Catalytic processes under continuous flow- Current trends and applications

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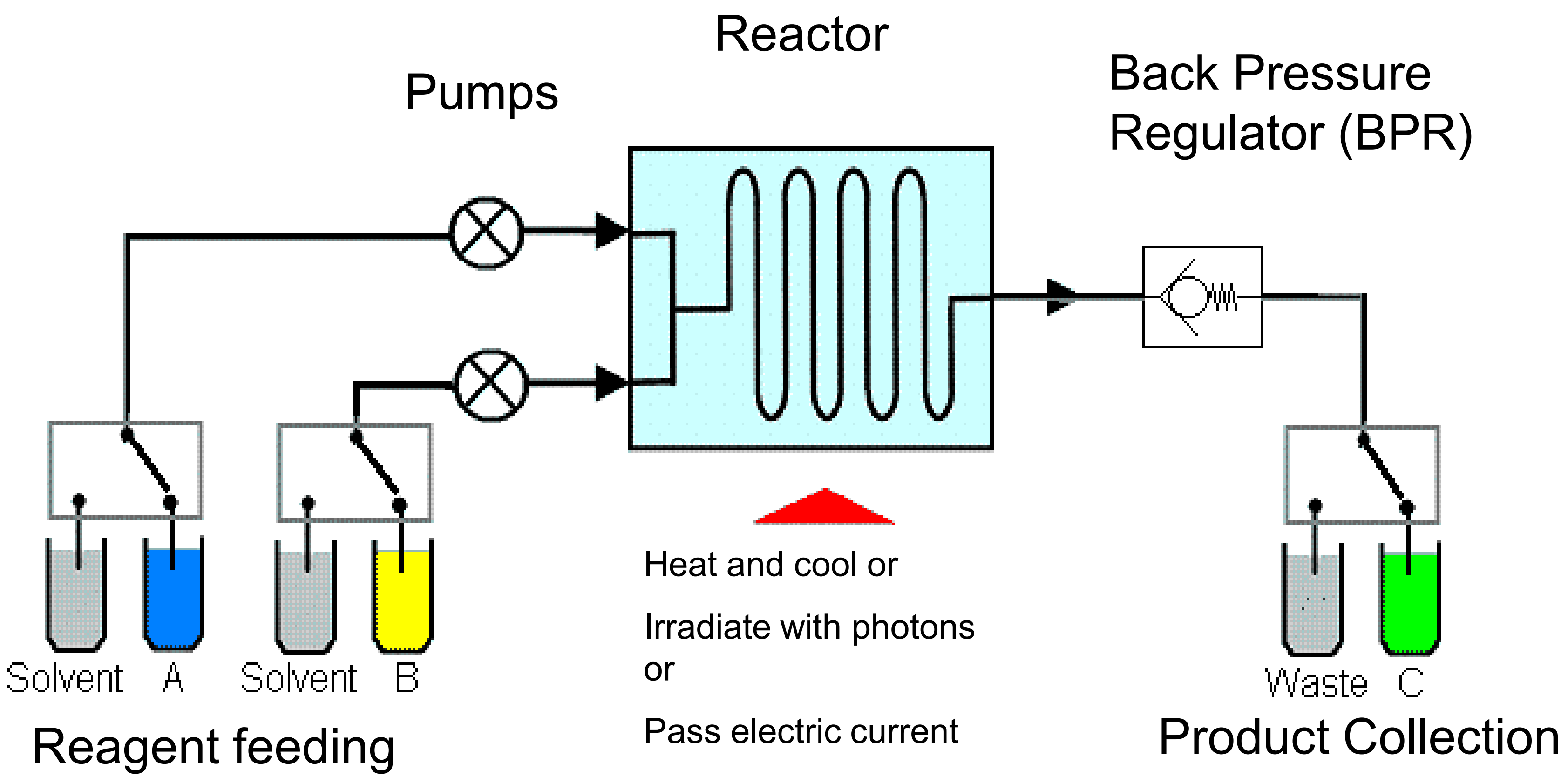
Vapourtec Key Facts

- Established 2003
- First Flow Chemistry System sold – May 2006
- Installed – Over 500 R-Series & 230 E-Series systems
- More than 300 UV-150 photochemical reactors in use
- Vapourtec only produce flow chemistry systems
- Strong patent portfolio
- New product pipeline in development

Important features of flow chemistry

- Excellent Heat transfer – surface area to volume ratio
- High rates of mass transfer – small sizes
- Precise control of reaction parameters
- Low back-mixing = separation of products from reactants
- Only small quantities of hazardous materials “in-process”
- Reactive intermediates don’t need to be isolated
- Zero head space = effective & safe at high pressure
- Run for longer to scale-up reactions

