 80 °C, 1.5 mL/min,100% conv

Hydrogenation of Substituted Pyridines (H-Cube)

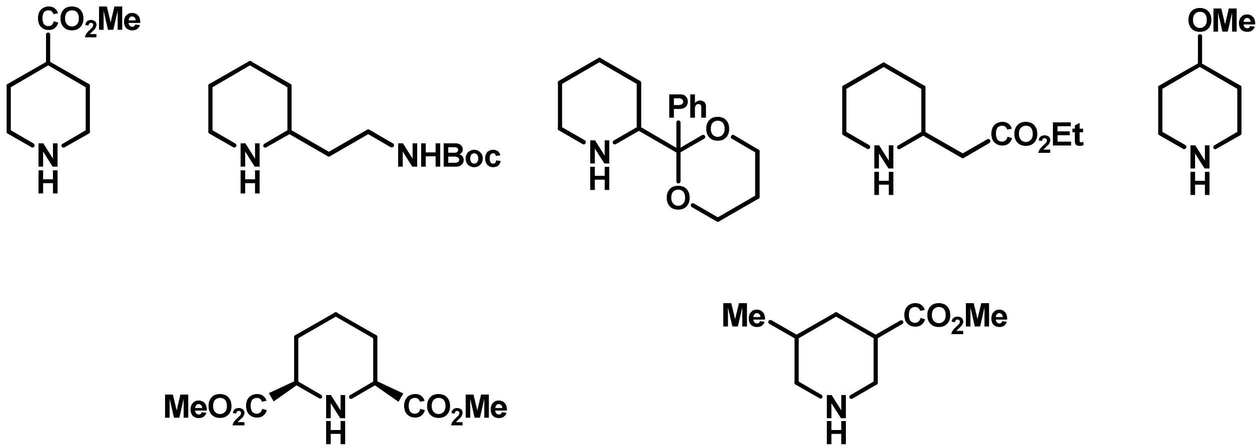


7 examples
(74-93 %)

MW batch conditions (PtO_2):
AcOH, 8 bar H_2, 80 °C, 20-60 min

Piras, L. et al. *Synlett* **2008**, 1125

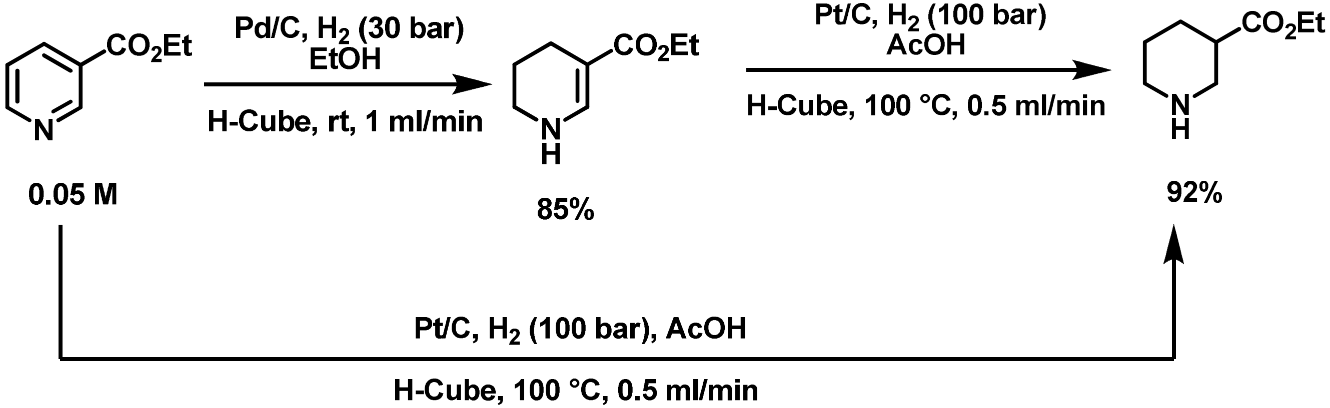
Products:



cis
(> 99%)

***cis/trans* mixture**
(~ 1:1 ratio)

Hydrogenation of Ethyl Nicotinate – Tuning Selectivity

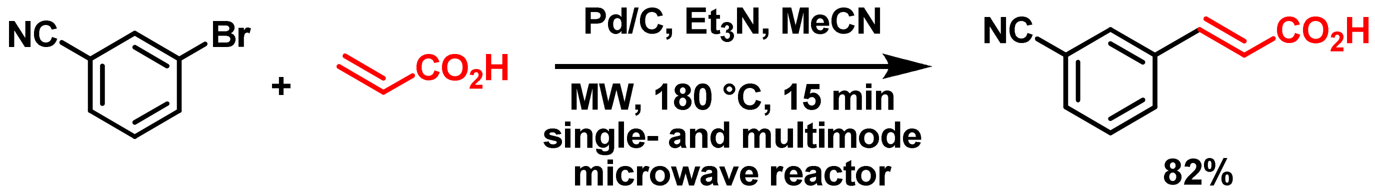


Deuteration of Ethyl Cinnamate with D_2

Irfan, M.; Petricci, E.; Glasnov, T. N.; Taddei, M.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, doi: 10.1002/ejoc.200801131

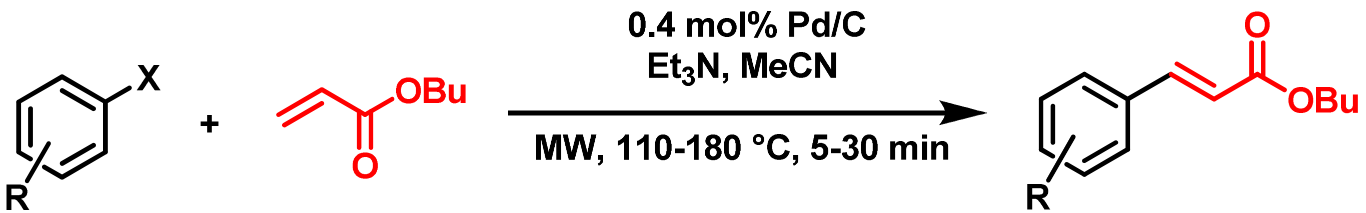
Heck C-C Coupling of 4-Iodo and 3-Bromobenzonitrile with *n*-Butylacrylate

