Leibniz Universität Hannover

“Enabling Technologies in Organic Chemistry – From Minireactors to New Heating Techniques”

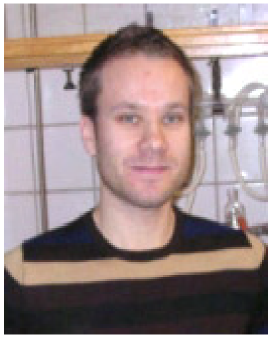
Andreas Kirschning

1st RSC/SCI Symposium on Continuous Processing and Flow Chemistry, 3rd – 4th November 2010

Institut für Organische Chemie

BMWZ

The **FLOW** Team



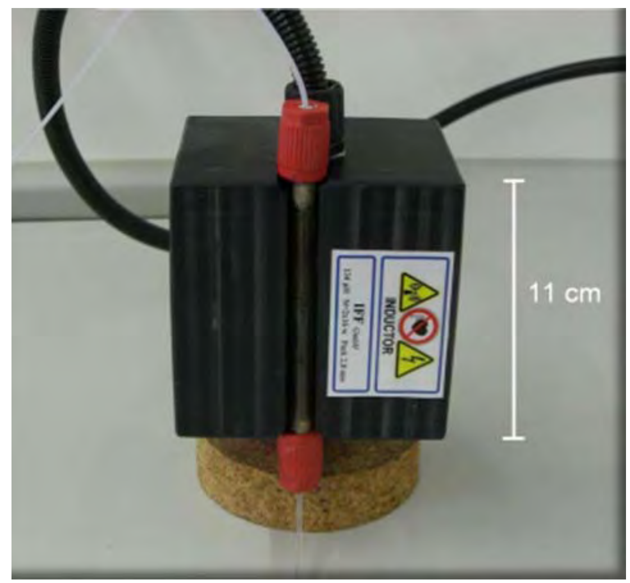
Sascha Ceylan

Jens Wegner

Dr. Ludovic Coutable

Dr. W. Solodenko

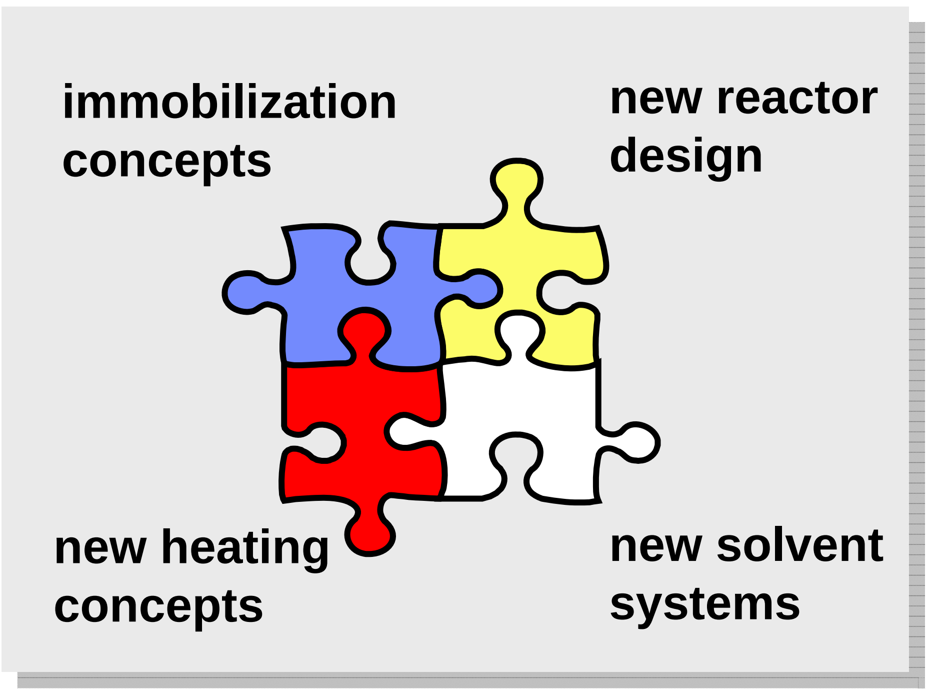
The Tools



Enabling Technologies in Organic Chemistry

Reviews:

A. Kirschning *et al*. *Chem. Eur. J.* **2003**, *9*, 5708-5723.
Chem. Eur. J. **2006**, *12*, 5972-5990.
S. Ceylan, A. Kirschning, *Organic synthesis with mini flow reactors using immobilised catalysts,* John Wiley & Sons **2009**, 379-410.



The ideal technology platform for synthesis combines facilitating technologies in a flexible manner

1st paper on functionalized monoliths within a flow device:

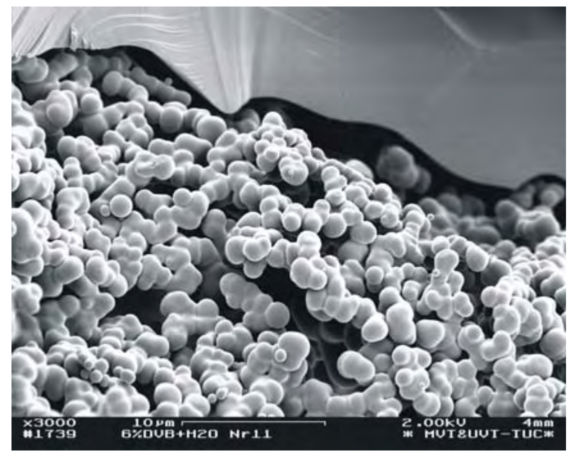
A. Kirschning, U. Kunz *et al. Angew. Chem. Int. Ed.* **2001**, *40*, 3995-3998.

PASSflow syntheses using functionalized monolithic polymer/glass composites in flow-through microreactors

Founding of CHELONA GmbH in 2001.

The PASSflow Reactor

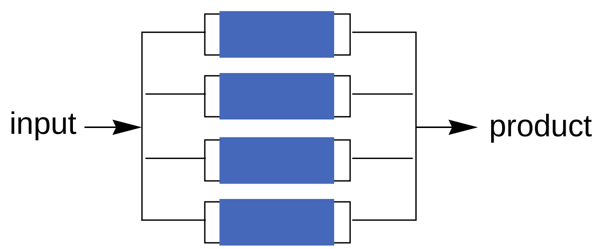
The Synthesizer



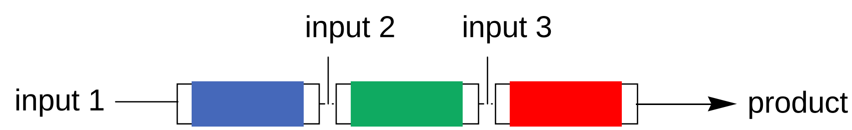
The Monolithic Solid Phase
(Glass/Polymer composite)

Concepts for continuous flow syntheses

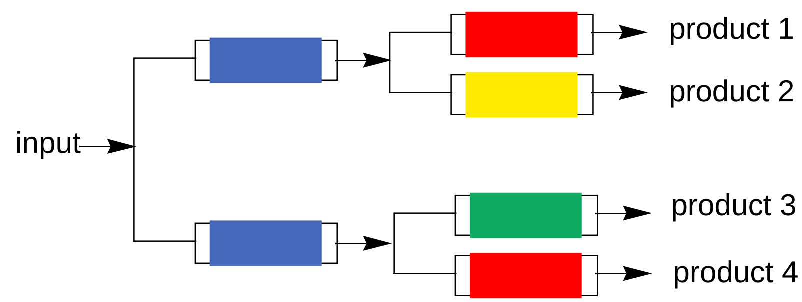
Upscale



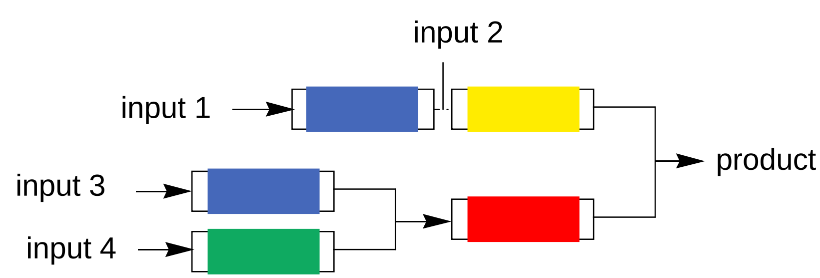
Linear series of flowthrough reactors



Divergent set up of flowthrough reactors

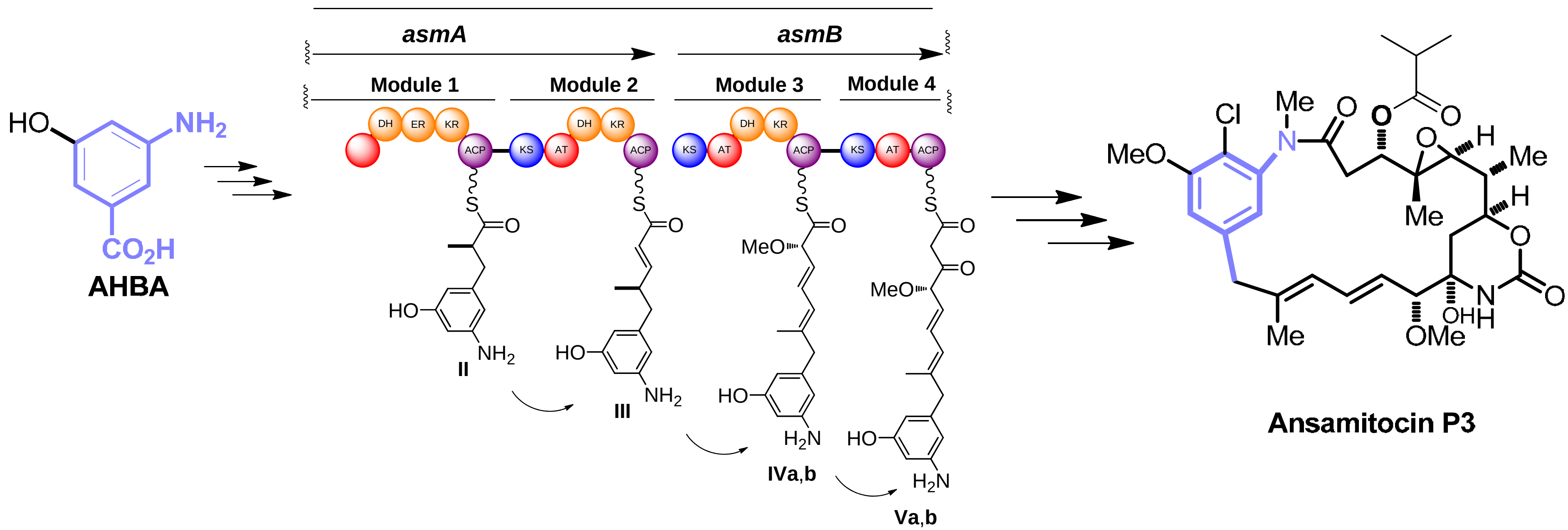


Convergent set up of flowthrough reactors

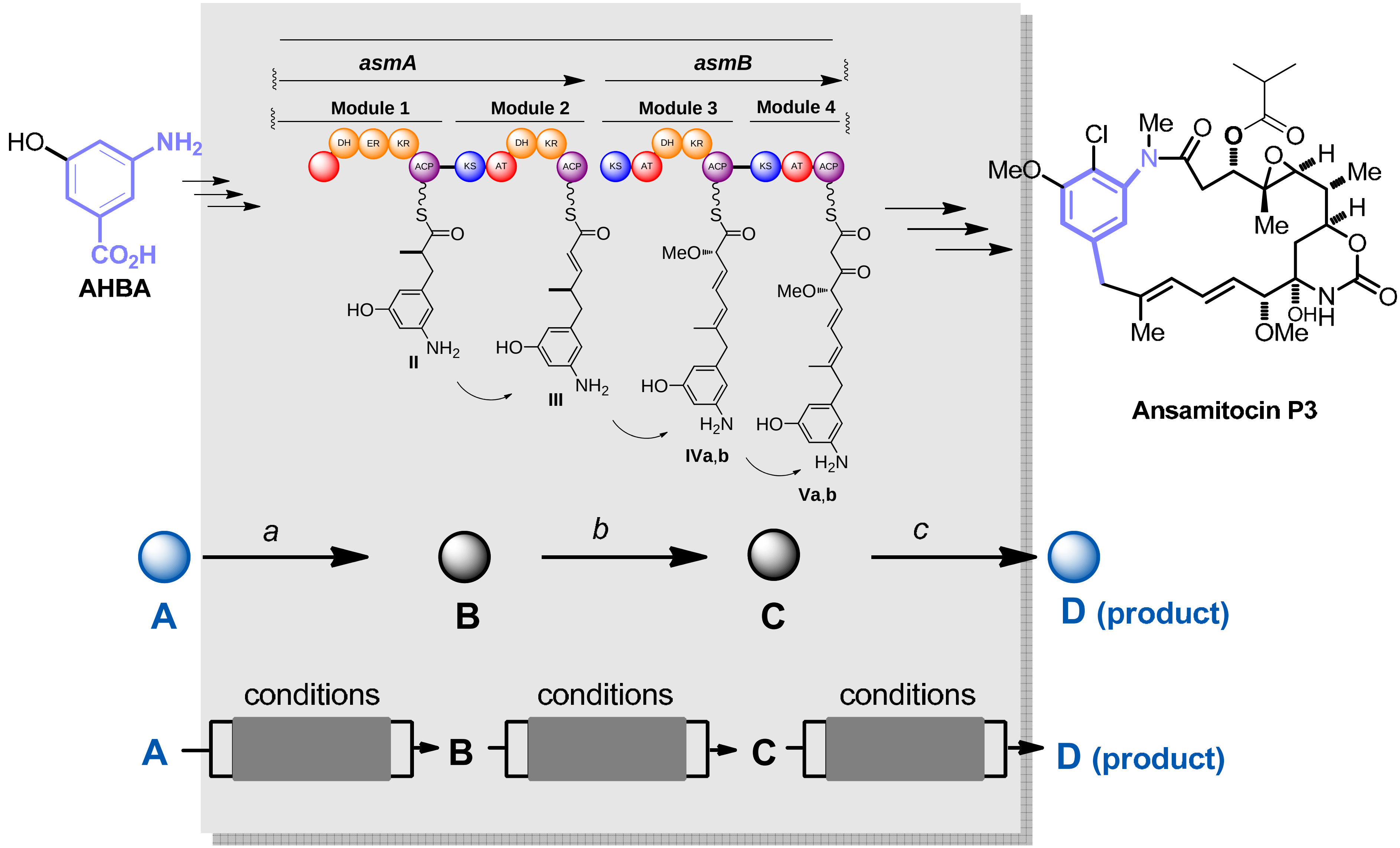


Kirschning, Solodenko, Jas
Chem. Eur. J. **2003**, *9*, 5708-5723.