Literature Background



Stadler, A. et al. *Org. Process Res. Dev.* **2003**, *7*, 707
Degussa Pd/C: Köhler, K. et al. *Chem. Eur. J.* **2002**, *8*, 622

Example for Batch and Flow Chemistry

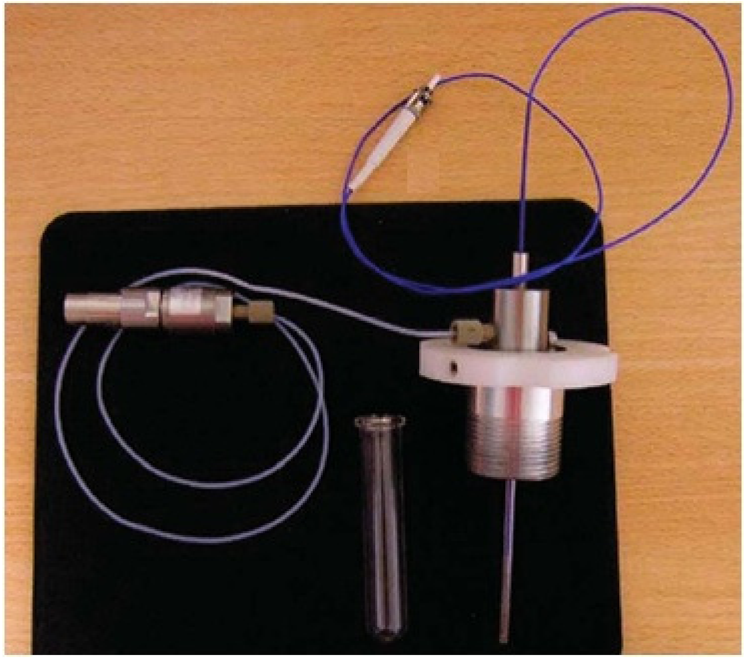


X = I, R = 4-CN
X = Br, 3-CN

cf. Nikbin, N.; Ladlow, M.; Ley, S. *Org. Process Res. Dev.* **2007**, *11*, 458 (monolithic nanoparticles)
cf. K. Mennecke, W. Solodenko, A. Kirschning, *Synthesis* **2008**, 1589 (immobilized palladacycles)

Accurate Comparison of Oil Bath and MW Experiments

Fiber-Optic (FO) Temperature Measurement

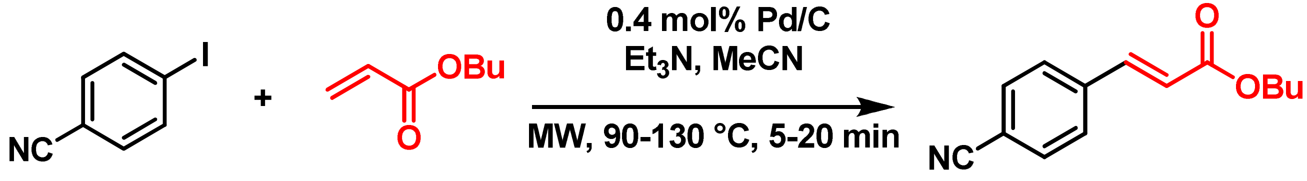


sealed vessel reactor system (10 mL) with FO probe can be inserted in oil bath or mw reactor

- same reaction vessel
- same temp measurement
- identical stirring speed

Hostyn, S.; Maes, B. U. W. et al. *Tetrahedron* **2006**, *62*, 4676

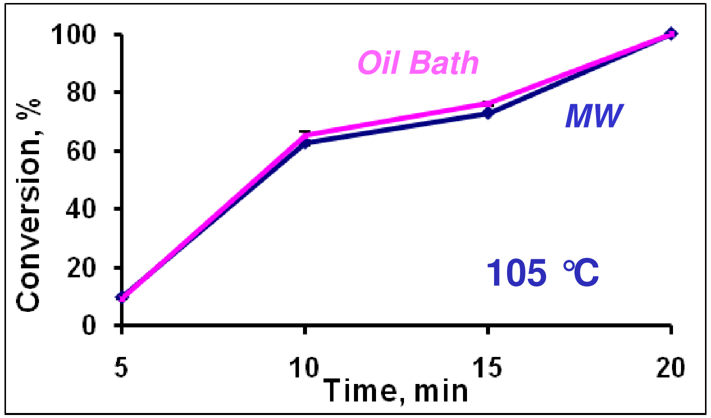
Heck Reaction: Microwave Versus Oil Bath Heating

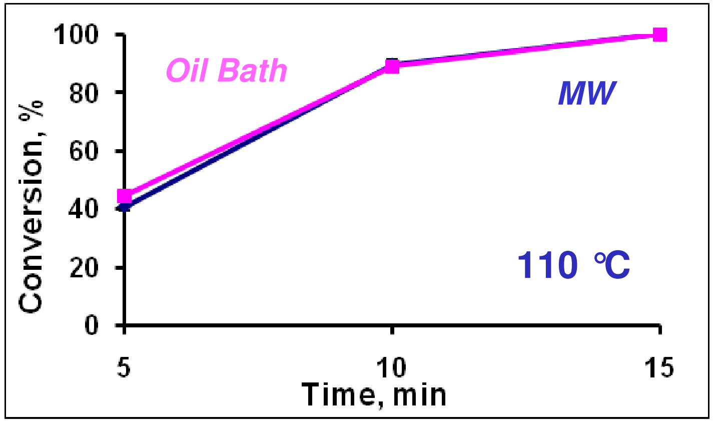


ca 80 °C (reflux): >99% conv after 3 h
90 °C: <1% conv after 20 min
130 °C: >99% conv after 5 min (96% isol. yield)
150 °C: >99% conv after 2 min
105-110 °C: suitable for kinetic studies

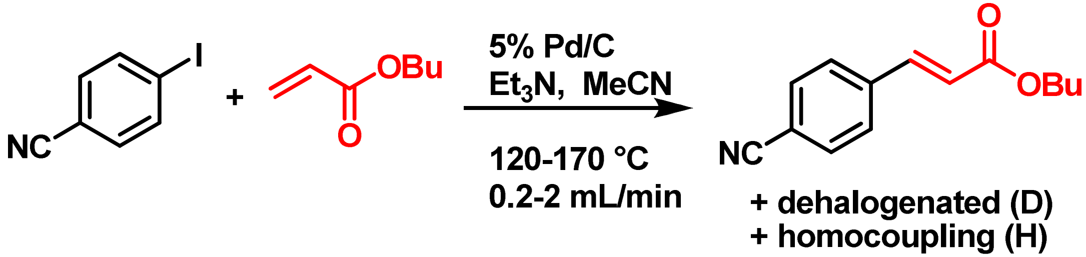
0.4 mol% (6.5 mg 5% Pd/C)
0.65 mmol aryliodide/arylbromide
1.5 equiv Et_3N, 1.5 equiv butyl acrylate
1 mL MeCN

Kinetic Analysis (GC-FID)

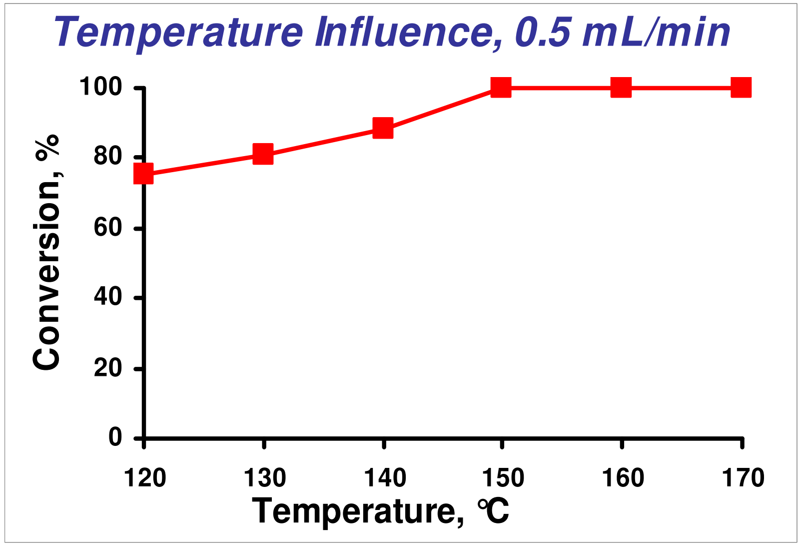


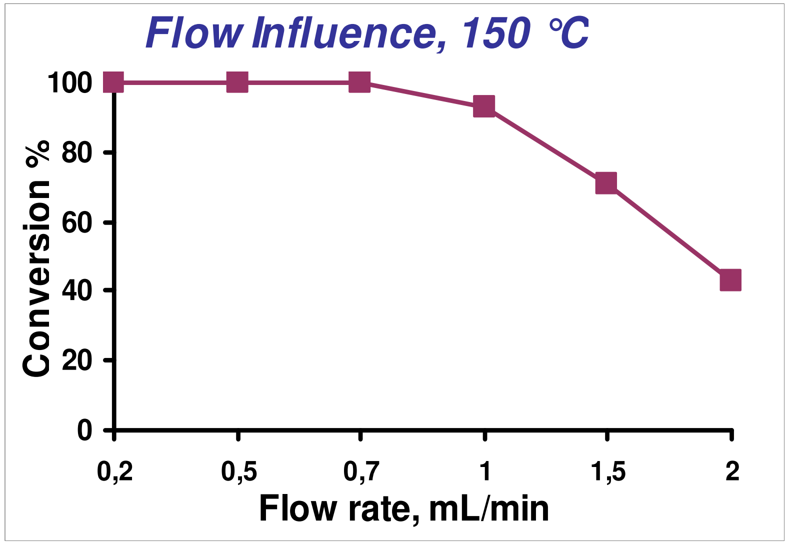


Heck Chemistry under Flow Conditions (Pd/C)



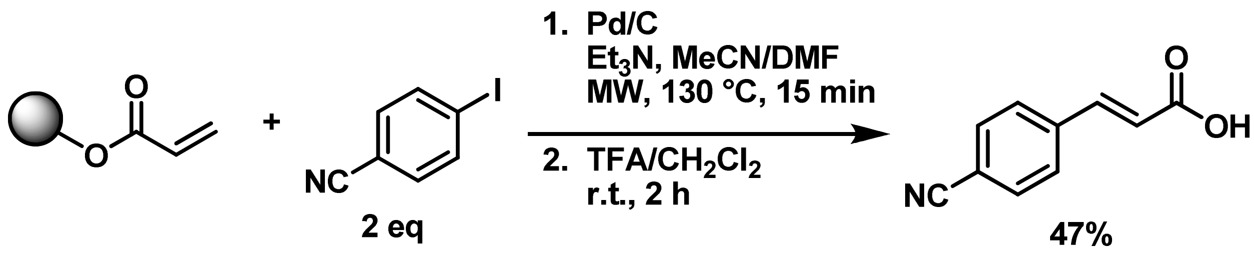
X-Cube
(200 °C, 150 bar)
www.thalesnano.com





Homogeneous vs. Heterogeneous?