Mimicking Nature´s Concept of Multistep Synthesis

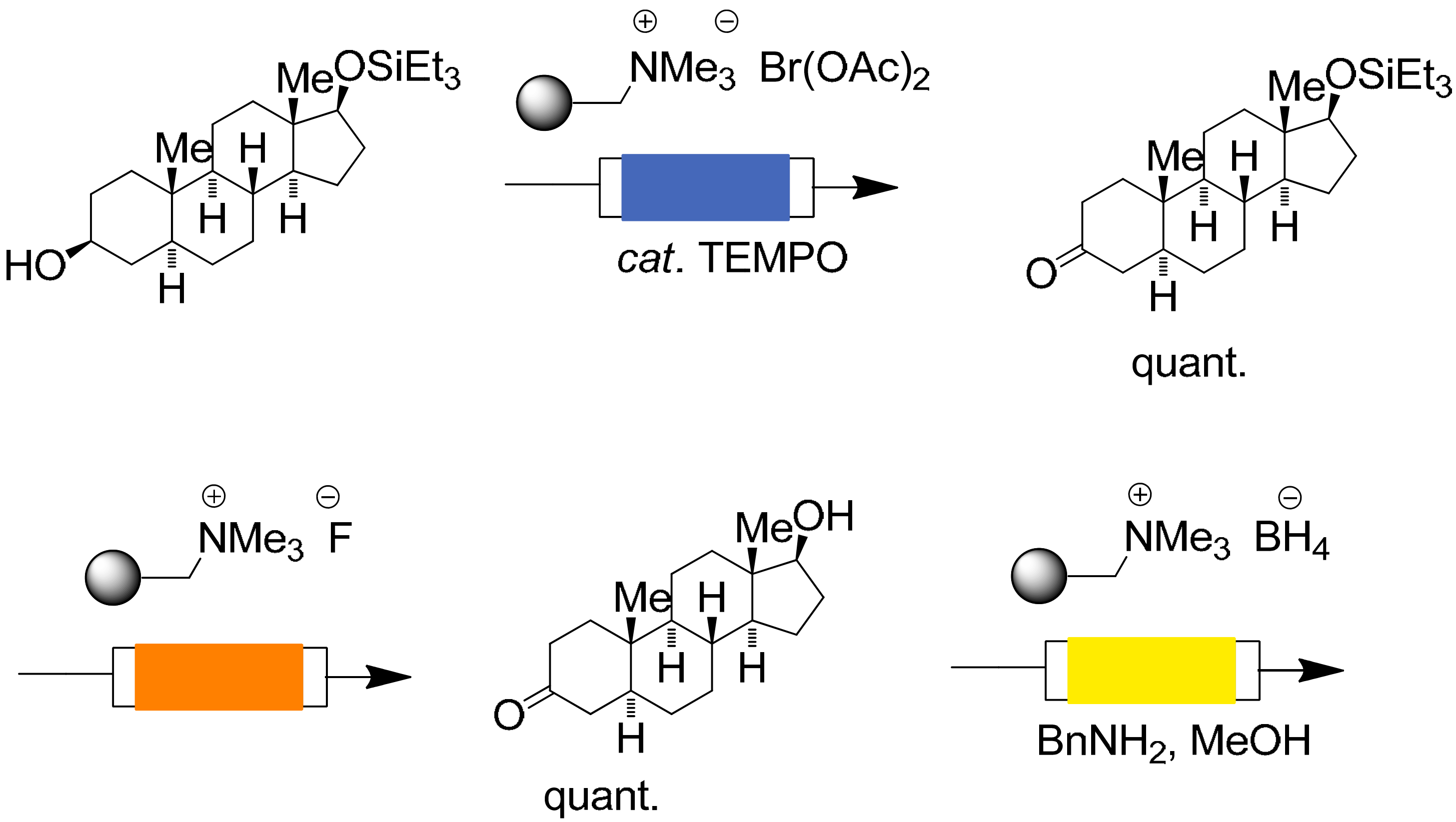


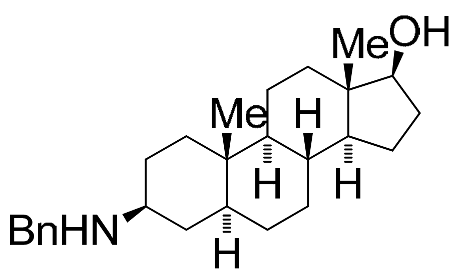
Mimicking Nature´s Concept of Multistep Synthesis



a - c= enzymes; A= starting material; B and C= intermediates; D= product

Multistep synthesis: A telling example





85% (3:1 *de*)

All reactions were carried out in a sequence mode. One reactor served for each reaction. None of the intermediates or the final product was further purified.

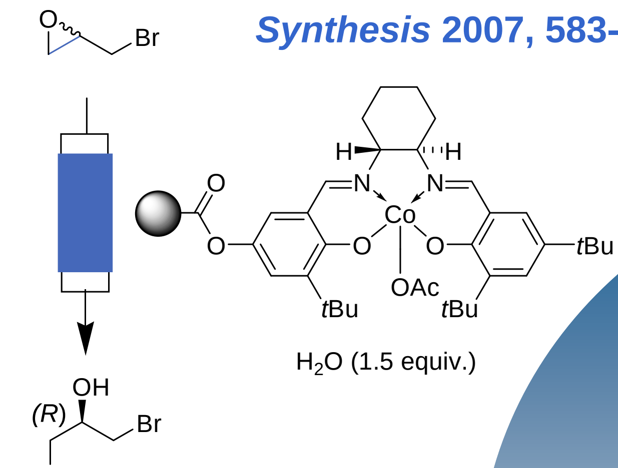
Angew. Chem. Int. Ed. **2001**, *40*, 3995-3998.

Catalysis

Immobilization Concepts for Catalysis

covalent

Synthesis 2007, 583-589.