Three-Phase Test (Batch)



Cf. Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 10139

Homogeneous Process: Reaction proceeds via leaching of Pd from Pd/C into solution with readsorption onto the support

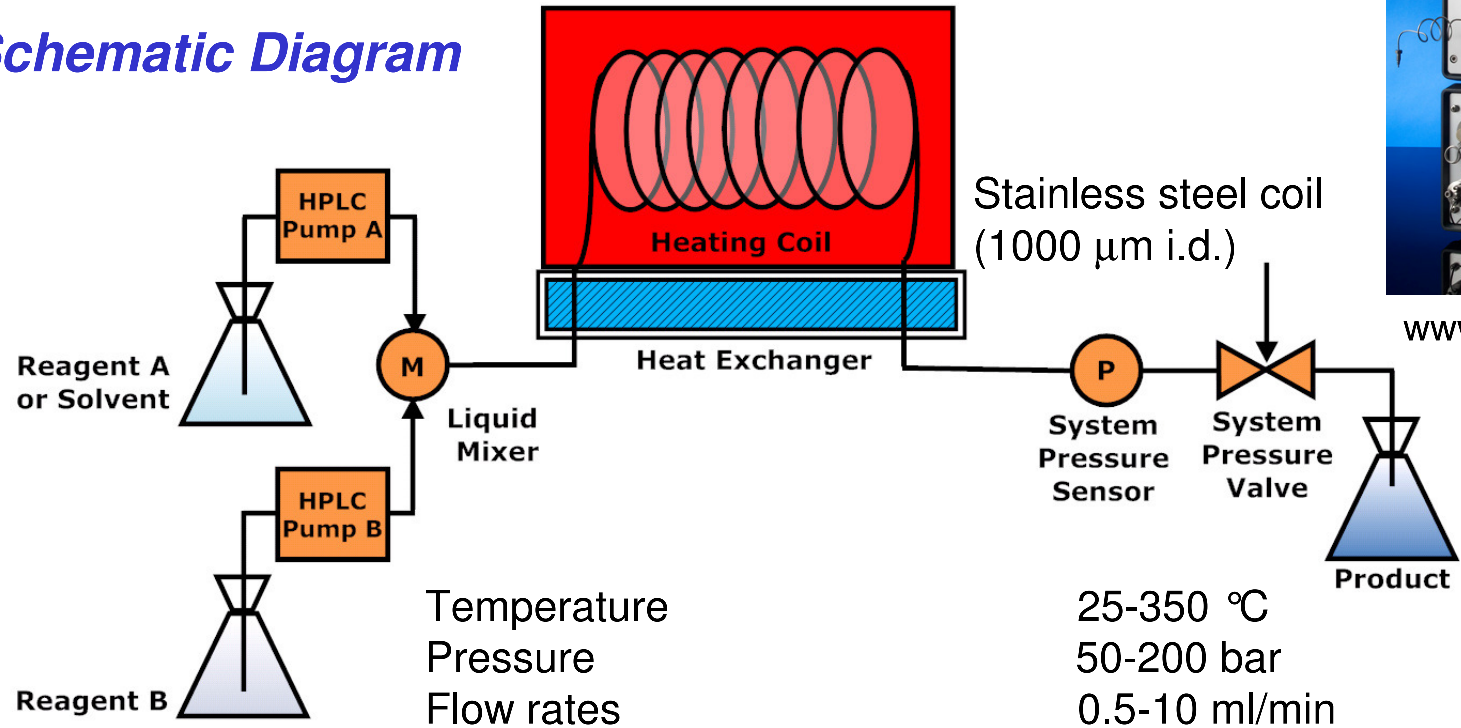
Follow-Up Problems in Flow

- decreased selectivity (high catalyst loading)
- leaching (ICP-MS)
- chromatography effect

Glasnov, T. N; Findenig, S.; Kappe, C. O. *Chem. Eur. J.* **2009**, *15*, 1001

High-Temperature/Pressure Flow Reactor (X-Cube Flash)

Schematic Diagram

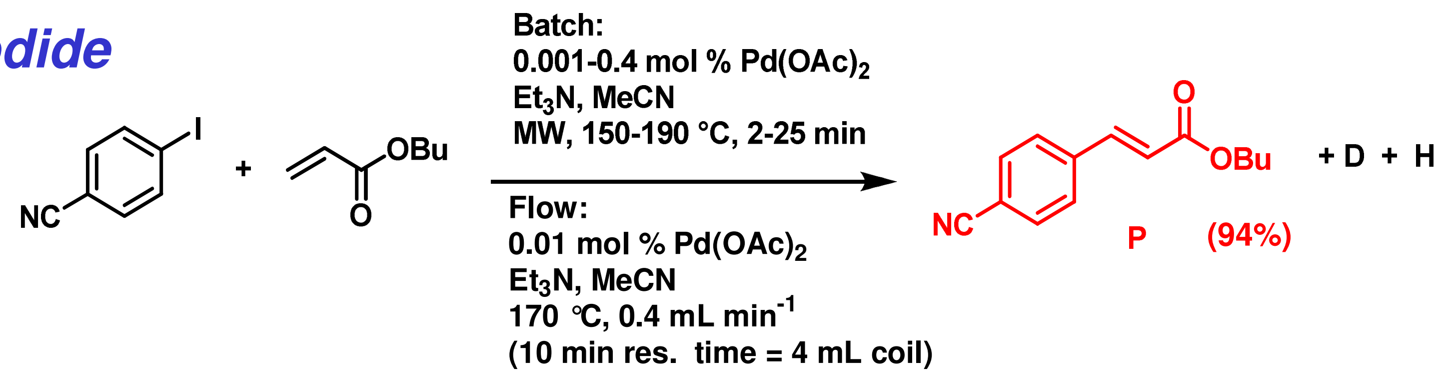


Temperature	25-350 °C
Pressure	50-200 bar
Flow rates	0.5-10 ml/min
Changeable size of reaction zone	4,8,16 mL

Razzaq, T.; Glasnov, T. N.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, **doi:**10.1002/ejoc.200900077

Heck Chemistry (MW / Flow) – Homogeneous Catalysis with $Pd(OAc)_2$

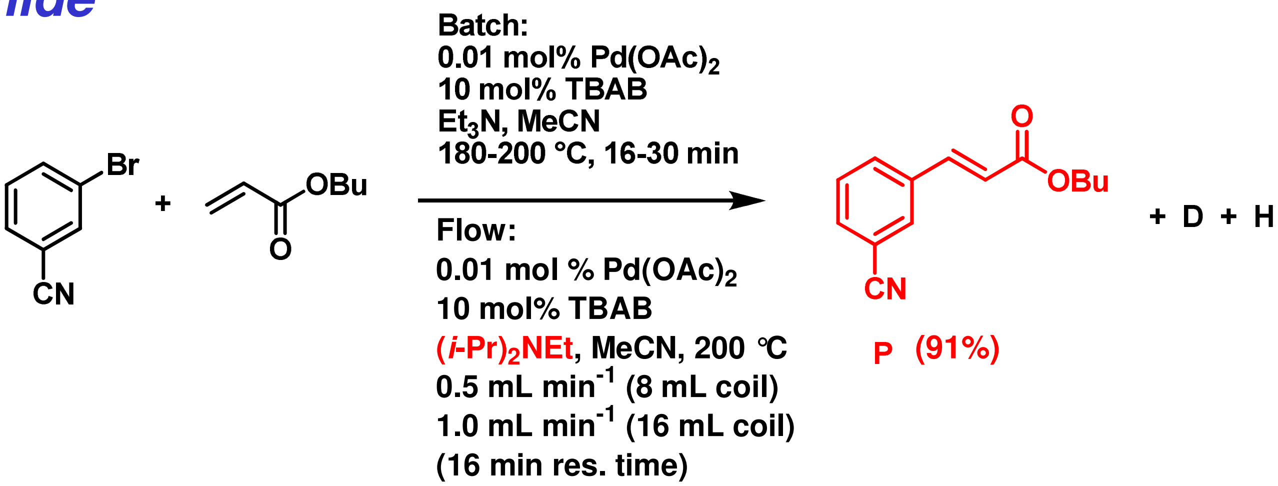
Aryl Iodide



Entry	Conditions	$Pd(OAc)_2$ [mol%]	Temp [°C] / Time [min]	Conversion [%, GC-FID]	Selectivity P/D/H [%, GC-FID]
1	Batch/MW	0.4	150 / 2	>99	89 / 5 / 6
2	Batch/MW	0.1	150 / 2	>99	93 / 2 / 5
3	Batch/MW	0.05	150 / 5	>99	98 / 1 / 1
4	Batch/MW	0.01	150 /25	>99	99 / <1 / 0
5	Batch/MW	0.01	170 / 10	>99	99 / <1 / 0
6	Batch/MW	0.001/ 10 mol% TBAB	190 / 15	>99	99 / <1 / 0
7	Batch/OB	0.01	150 / 25	>99	99 / <1 / 0

Heck Chemistry (MW / Flow) – Homogeneous Catalysis with $Pd(OAc)_2$

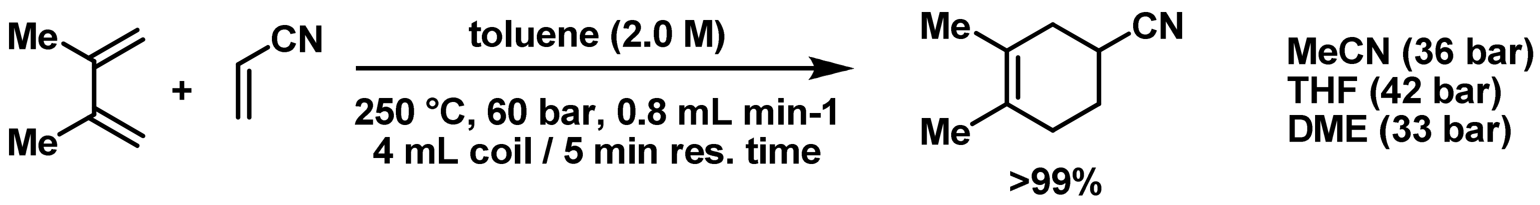
Aryl Bromide



Entry	Conditions	$Pd(OAc)_2$ [mol%]	Temp [°C] / Time [min]	Conversion [%, GC-FID]	Selectivity P/D/H [%, GC-FID]
1	Batch/MW	0.01	180 / 30	90	**99** / <1 / 0
2	Batch/MW	0.01	200 / 16	>99	**99** / <1 / 0
3	Flow (1 mL min^{-1})	0.01	200 / 16	>99	**99** / <1 / 0

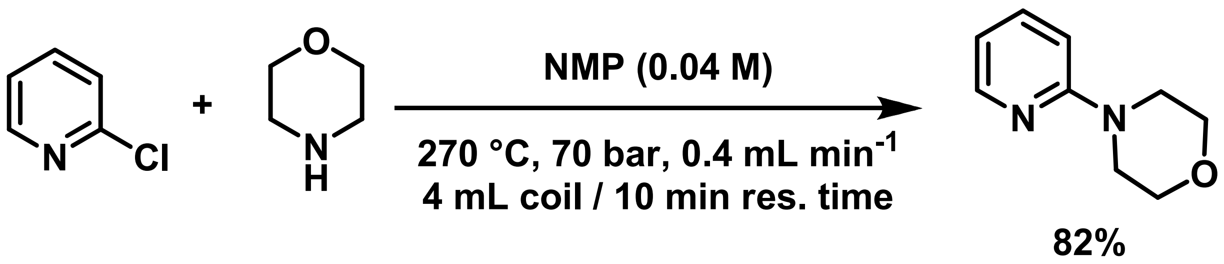
High-Temperature / High-Pressure Flow Chemistry (X-Cube Flash)