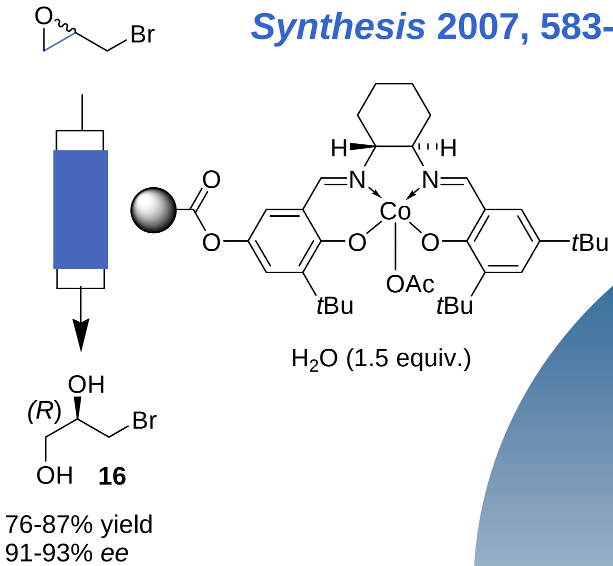
16

76-87% yield
91-93% *ee*

Immobilization Concepts for Catalysis

Covalent

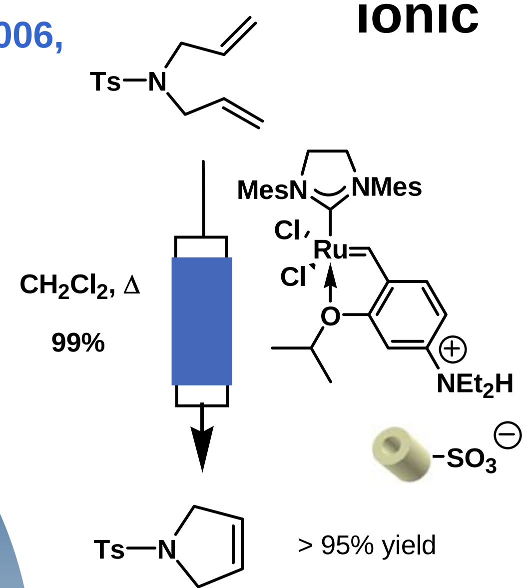
covalent



Synthesis **2007, 583-589.**

J. Am. Chem. Soc. **2006,** ***128*****, 13261-13267**

ionic



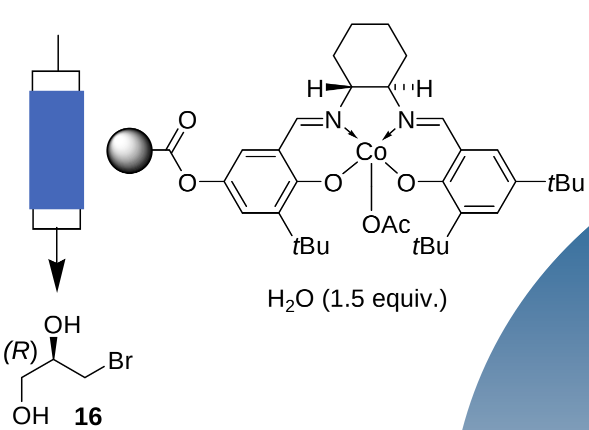
Immobilization Concepts for Catalysis

Covalent

Ionic

covalent

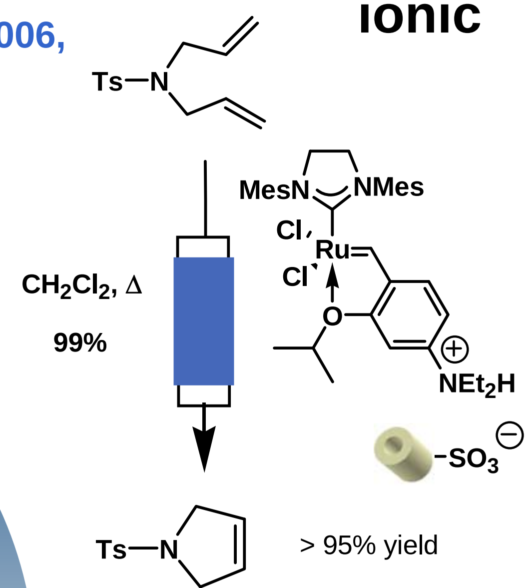
Synthesis **2007, 583-589.**



76-87% yield
91-93% *ee*

ionic

***J. Am. Chem. Soc.* 2006, *128*, 13261-13267**



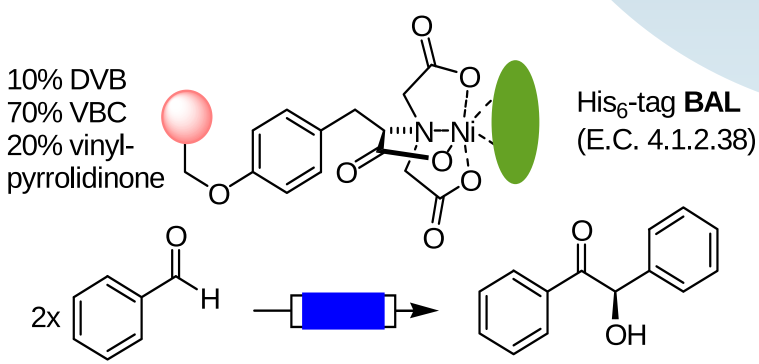
> 95% yield

Immobilization Concepts for Catalysis

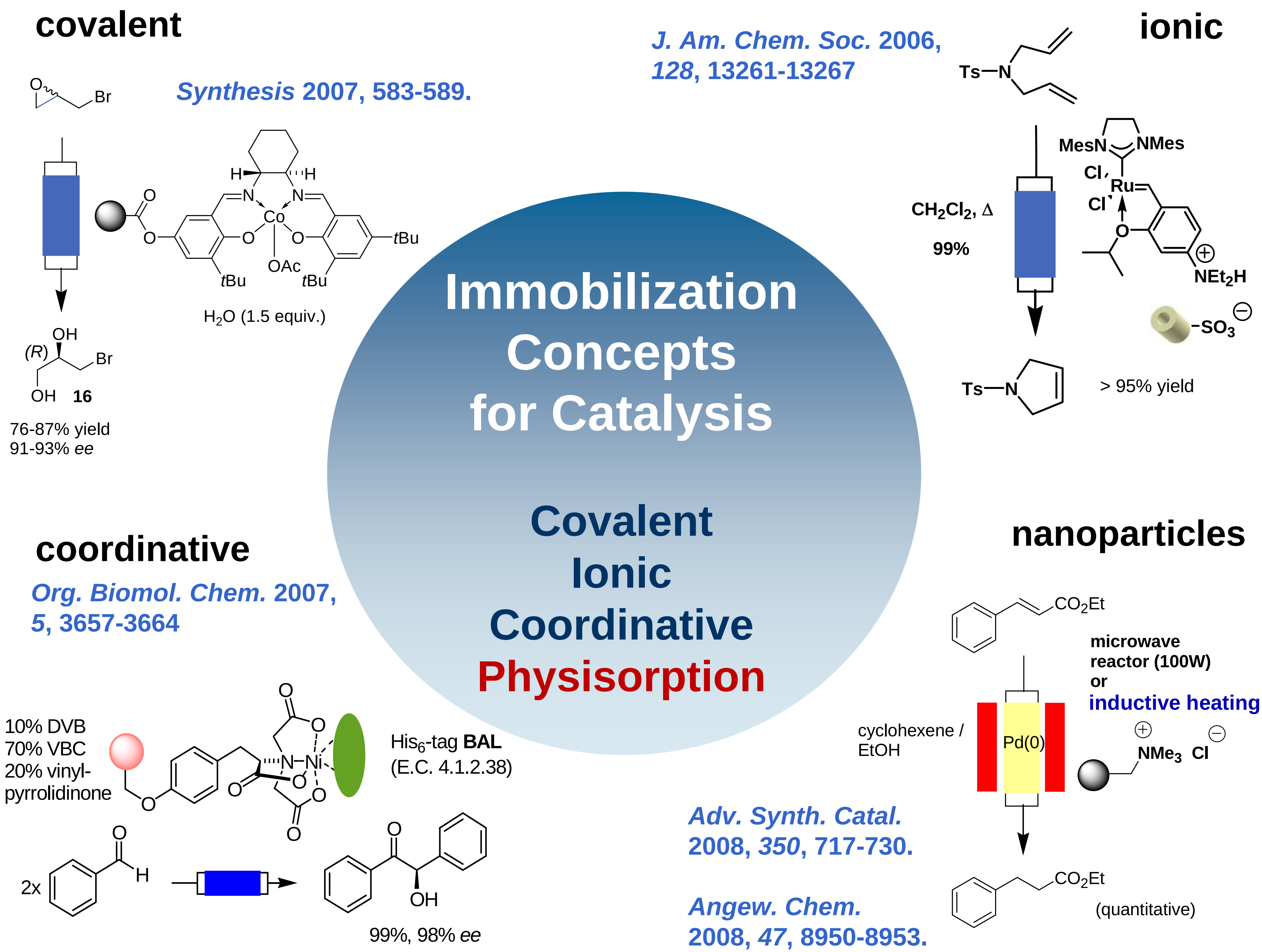
Covalent
Ionic
Coordinative

coordinative

***Org. Biomol. Chem.* 2007, *5*, 3657-3664**

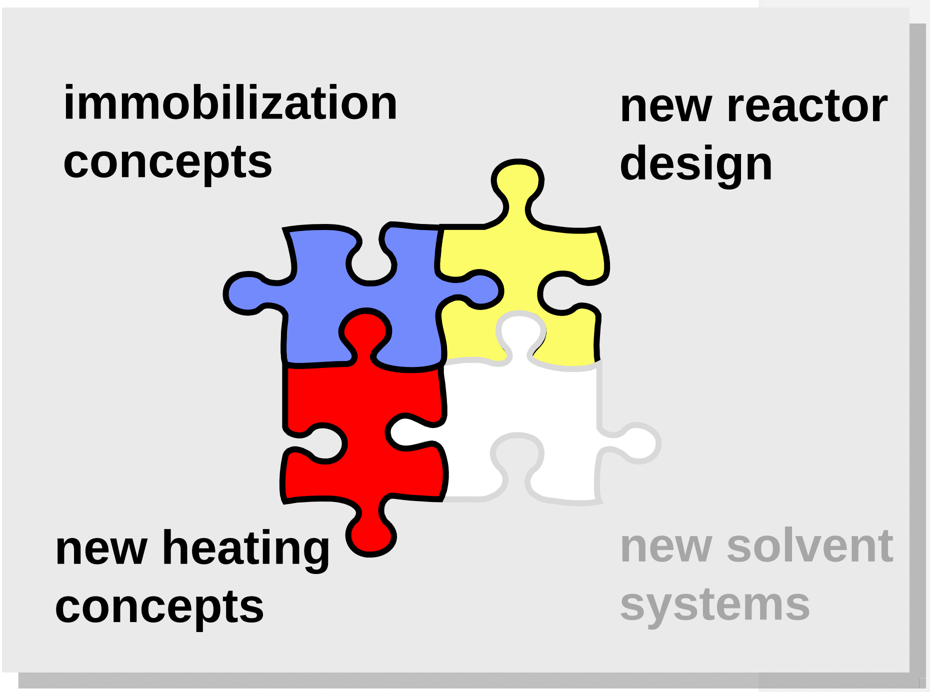


99%, 98% *ee*

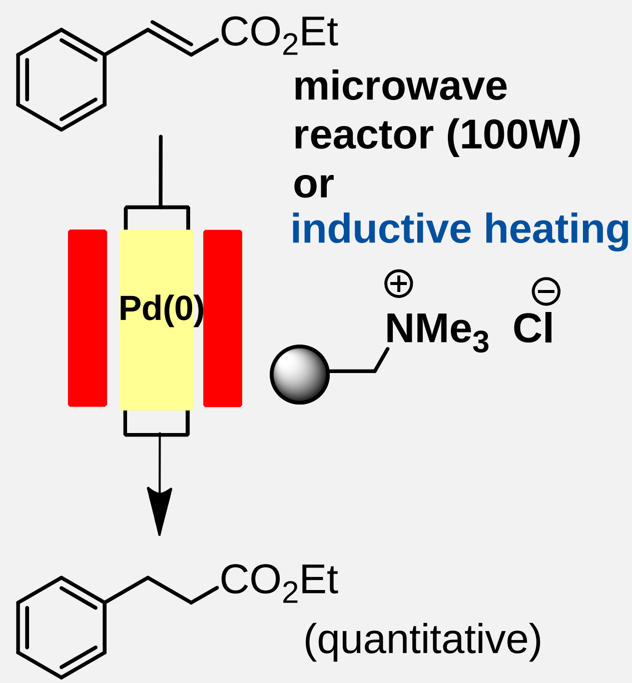

Immobilization Concepts for Catalysis
Covalent
Ionic
Coordinative
Physisorption
covalent
Synthesis 2007, 583-589.
Br
Co
OAc
tBu
H₂O (1.5 equiv.)
(R)
OH
16
76-87% yield
91-93% ee
ionic
J. Am. Chem. Soc. 2006, 128, 13261-13267
Ts–N
MesN
NMes
Ru
CH₂Cl₂, Δ
99%
NEt₂H
SO₃
> 95% yield
coordinative
Org. Biomol. Chem. 2007, 5, 3657-3664
10% DVB
70% VBC
20% vinyl-pyrrolidinone
Ni
His₆-tag BAL
(E.C. 4.1.2.38)
2x
99%, 98% ee
nanoparticles
CO₂Et
microwave reactor (100W)
or
inductive heating
cyclohexene / EtOH
Pd(0)
NMe₃ Cl
(quantitative)
Adv. Synth. Catal. 2008, 350, 717-730.
Angew. Chem. 2008, 47, 8950-8953.

Combination of three enabling techniques

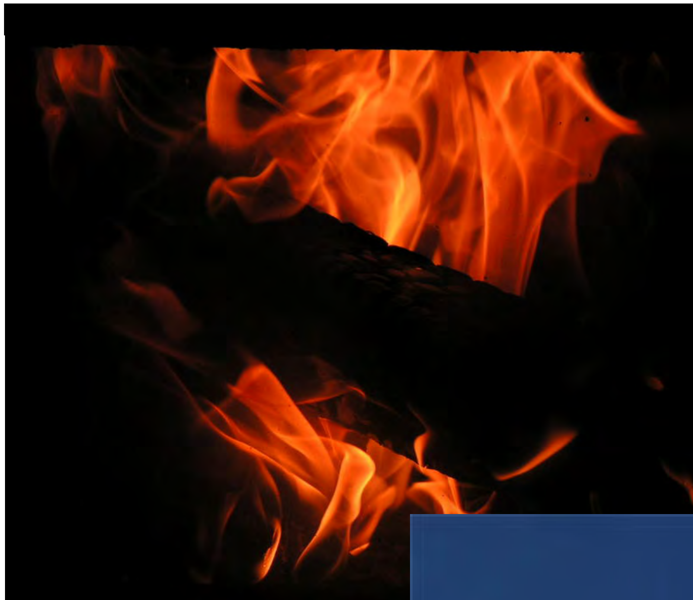
Adv. Synth. Catal. **2008**, *350*, 717-730.



Transfer hydrogenation

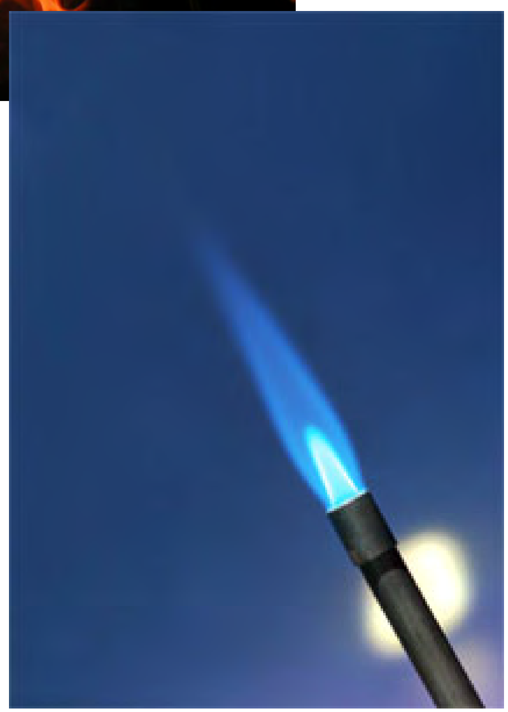


Thermal heating – a classical enabling technology



It all started with the invention of FIRE

A new technology – the Bunsen burner



The latest trend – microwave irradiation

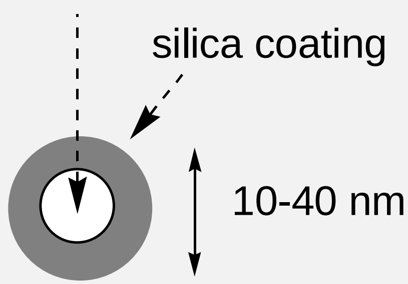
Magnetic nanoparticles

Common use

- magnetic liquids
- biomedicine
- magnetic resonance

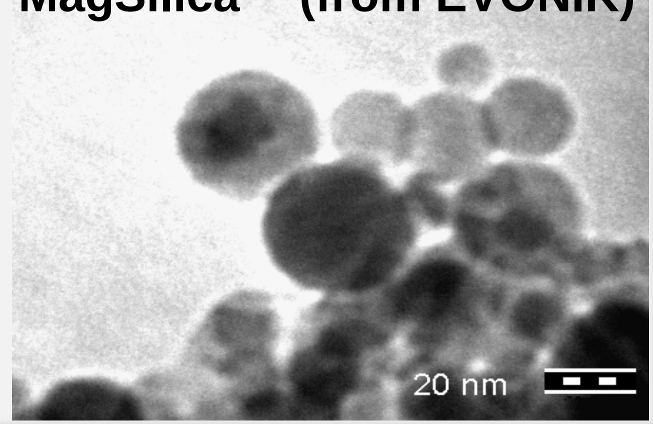
Silica coated maghemite/magnetite particles

nanoparticle based on Fe_2O_3/Fe_3O_4



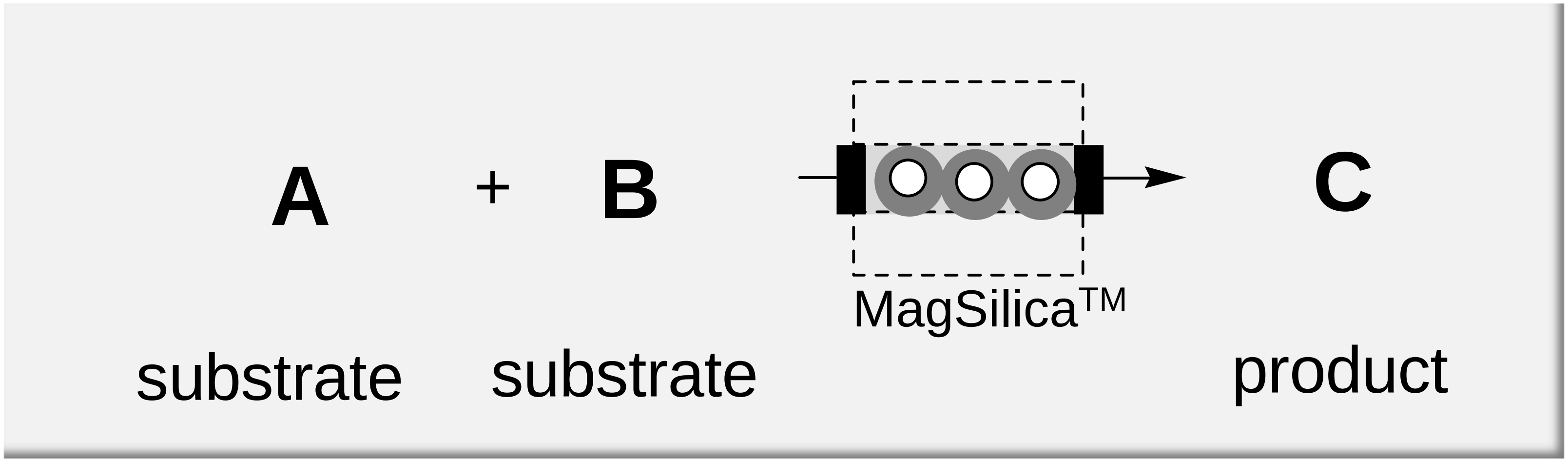
TEM micrographs of unfunctionalized magnetic nanoparticles before heating

MagSilica^{TM} (from EVONIK)



Review: F. Schüth et al., *Angew. Chem*. **2007**, *119*, 1242-1266; *Angew. Chem. Int. Ed.* **2007**, *46*, 1222-1244

Inductive Heating: A new heating technology for synthesis



MagSilica™ (from EVONIK)

- application in adhesive technologies
- magnetite (Fe_2O_3) / maghemite (Fe_3O_4) core
  silica shell
- stable against most chemicals
- high surface due to nano-sized dimensions

Inductive Heating with Functionalized Magnetic Nanoparticles inside Flowreactors

Magnetic nanoparticles (1-10 nm) show superparamagnetism.

- No remanent magnetization
- Energy to alter direction of magnetic moment equals thermal energy

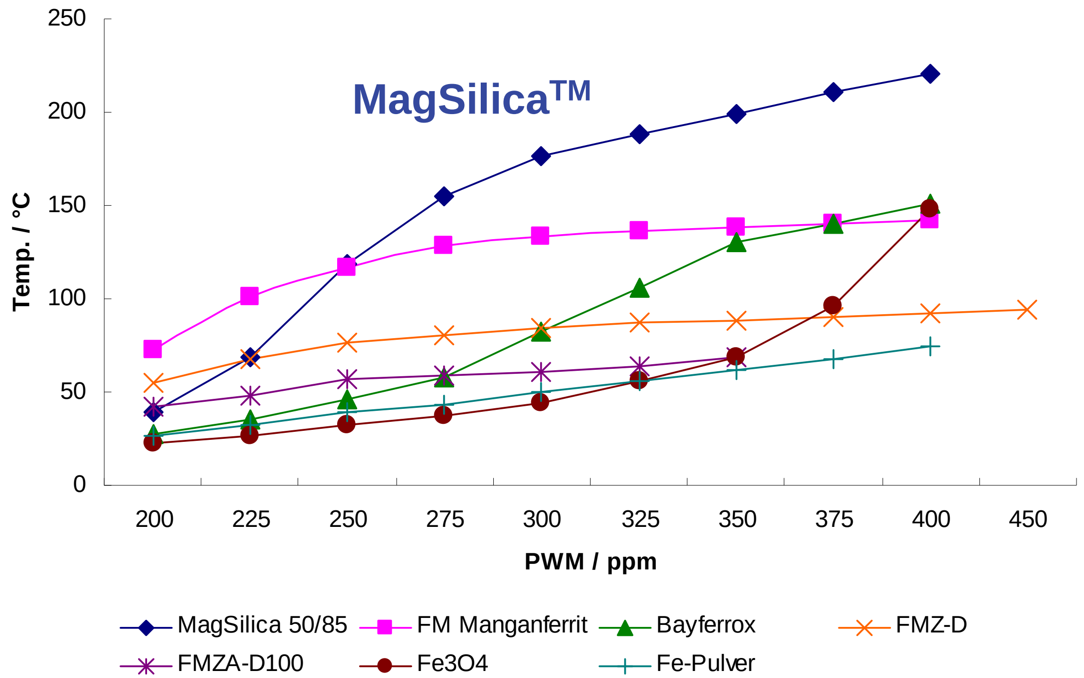
Inductive Heating with Functionalized Magnetic Nanoparticles inside Flowreactors

Magnetic nanoparticles (1-10 nm) show superparamagnetism.

- No remanent magnetization
- Energy to alter direction of magnetic moment equals thermal energy

High frequency electromagnetic field (25 KHz to > 100 KHz) leads to dramatic heating.

For **100 KHz** inductors temperatures well above **500 °C** are possible.



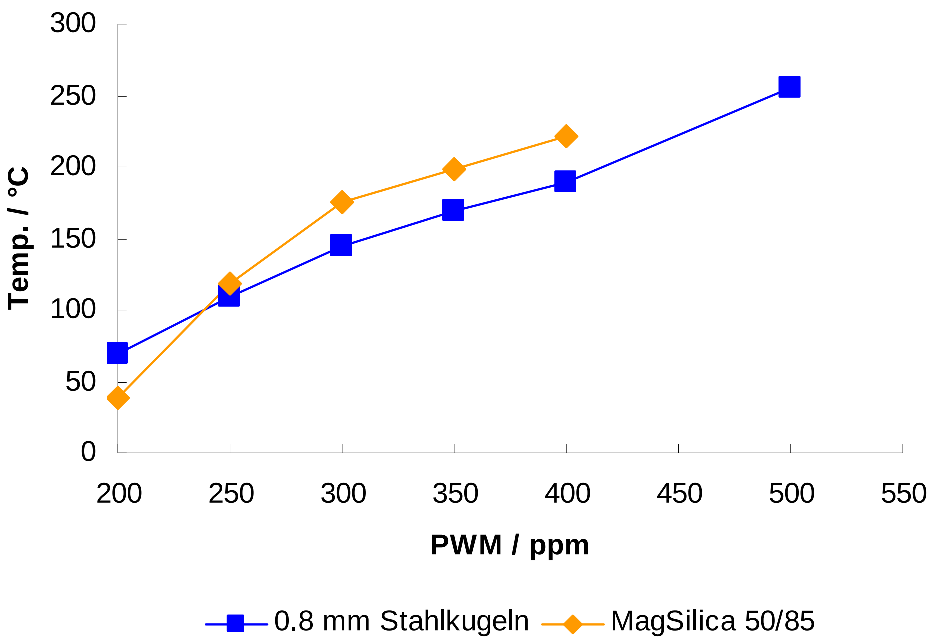
for 25 KHz inductor

Heating media

Alloys (steel)

Ferrites (Fe_3O_4, $CoFe_2O_4$)

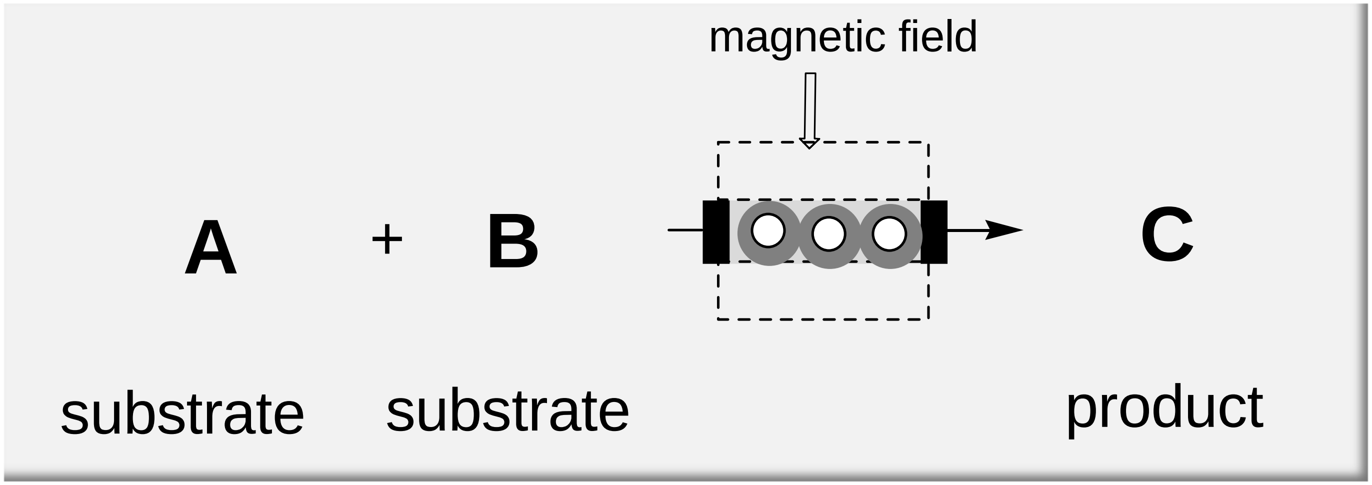
Metals (Cu, Fe etc.)



MagSilica^{TM} superior

Steel beads (0.8 mm diameter) competitive

Magnetic heat induction



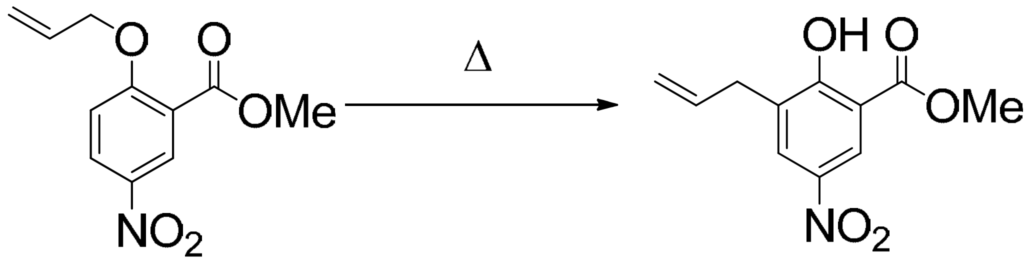
- heat by magnetic induction inside conductive materials → iron, copper, alloys etc.

- superparamagnetic nanoparticles can be easily heated up to 250 °C at 25 KHz within seconds

→ direct heat formation at reaction center
→ no safety risks

→ hot-spot effects ?

A comparison study in batch: oil bath *vs.* MW *vs.* induction



entry[a]	*heating*	*time*	*temp.*	*solvent*	*yield*[b]
1	oil bath	2 h	200 °C	toluene	**17 %**
2	oil bath	5 h	150 °C	DMF	**0 %**
3	MW, SiC	2 h	200 °C	toluene	**38 %**
4	MW, SiC	1 h	250 °C	solvent free	**40 %**
5	induction	2 h	200 °C	toluene	**39 %**
6	induction	0.5 h	200 °C	solvent free	**25 %**
7	Induction	1.5 h	200 °C	solvent free	**40 %**

[a] MW vial, sealed, MagSilica™, 25 kHz.; [b] isolated yield.

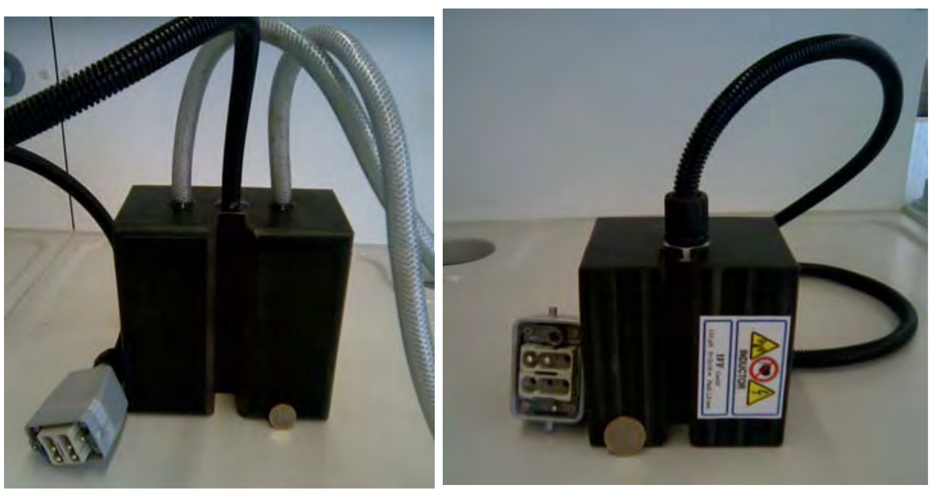
Inductive Heating: equipment

Glass reactors:

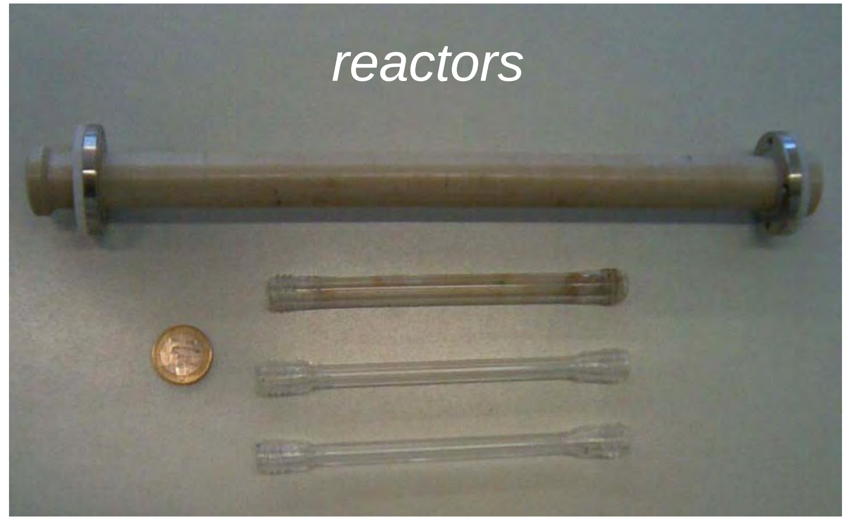
- easy to produce and versatile
- stable up to 3 bar and 200 °C

PEEK reactors:

- stable up to 20 bar and 200 °C
- directly connectable to HPLC fittings
- expensive



inductors

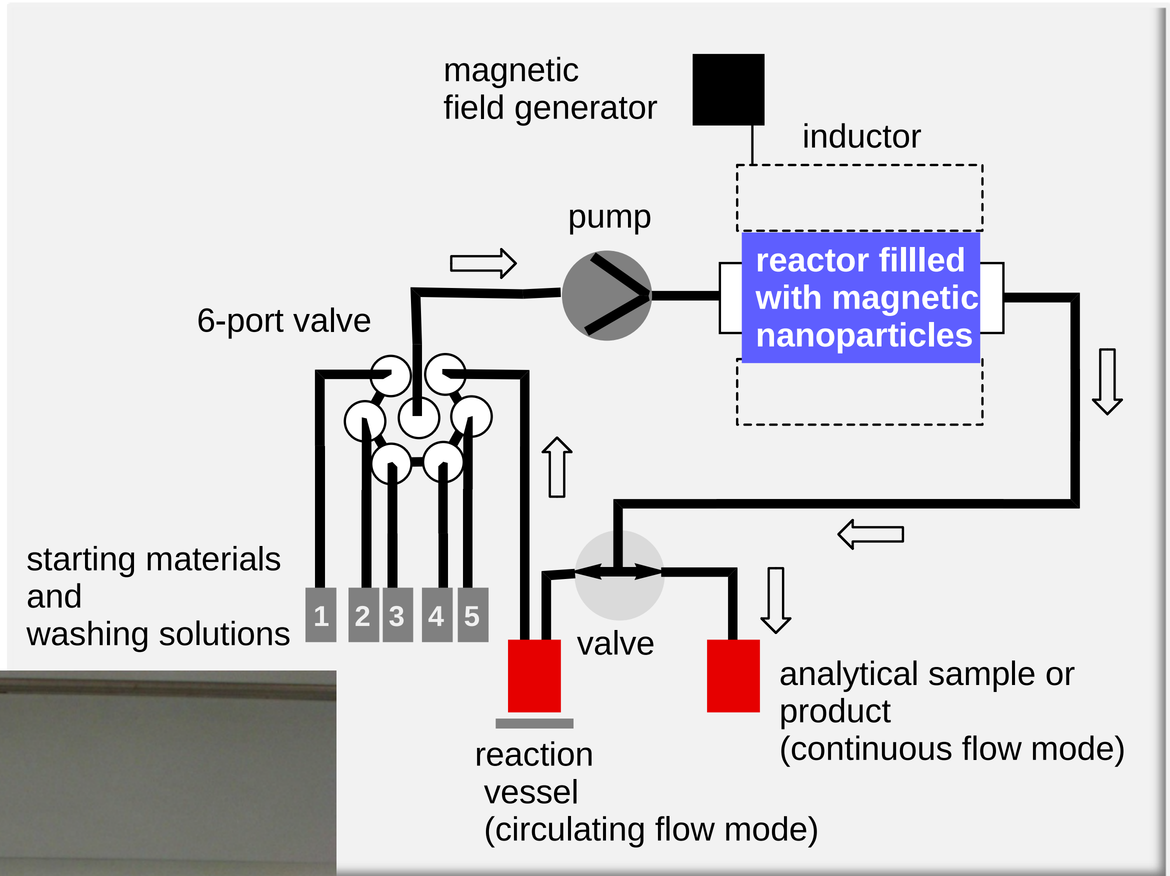


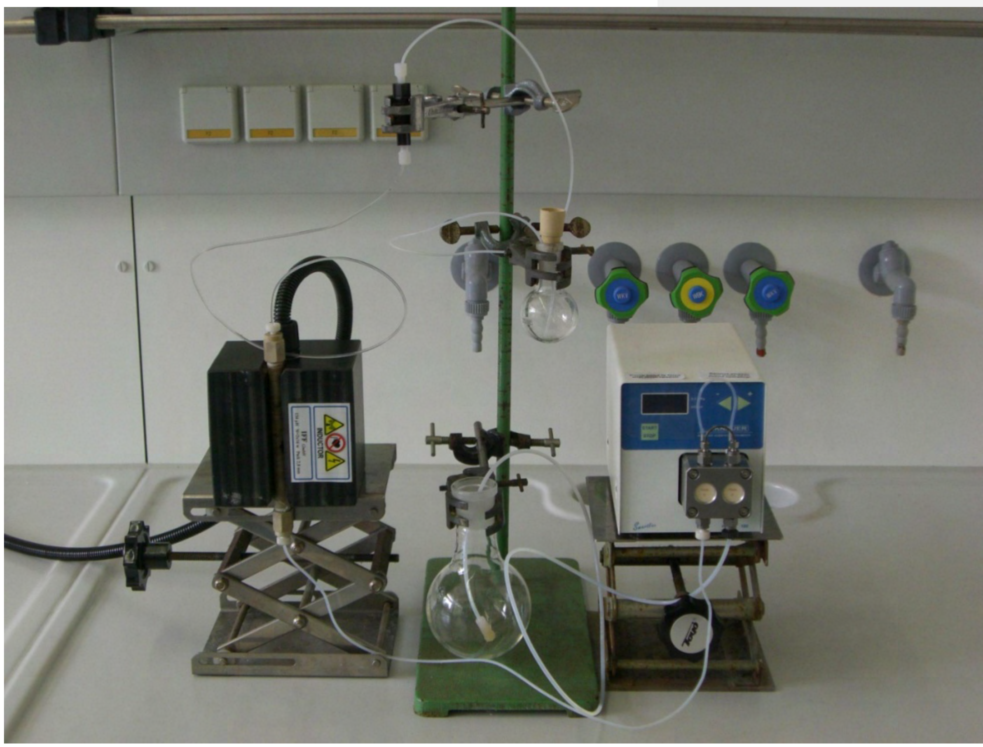
- possibility of back-pressure application

- all common solvents/reagents usable

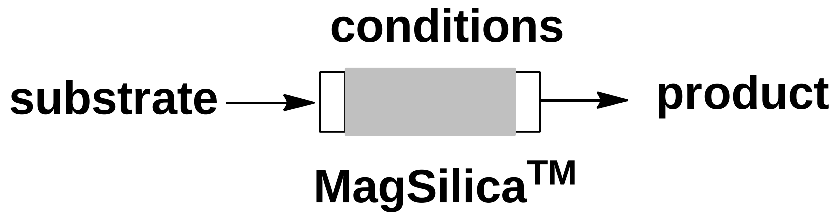
- tailor-made inductors for individual reactors
- differ in slit diameter

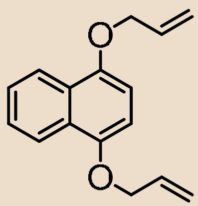
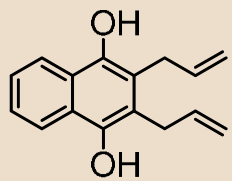
The setup – the inductor – the reactor





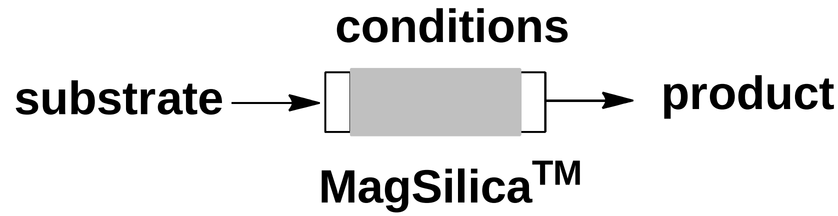
Selected inductively heated flow reactions

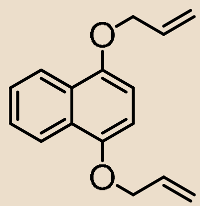
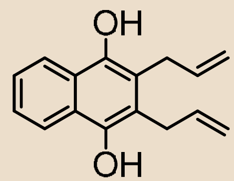
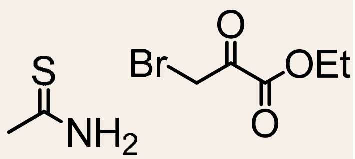
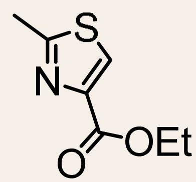


entry[a]	substrate	product	conditions	result[b]
Claisen			170 °C, dodecane, 0.5 mL/min	**85 %**

[a] conditions: MagSilica™, glass reactor (12 cm x 8.5 mm, 4 mL void volume), induction frequency 25 kHz. [b] isolated yield.