Diels-Alder Reaction



cf. MW conditions (toluene, 250 °C, 10 min): Kremsner, J. M.; Kappe, C. O. *J. Org. Chem*. **2006**, *51,* 4651

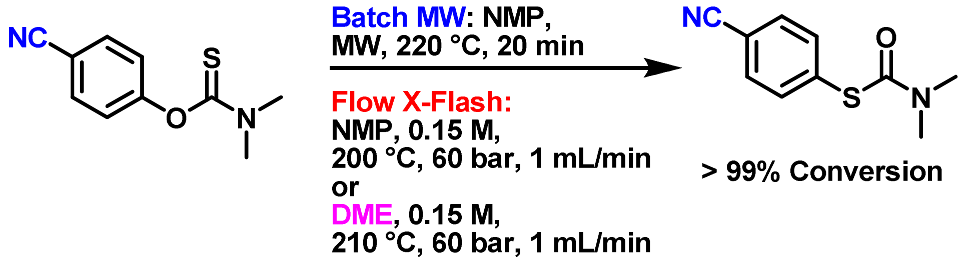
Nucleophilic Aromatic Substitution

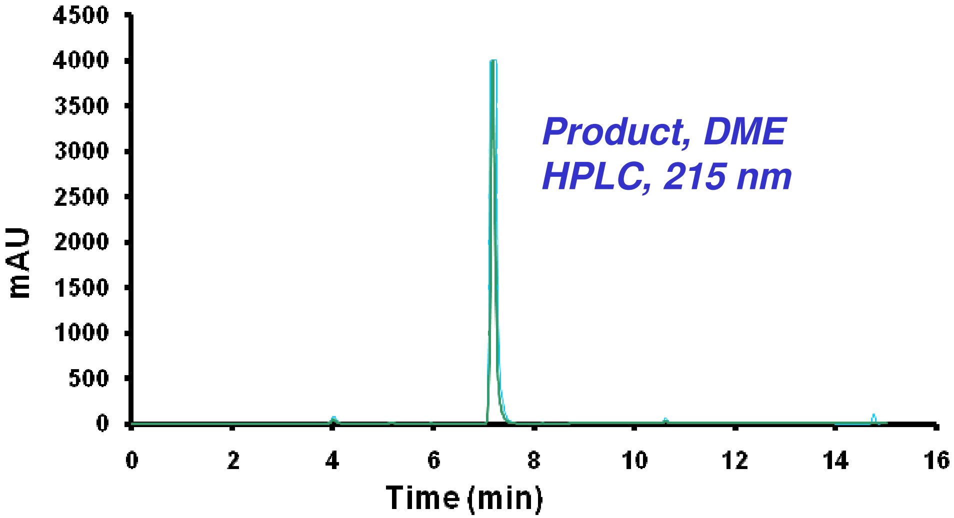


cf. MW/flow reaction: Hamper, B. C.; Tesfu, E. *Synlett* **2007**, 2257

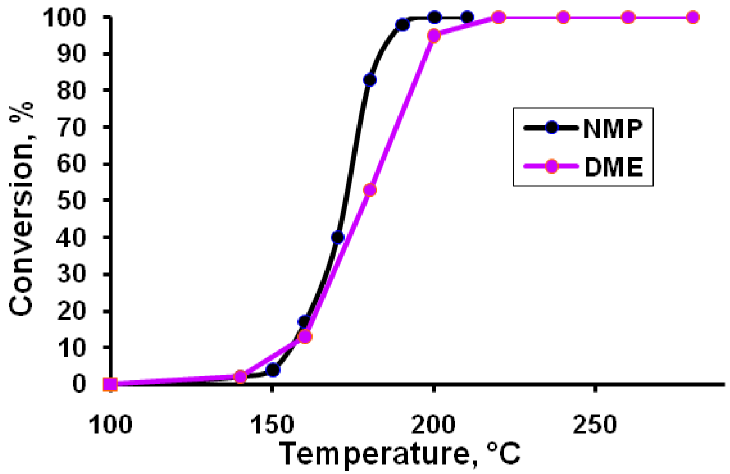
Newmann-Kwart Rearrangement – MW vs. Flow Experiments

"Easy" Case





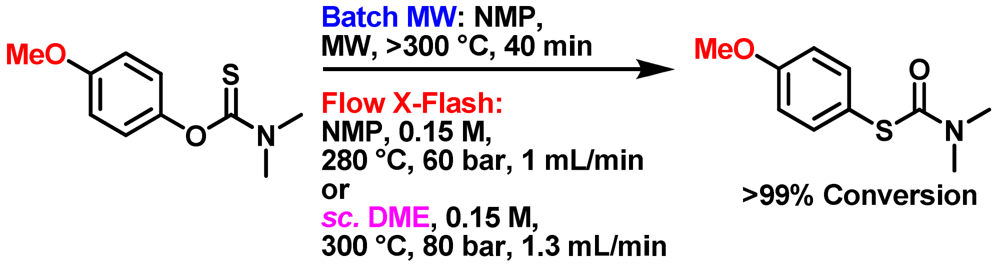
Kinetic Analysis (HPLC)



Moseley, J. D. et al. *Tetrahedron*, **2006,** *62,* 4685; Moseley, J. D.; Lenden, P. *Tetrahedron*, **2007,** *63,* 4120