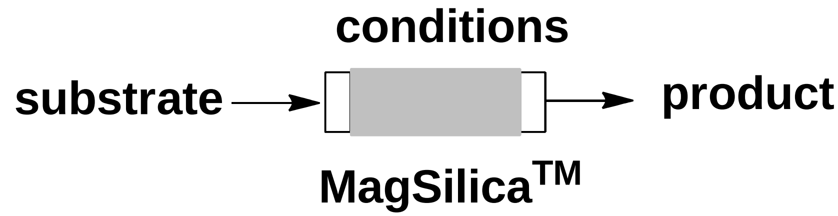
Selected inductively heated flow reactions

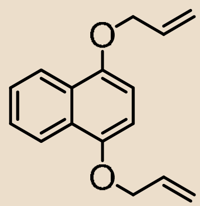
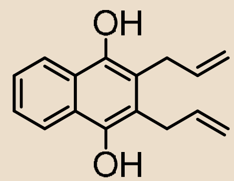
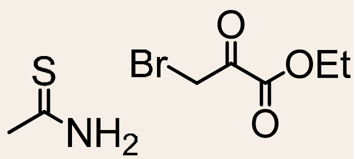
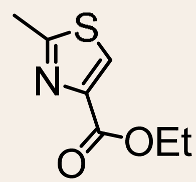
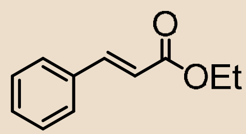
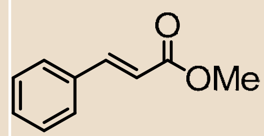


entry[a]	substrate	product	conditions	result[b]
Claisen			**170 °C**, dodecane, 0.5 mL/min	**85 %**
Cond.			**70 °C**, EtOH, 0.5 mL/min,	**85 %**

[a] conditions: MagSilica™, glass reactor (12 cm x 8.5 mm, 4 mL void volume), induction frequency 25 kHz. [b] isolated yield.

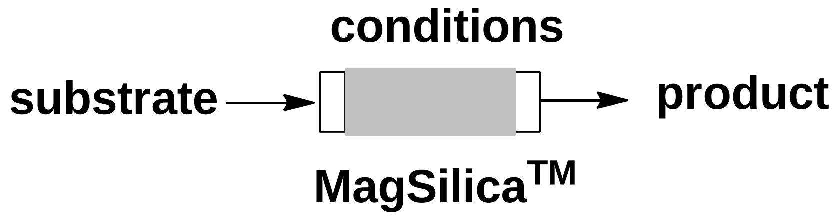
Selected inductively heated flow reactions

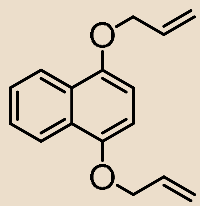
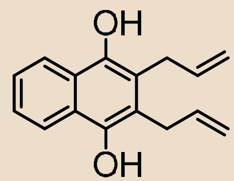
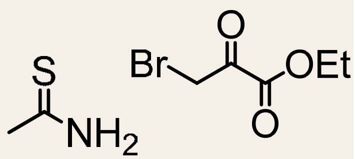
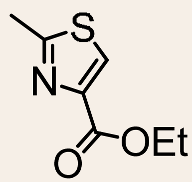
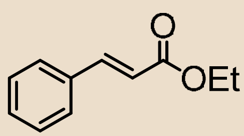
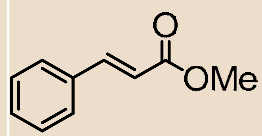
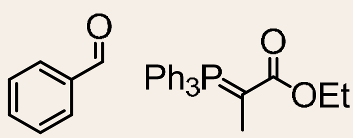
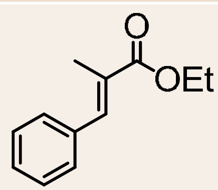


entry[a]	substrate	product	conditions	result[b]
Claisen			**170 °C**, dodecane, 0.5 mL/min	**85 %**
Cond.			**70 °C**, EtOH, 0.5 mL/min,	**85 %**
Trans-esterif.			**60 °C**, NaOMe, MeOH, 0.5 mL/min	**88 %**

[a] conditions: MagSilica™, glass reactor (12 cm x 8.5 mm, 4 mL void volume), induction frequency 25 kHz. [b] isolated yield.

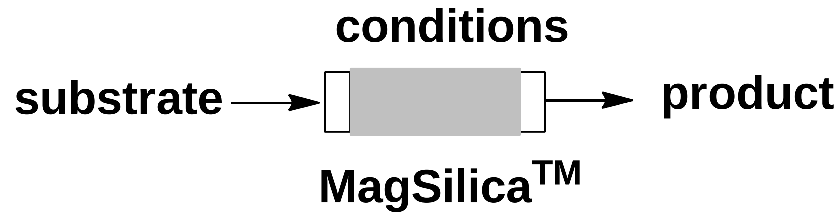
Selected inductively heated flow reactions

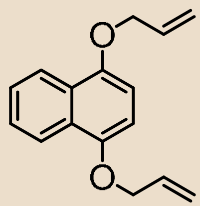
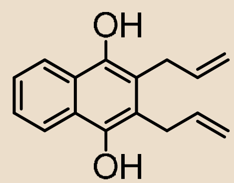
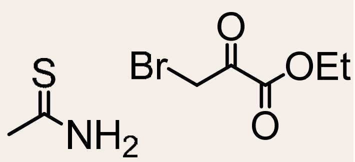
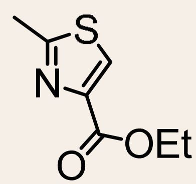
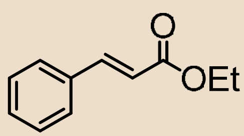
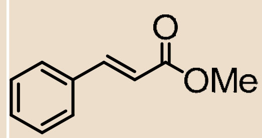
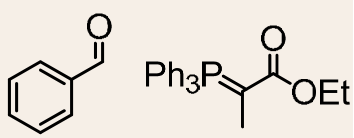
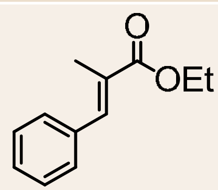
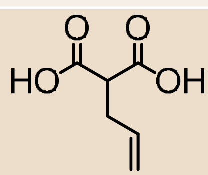
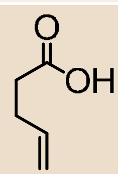


entry[a]	*substrate*	*product*	*conditions*	*result*[b]
Claisen			**170 °C**, dodecane, 0.5 mL/min	**85 %**
Cond.			**70 °C**, EtOH, 0.5 mL/min,	**85 %**
Trans-esterif.			**60 °C**, NaOMe, MeOH, 0.5 mL/min	**88 %**
Wittig			**100 °C**, toluene, 0.5 mL/min	**> 99 %**

[a] conditions: MagSilica™, glass reactor (12 cm x 8.5 mm, 4 mL void volume), induction frequency 25 kHz. [b] isolated yield.

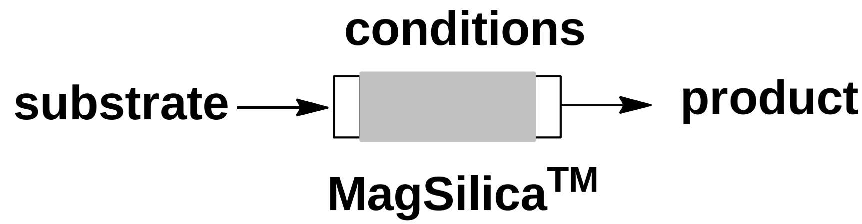
Selected inductively heated flow reactions

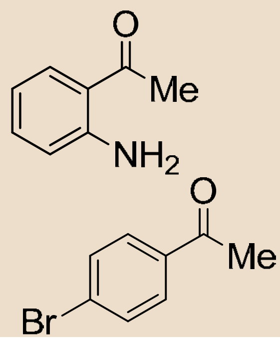
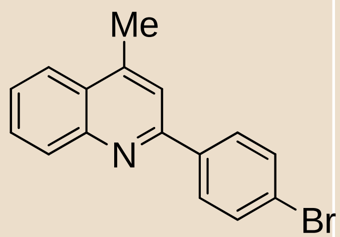


entry[a]	*substrate*	*product*	*conditions*	*result*[b]
Claisen			**170 °C**, dodecane, 0.5 mL/min	**85 %**
Cond.			**70 °C**, EtOH, 0.5 mL/min,	**85 %**
Trans-esterif.			**60 °C**, NaOMe, MeOH, 0.5 mL/min	**88 %**
Wittig			**100 °C**, toluene, 0.5 mL/min	**> 99 %**
Decarb.			**140 °C**, DMF, 0.2 mL/min	**76 %**

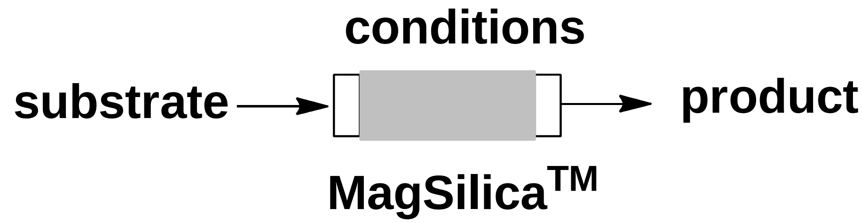
[a] conditions: MagSilica™, glass reactor (12 cm x 8.5 mm, 4 mL void volume), induction frequency 25 kHz. [b] isolated yield.

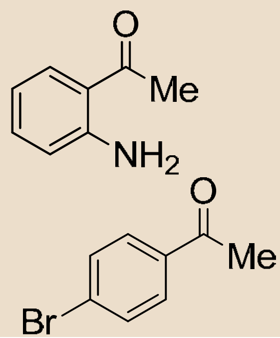
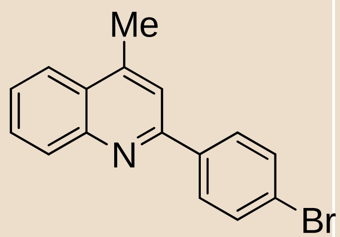
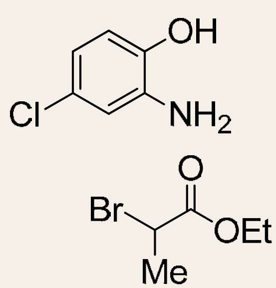
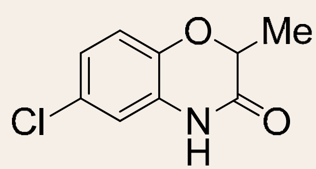
Selected Inductively heated flow reactions



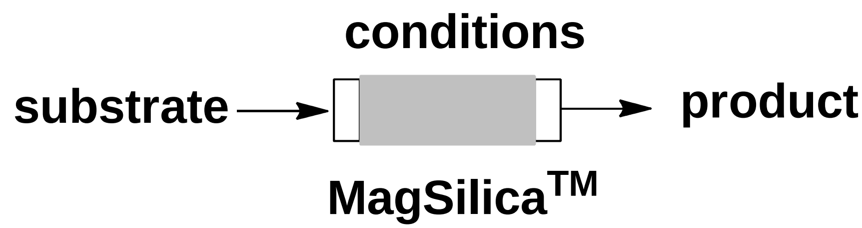
entry[a]	substrate	product	conditions	result[b]
Domino Friedländer quinoline			**70°C**, EtOH, KOH, 0.05 mL/min	**67 %**

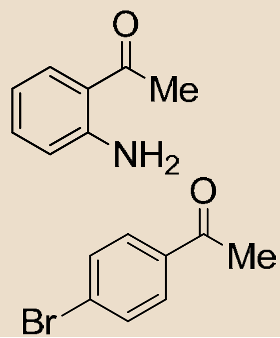
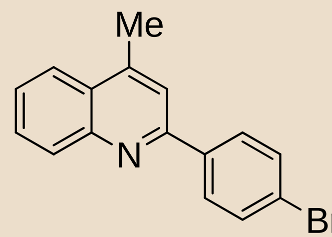
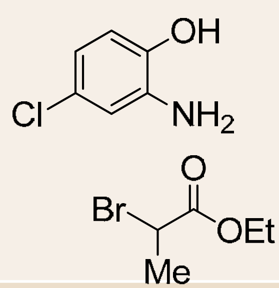
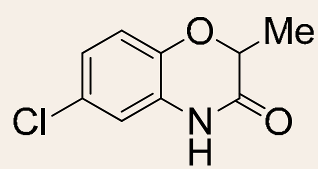
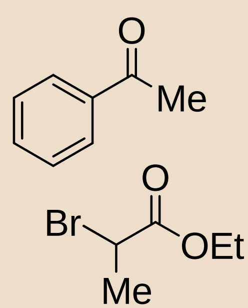
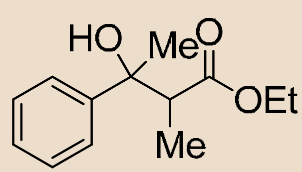
Selected Inductively heated flow reactions



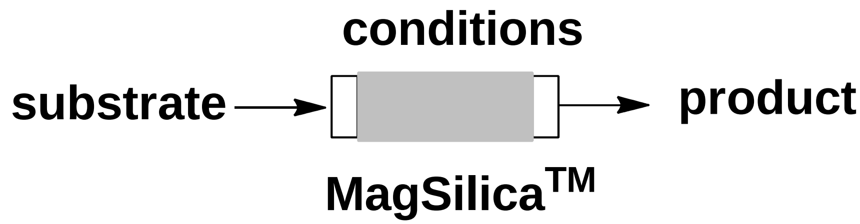
entry[a]	substrate	product	conditions	result[b]
Domino Friedländer quinoline			**70°C**, EtOH, KOH, 0.05 mL/min	**67 %**
Domino benzoxazine			**135 °C**, DBU (2 eq.), DMF, 0.2 mL/min	**82 %**

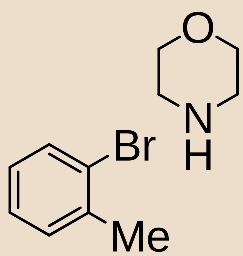
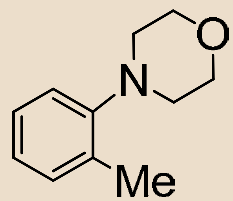
Selected Inductively heated flow reactions



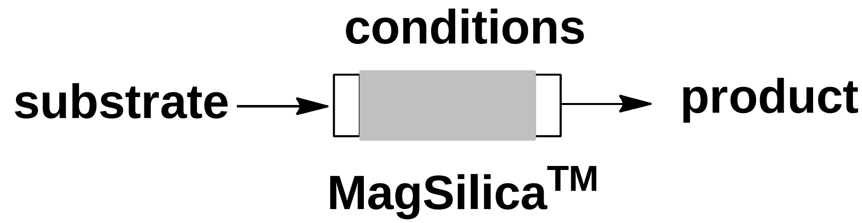
entry[a]	substrate	product	conditions	result[b]
Domino Friedländer quinoline			**70°C**, EtOH, KOH, 0.05 mL/min	**67 %**
Domino benzoxazine			**135 °C**, DBU (2 eq.), DMF, 0.2 mL/min	**82 %**
Organo-metallic			**60 °C**, Zn (30 eq.), THF, 0.1 mL/min (d.r. 4:1)	**70% (batch 35%)**

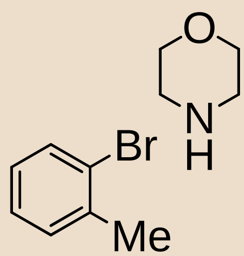
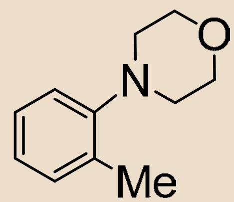
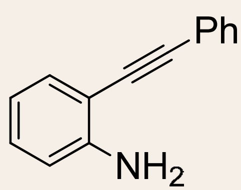
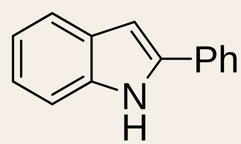
Selected Inductively heated flow reactions



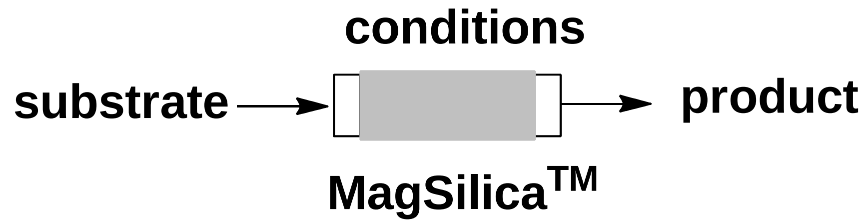
entry[a]	substrate	product	conditions	result[b]
Hartwig Buchwald			120°C, 4 mol% PEPPSI™ *n*-Bu_3N, DME, 25 kHz, 0.5 mL/min	**87 %**

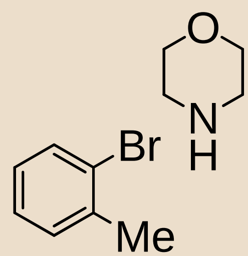
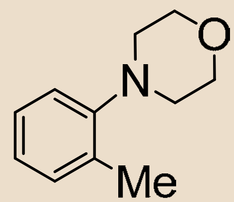
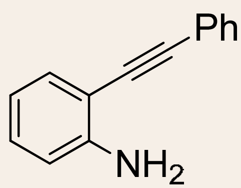
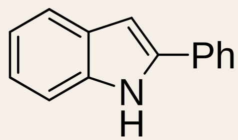
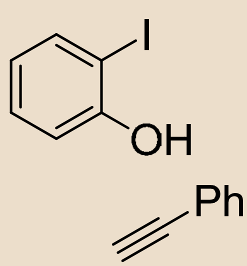
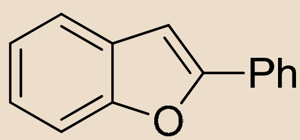
Selected Inductively heated flow reactions



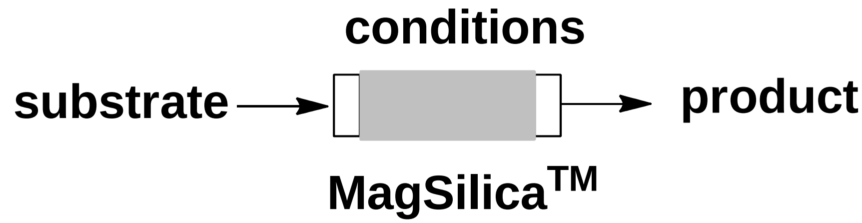
entry[a]	substrate	product	conditions	result[b]
Hartwig Buchwald			**120°C**, 4 mol% PEPPSI™ *n*-Bu_3N, DME, 25 kHz, 0.5 mL/min	**87 %**
Catalysis, hydro-amination			**80°C**,$(MeCN)_4Pd(BF_4)_2$, $FeCl_3.6H_2O$ $(ClCH_2)_2$/DMF (5:1) 0.1 mL/min	**70 %**

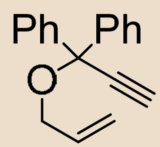
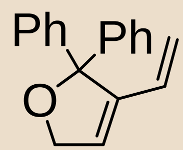
Selected Inductively heated flow reactions



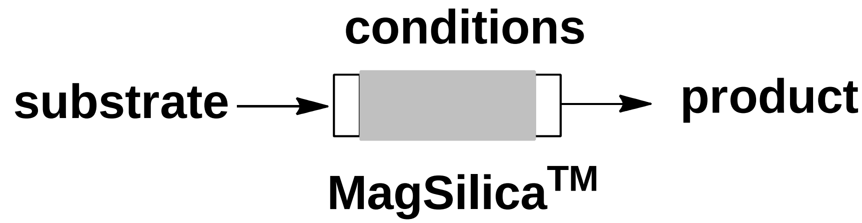
entry[a]	substrate	product	conditions	result[b]
Hartwig Buchwald			**120°C**, 4 mol% PEPPSI™ *n*-Bu_3N, DME, 25 kHz, 0.5 mL/min	**87 %**
Catalysis, hydro-amination			**80°C**,$(MeCN)_4Pd(BF_4)_2$, $FeCl_3.6H_2O$ $(ClCH_2)_2$/DMF (5:1) 0.1 mL/min	**70 %**
Catalysis, domino Sonogashira			**110 °C**, $PdCl_2$, TBAA, NMP, 0.15 mL/min **Steel beads**	**82 %**

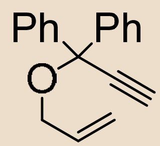
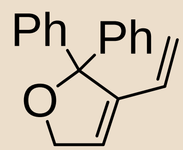
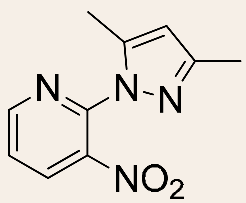
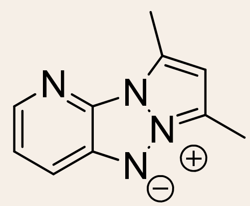
Selected Inductively heated flow reactions



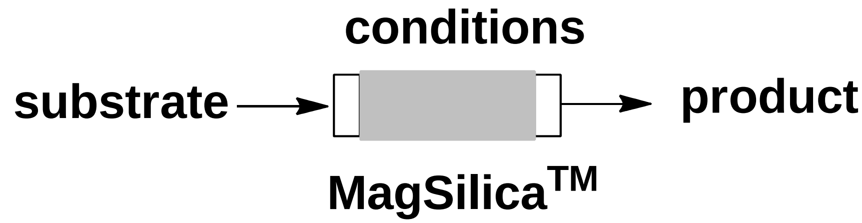
entry[a]	substrate	product	conditions	result[b]
Enyne Metathesis			**90°C**, 5 mol% Grubbs II toluene, 0.2 mL/min,	**92 %**

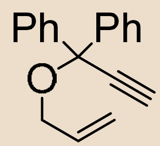
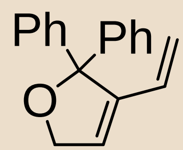
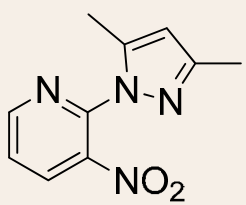
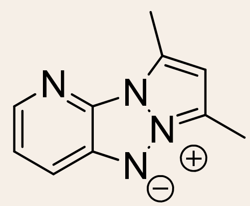
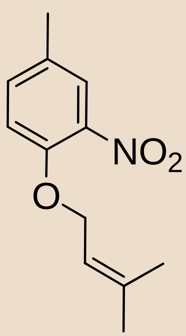
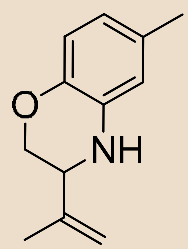
Selected Inductively heated flow reactions



entry[a]	substrate	product	conditions	result[b]
Enyne Metathesis			**90°C**, 5 mol% Grubbs II toluene, 0.2 mL/min,	**92 %**
Reductive cyclization			**150°C**, $P(OEt)_3$/ DMF 3:1, 0.05 mL/min	**44 %**

Selected Inductively heated flow reactions

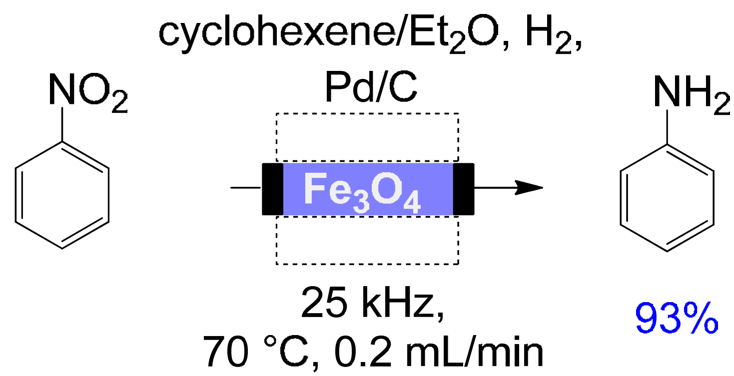


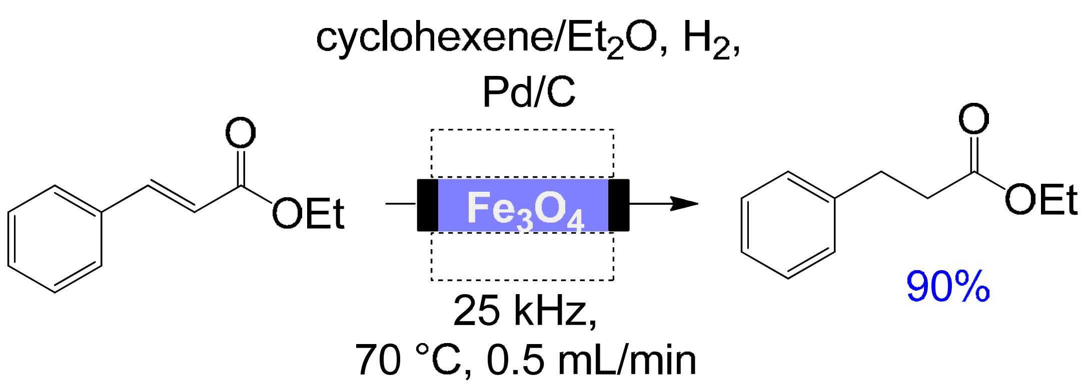
entry[a]	substrate	product	conditions	result[b]
Enyne Metathesis			**90°C**, 5 mol% Grubbs II toluene, 0.2 mL/min,	**92 %**
Reductive cyclization			**150°C**, $P(OEt)_3$/ DMF 3:1, 0.05 mL/min	**44 %**
Catalysis, Domino dihydrobenz -oxazine			**150 °C**, $P(OEt)_3$/ toluene 3:1, 0.05 mL/min **Superheated**	**52 %**

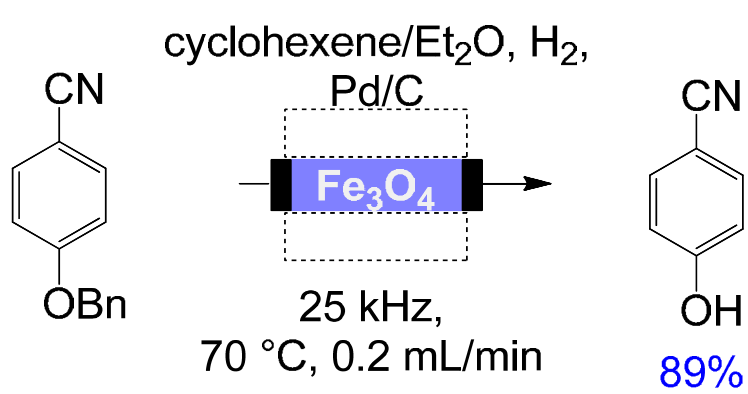
Inductively heated flow reactions

Catalytic transfer Hydrogenations

(isolated yields)



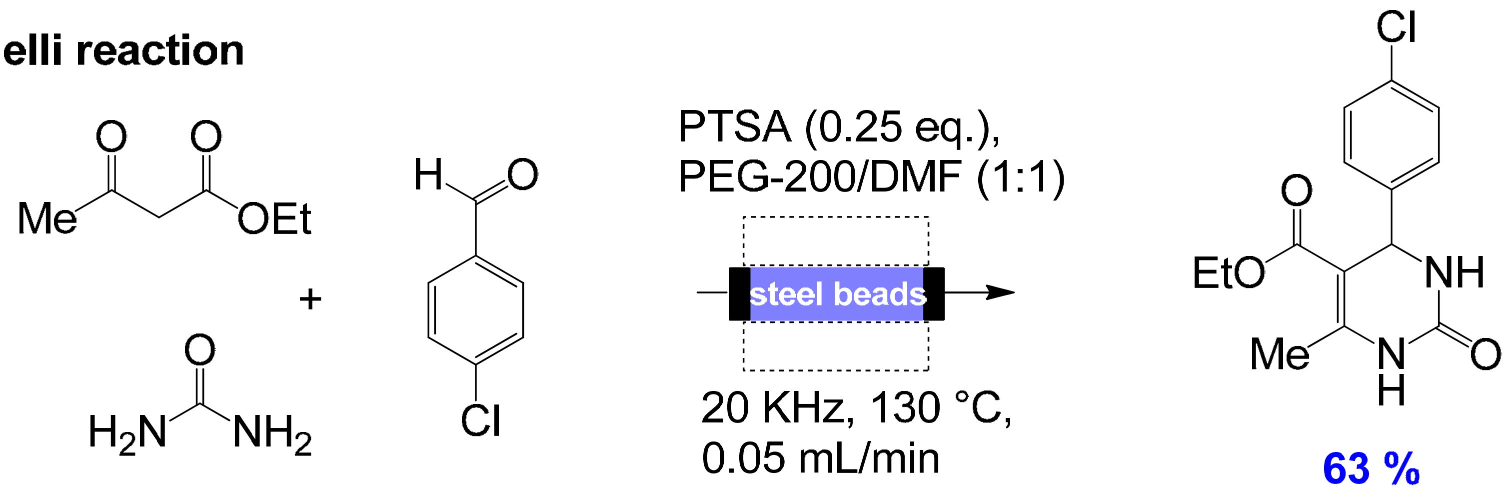




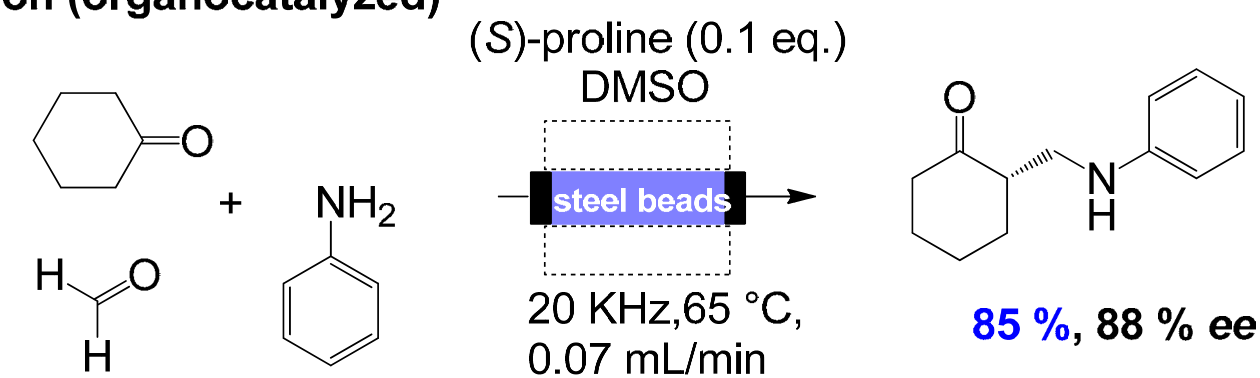
Multicomponent reactions

(isolated yields)