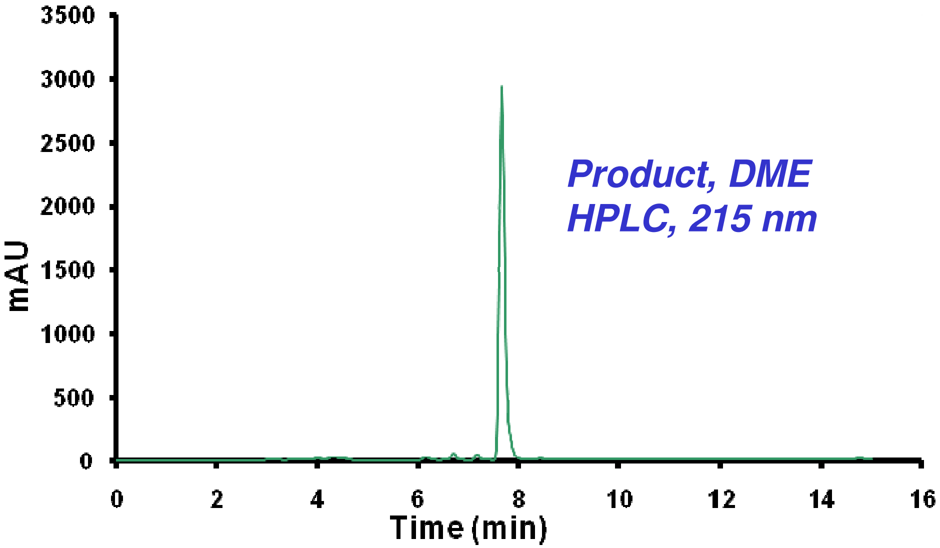
Newmann-Kwart Rearrangement – MW vs. Flow Experiments

"Difficult" Case

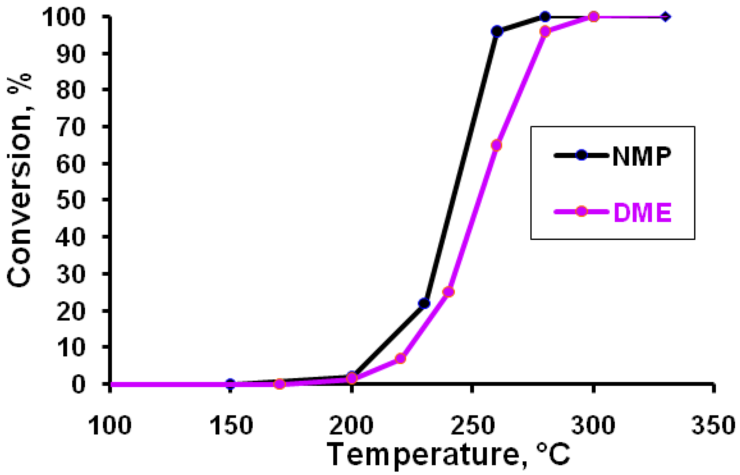


sc. DME

critical point:
263 °C; 39 bar

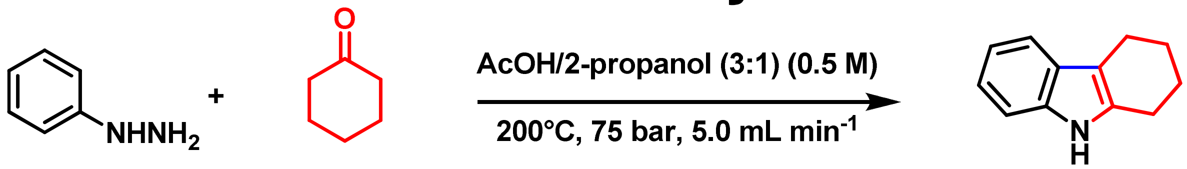


Kinetic Analysis (HPLC)



Moseley, J. D. et al. *Tetrahedron*, **2006**, *62*, 4685; Moseley, J. D.; Lenden, P. *Tetrahedron*, **2007**, *63*, 4120

Fischer Indole Synthesis



96 %

cf. MW reaction: Bagley, M. C.; et al. *J. Org. Chem.* **2005,** *70* , 7003

Continuous Flow Results (4 mL or 16 mL Coil)

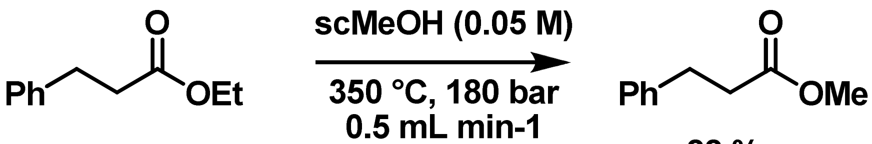
In AcOH/2-propanol (3:1) (0.5M)
150 ℃, 60 bars,
1.0 mL min^{-1} (4 min res. time)
88% isolated yield

Scale-up
200 ℃, 75 bars,
5.0 mL min^{-1} (~3 min res. time)
96% isolated yield

➡ 25 g indole/hour

Reactions in Supercritical Alcohols

Transesterification

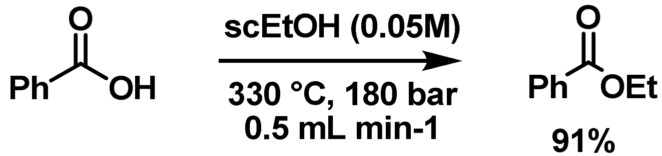


88 %

MeOH
T_c = 239 °C, P_c = 81 bar

cf. Socher, G. et al. *Fresensius J. Anal. Chem.* **2001**, *371*, 369

Esterification

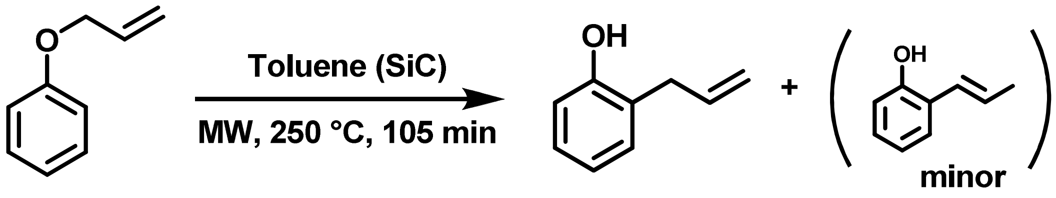


91%

EtOH
T_c = 268 °C, P_c = 61 bar

Claisen Rearrangement

MW Experiments:



cf. Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2006**, 71, 4651.
cf. Razzaq, T.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2008,** *73*, 6321