Biginelli reaction



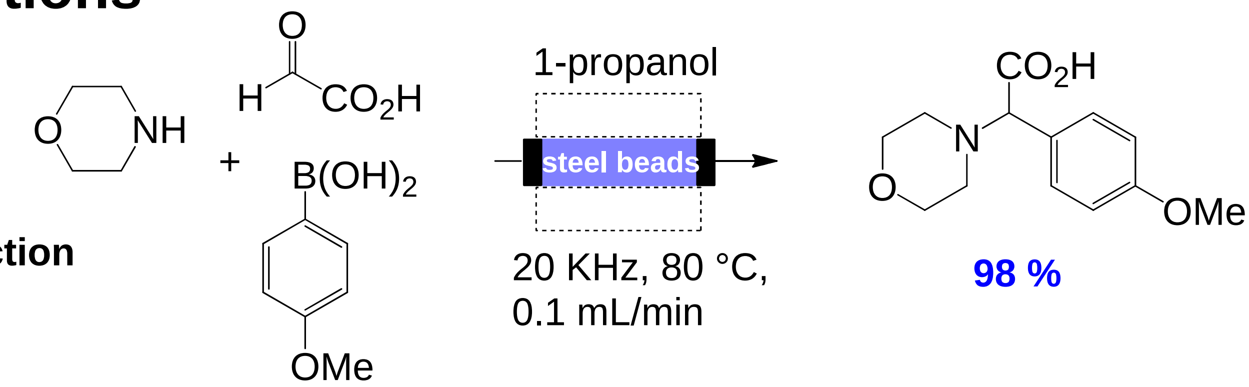
Mannich reaction (organocatalyzed)

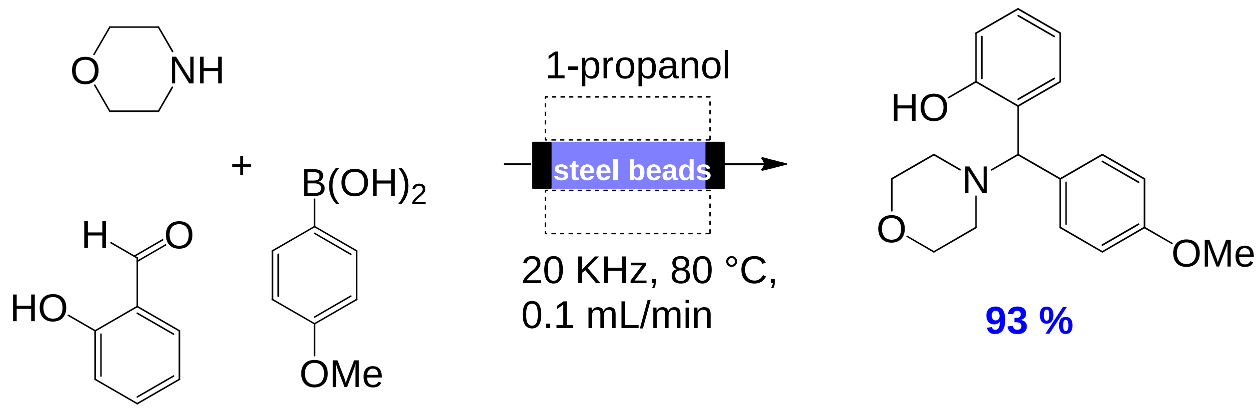


S. Ceylan, L. Coutable, J. Wegner, A. Kirschning, *Chem. Eur. J.*, **2010**, accepted.

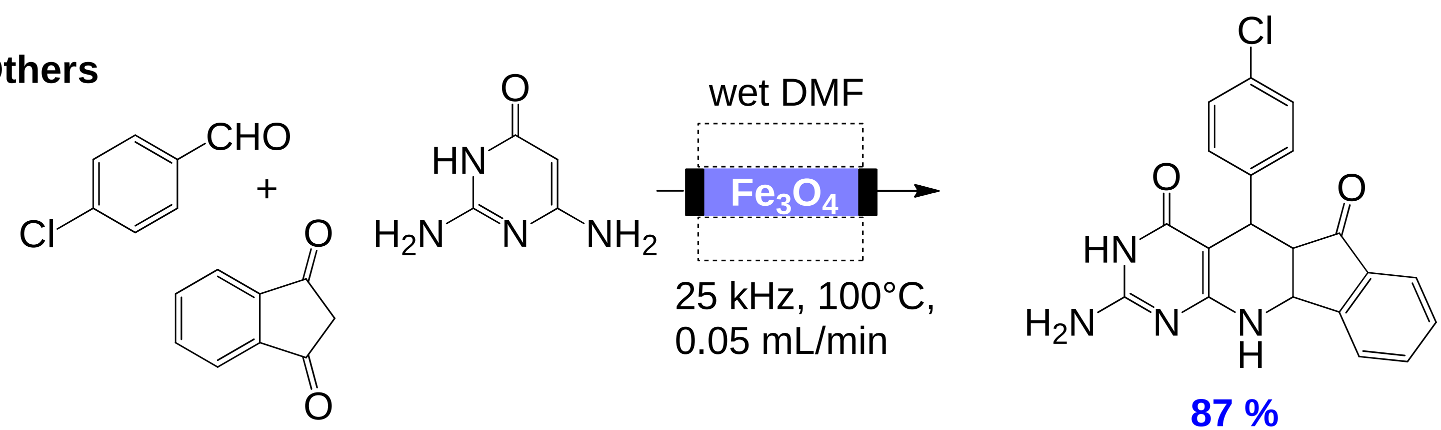
Multicomponent reactions
(isolated yield)

Petasis-reaction



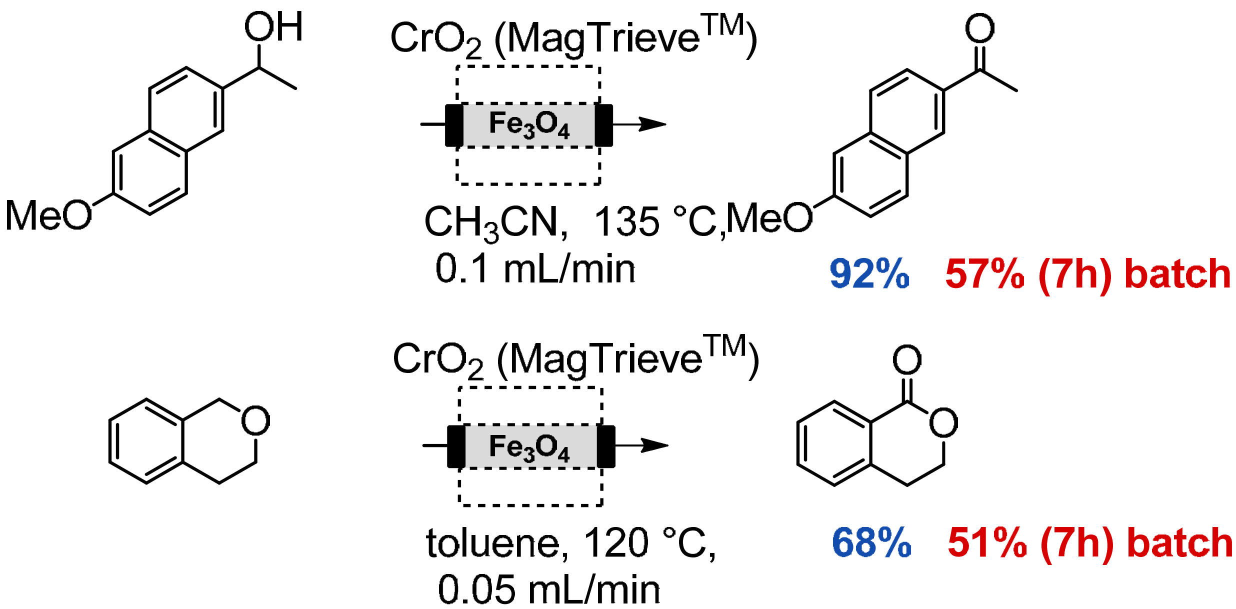


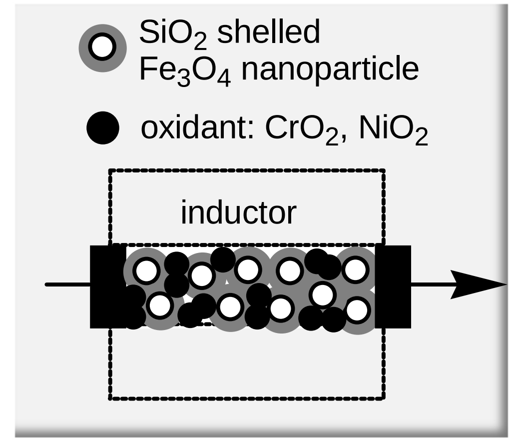
Others



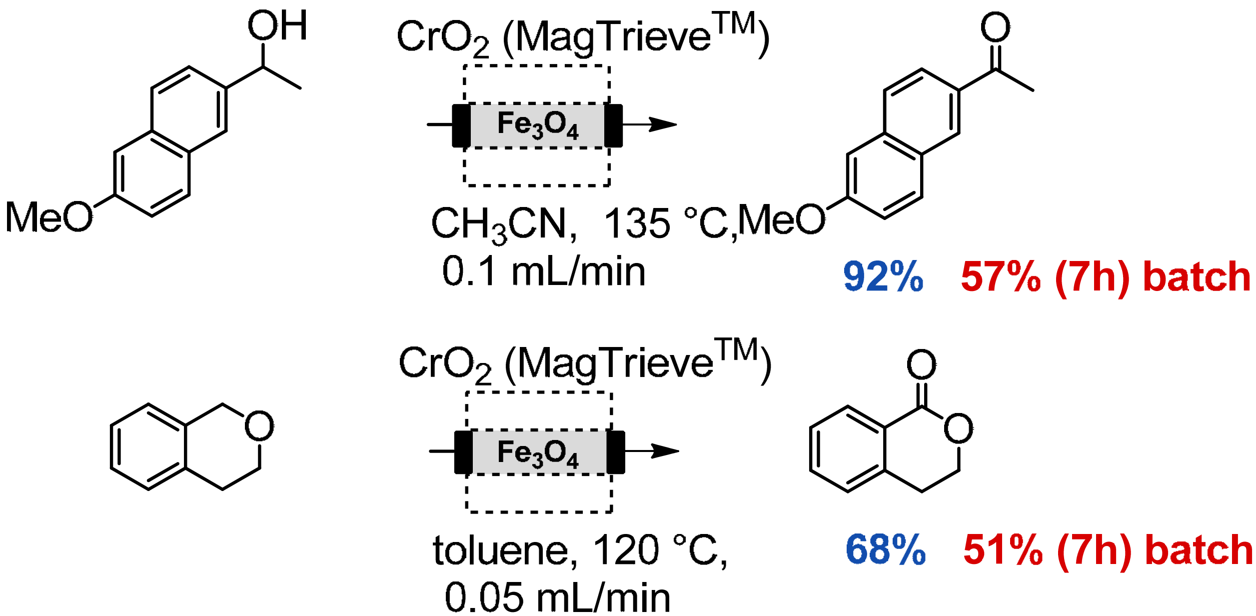
S. Ceylan, L. Coutable, J. Wegner, A. Kirschning, *Chem. Eur. J.*, **2010**, accepted.

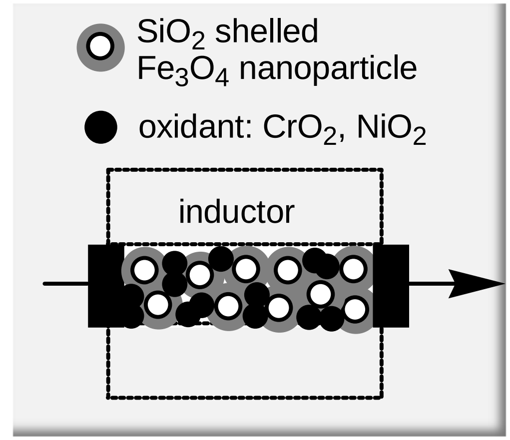
High pressure, high temperature oxidations in flow

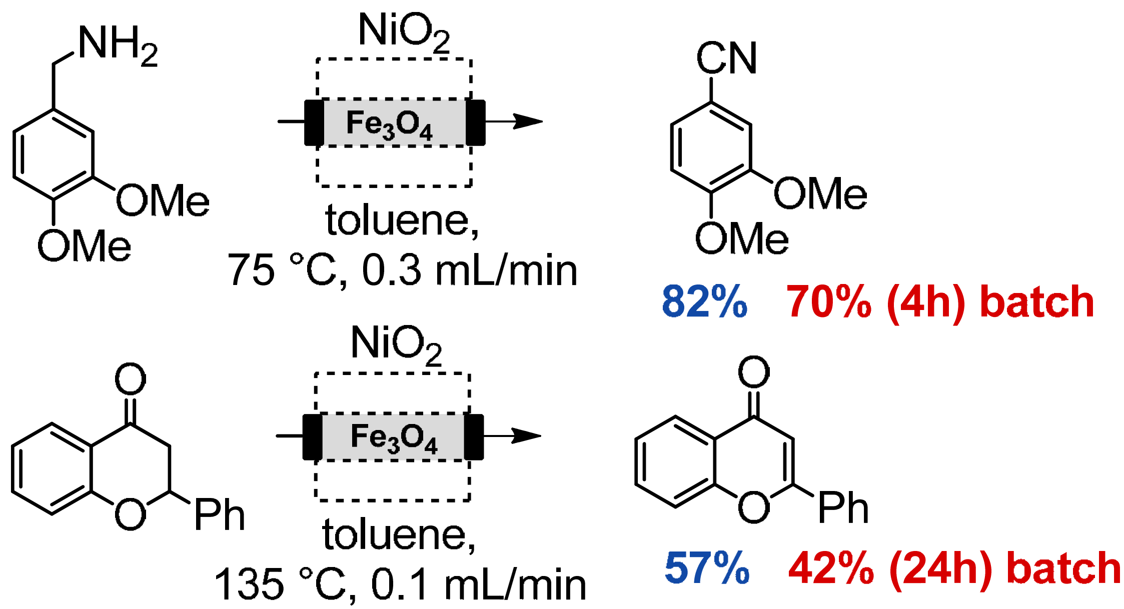




High pressure, high temperature oxidations in flow

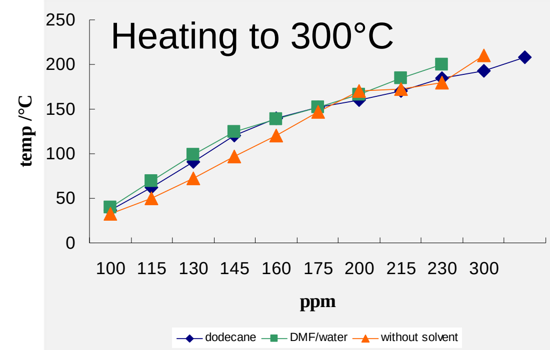






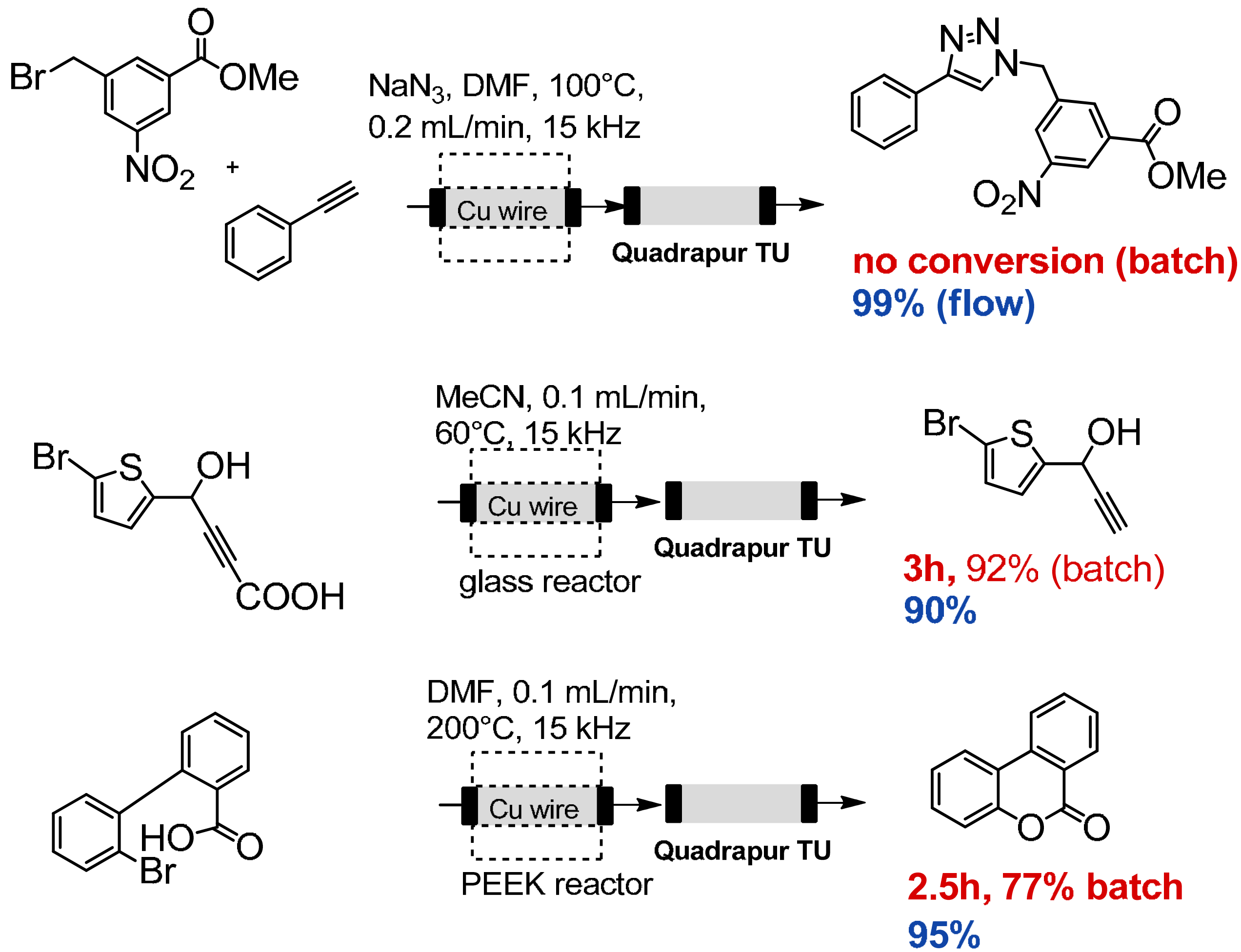
A. Kirschning, C. Friese, S. Ceylan, J. Wegner, *Eur. J. Org. Chem.* **2010**, 4372-4375.

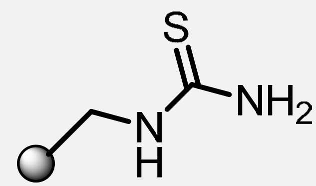
Chemical synthesis with inductively heated copper flow reactors



Residence time: 0.5 h

Chemical synthesis with inductively heated copper flow reactors





QP-TU

Residence time: 0.5 h

S. Ceylan, T. Klande, C. Vogt, C. Friese, A. Kirschning, *Synlett* **2010**, 2009-2013.

Leaching experiments

- Determination of metal residues

- ICP-OES measurements

thermal reactions

solvent[a]	Fe content[b]
dodecane	0.46 ppm
toluene	0.11 ppm
DMF	0.34 ppm
PEG	2.65 ppm
EtOH	0.25 ppm

[a] taken at 120 °C, flow rate 0.1 mL/min, MagSilica™
[b] average of three runs

oxidations

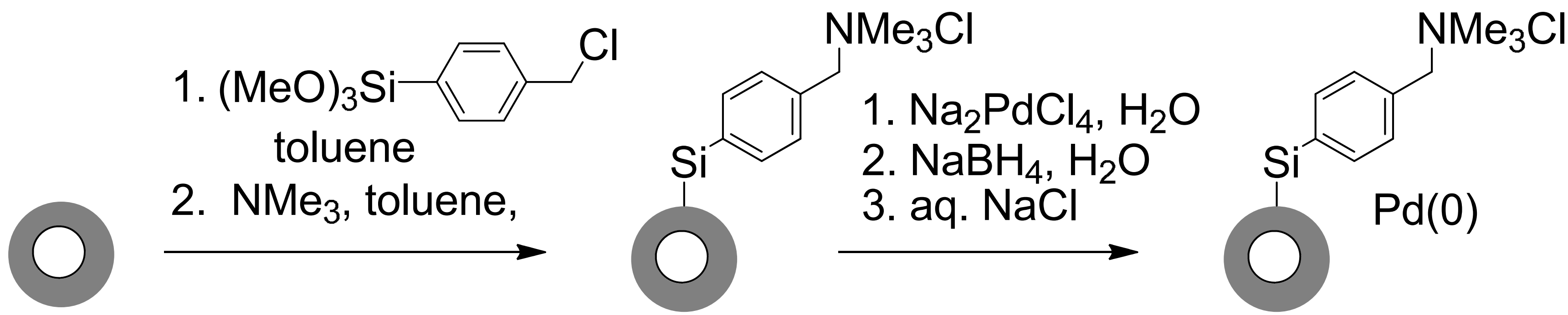
metal	metal content[a]
Fe	4.15 ppm
Ni	0.15 ppm
Cr	1.75 ppm

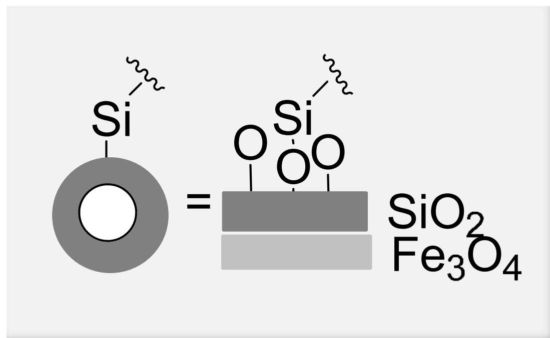
[a] average of three runs

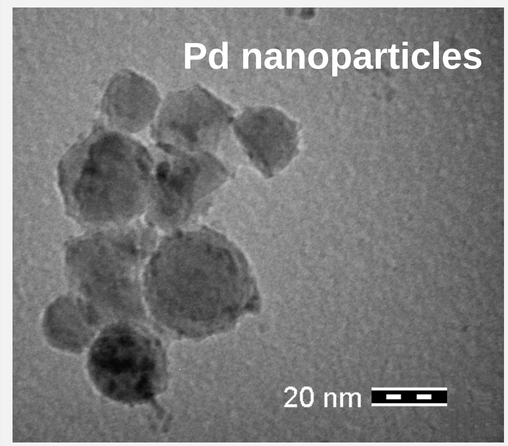
Cu catalysis

reaction	Cu content
„click“	3.52 ppm
decarboxylation	> 0.01 ppm
C-O-coupling	12.65 ppm

Immobilisation of Pd nanoparticles on magnetic nanoparticles



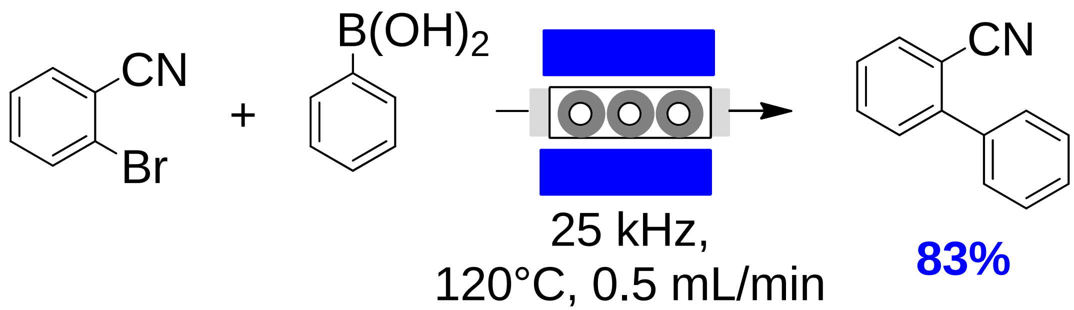




TEM micrograph

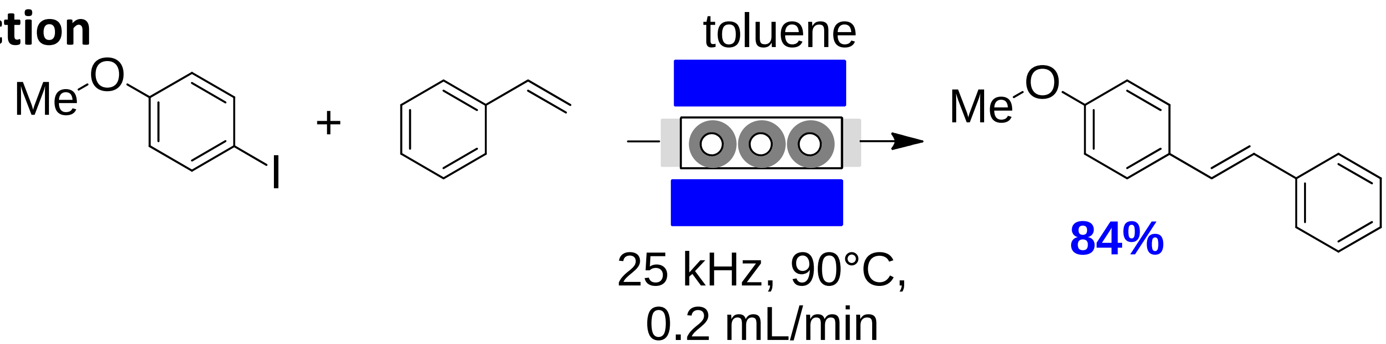
Pd nanoparticles on core-shell magnetic nanoparticles

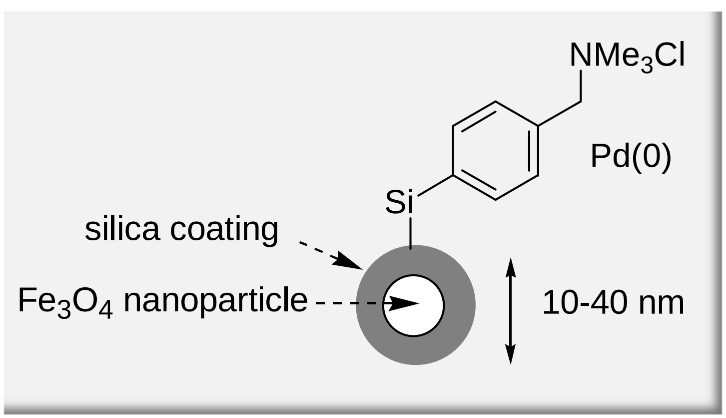
Suzuki-Miyaura reaction



34 ppm leaching of Pd

Heck-Mizoroki reaction

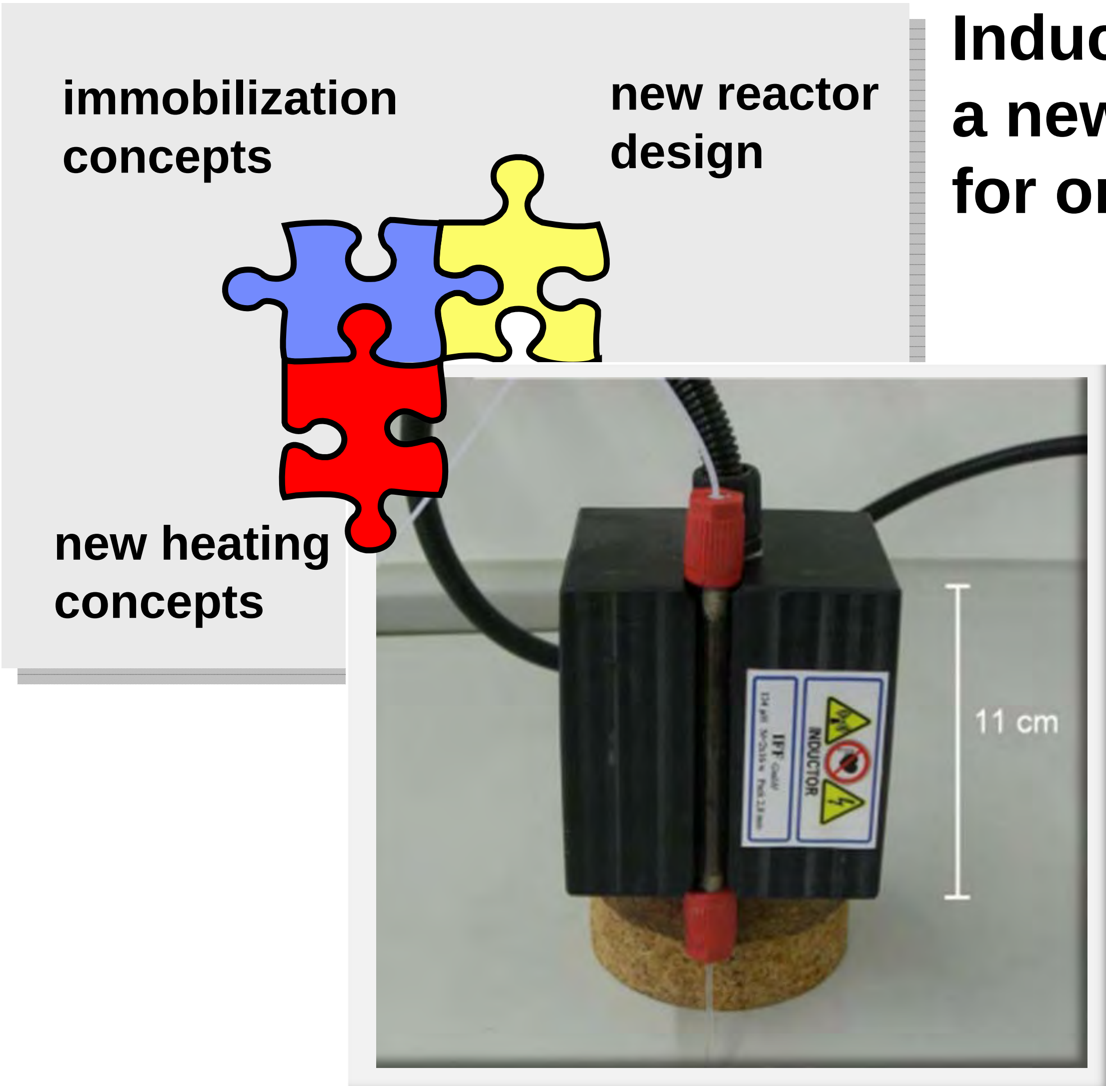




106 ppm leaching of Pd

Angew. Chem. **2008, *47*, 8950-8953.**

Inductive heating –
a new enabling technology for organic synthesis ?



a third, new heating technology

new tailor-made reactors and inductors

many reactions under flow conditions achieved (continuous processes)

synthesis under hypercritical conditions possible

successful immobilization of catalysts on MagSilica™

Leibniz Universität Hannover

Institut für Organische Chemie

BMWZ

The Key
Pioneers

Dr. G. Dräger

Dr. W. Solodenko

Dr. E. Kunst

Dr. K. Mennecke

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K. Grela (Warsaw)
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