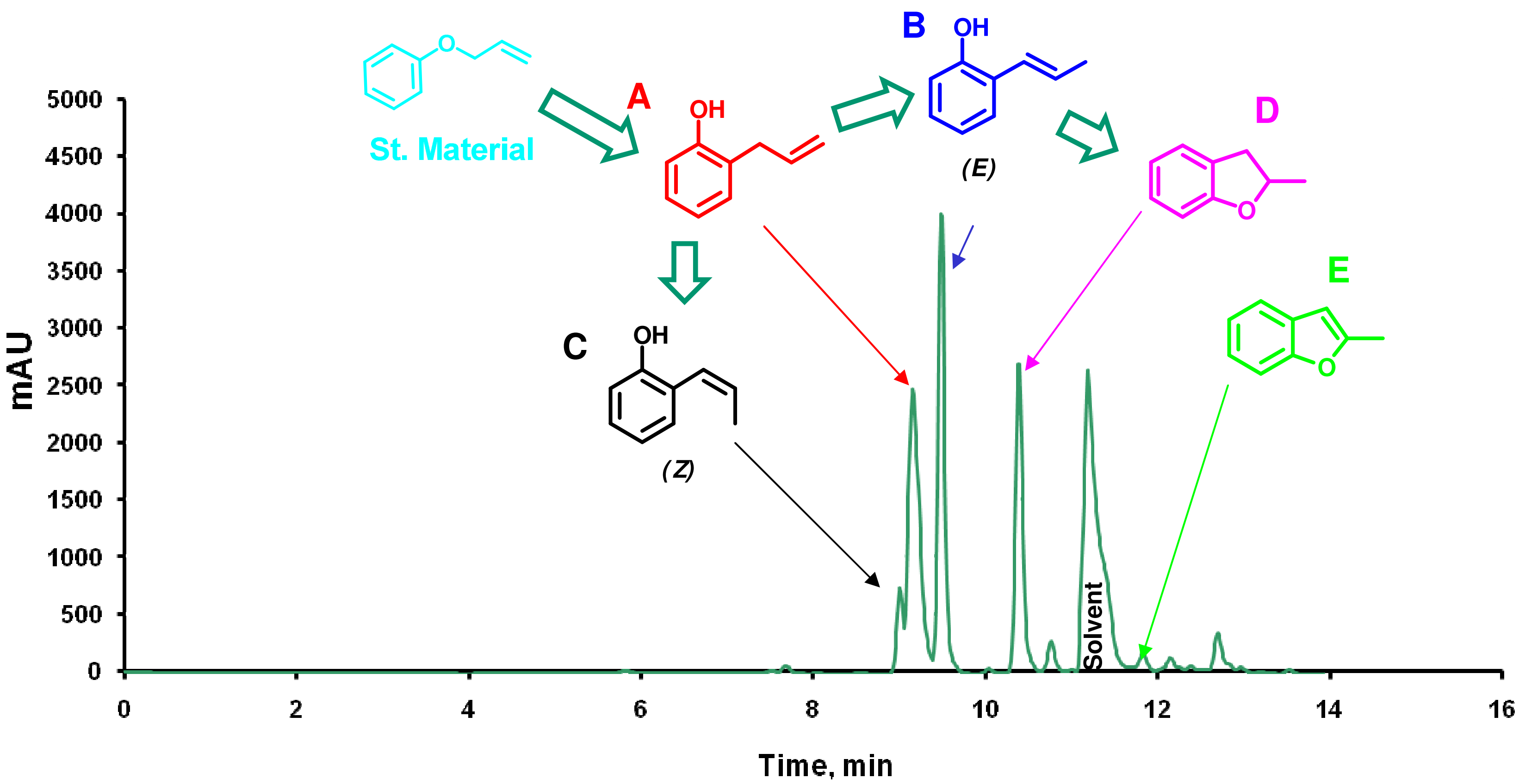
X-Flash Flow Experiments:

Solvents:	NMP, DMF, Toluene, *sc.* EtOH, *sc.*DME
Temperature Range:	275 – 325 °C
Flow Rates:	0.8 – 2 mL/min
Pressure:	60 – 125 bar

Best Conditions (Full Conversion, Cleanest Reaction Profile):

DMF, 275 °C, 60 bars, 2 ml/min
sc. EtOH (T = 268 °C, Pressure = 61 bar), 285 °C, 75 bars,1 mL/ min

Claisen Rearrangement – High Temperature Reaction Pathways (Toluene, 315 °C)



Christian Doppler Laboratory for Microwave Chemistry

A Public-Private-Partnership Initiative (2006-2013)

CHRISTIAN DOPPLER FORSCHUNGSGESELLSCHAFT

Prof. C. Oliver Kappe

Muhammad Irfan
Tahseen Razzaq
Dr. Elena Petricci
Silvia Findenig (ICP-MS)

Christian Doppler Society (CDG)
Austrian Science Fund (FWF)
Austrian Research Promotion Agency (FFG)
European Union COST, Land Steiermark
BM:BWK, Österreichische Nationalbank (ÖNB)

THALESNano

pi CHEM research & development

Anton Paar

BASF The Chemical Company

Biotage
CEM
Milestone

Novartis, Abbott
Boehringer Ingelheim
Organon, BASF