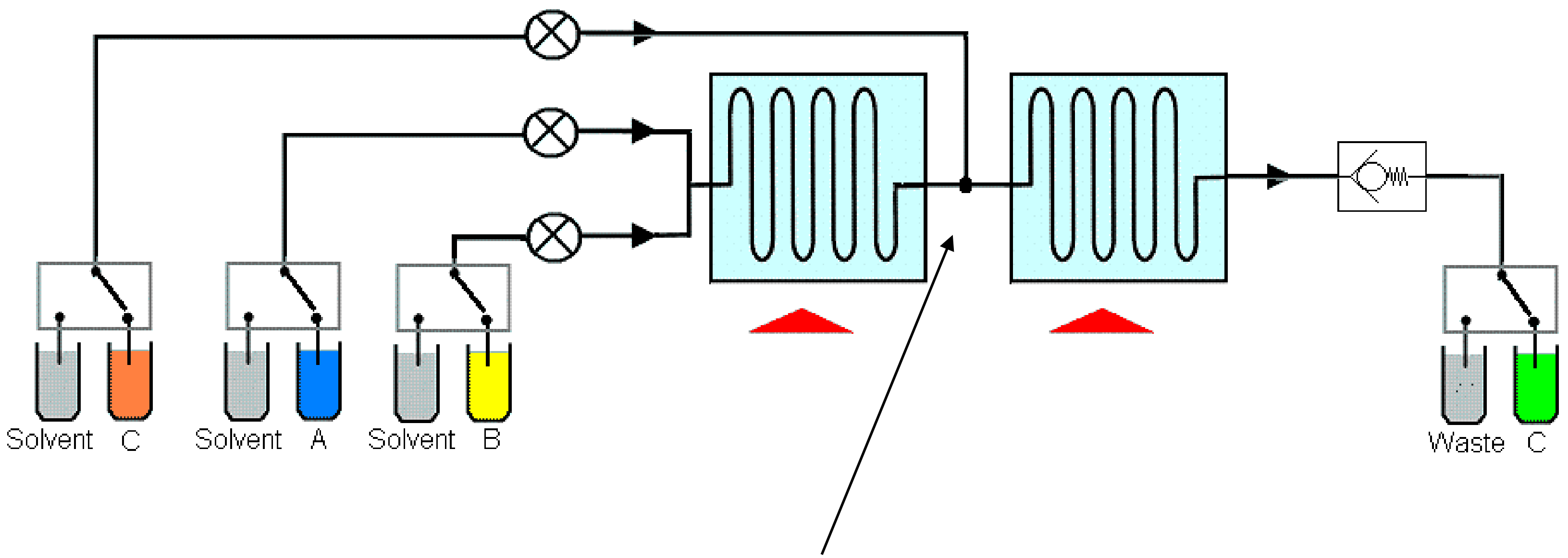
Flow chemistry – Basic set-up



Flow chemistry – Superheating of solvents

	TEMPERATURE (°C)															
	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250
1 Butanol	0.5	0.8	1.1	1.5	2.1	2.8	3.7	4.7	6.1	7.7	9.5	11.7	14.2	17.1	20.4	24.1
1 Propanol	1.2	1.6	2.3	3.2	4.1	5.4	7.0	9.0	11.3	14.0	17.2	20.9	25.2	30.0	35.5	41.7
Acetic Acid	0.6	0.8	1.1	1.4	1.9	2.5	3.2	4.1	5.1	6.3	7.8	9.5	11.4	13.7	16.3	19.2
Acetone	3.7	4.8	6.1	7.6	9.5	11.6	14.1	16.9	20.1	23.8	27.9	32.5	37.6	43.2	49.4	56.2
Acetonitrile	2.0	2.7	3.7	4.8	6.3	8.1	10.3	13.0	16.3	20.2	24.8	30.2	36.6	44.0	52.5	62.3
Benzene	1.8	2.5	3.1	3.9	4.9	5.9	7.2	8.6	10.3	12.2	14.4	16.9	19.6	22.7	26.1	29.9
Carbon tetrachloride	1.9	2.5	3.2	4.0	5.0	6.1	7.4	8.9	10.5	12.4	14.6	16.9	19.6	22.4	25.6	29.0
Chloroform	3.1	4.0	5.0	6.3	7.8	9.6	11.7	14.1	16.8	19.9	23.4	27.3	31.7	36.6	42.0	47.9
Cyclohexane	1.7	2.2	2.9	3.6	4.5	5.5	6.7	8.1	9.7	11.5	13.5	15.7	18.3	21.0	24.1	27.5
DCM	5.9	7.5	9.4	11.7	14.3	17.4	20.9	24.9	29.4	34.5	40.2	46.5	53.5	61.2	69.6	78.7
Di ethyl ether	6.1	7.6	9.4	11.5	14.0	16.8	20.0	23.6	27.7	32.2	37.3	42.9	49.0	55.7	63.1	71.0
Diglyme	0.1	0.2	0.3	0.4	0.6	0.8	1.0	1.3	1.7	2.2	2.8	3.6	4.4	5.5	6.7	8.1
Dioxane	1.0	1.3	1.7	2.3	2.9	3.7	4.7	5.9	7.2	8.8	10.6	12.7	15.2	17.9	21.0	24.4
DME	1.2	1.6	2.0	2.5	3.0	3.7	4.5	5.4	6.4	7.5	8.8	10.2	11.8	13.5	15.4	17.5
DMF	0.2	0.3	0.4	0.6	0.8	1.0	1.3	1.7	2.1	2.6	3.2	3.9	4.7	5.6	6.6	7.8
DMSO	0.1	0.1	0.1	0.2	0.2	0.3	0.4	0.7	0.9	1.2	1.5	2.0	2.5	3.2	4.0	5.0
Ethanol	2.1	2.9	4.0	5.3	7.0	9.1	11.6	14.7	18.3	22.6	27.6	33.4	40.1	47.7	56.3	65.9
Ether	6.1	7.6	9.4	11.5	14.0	16.8	20.0	23.6	27.7	32.2	37.3	42.9	49.0	55.7	63.1	71.0
Ethyl Acetate	2.0	2.7	3.5	4.4	5.6	6.9	8.5	10.4	12.5	14.9	17.6	20.7	24.1	27.9	32.1	36.8
Formic Acid	1.0	1.3	1.7	2.2	2.9	3.6	4.5	5.6	6.9	8.3	10.0	11.9	14.1	16.6	19.4	22.5
Heptane	1.2	1.7	2.2	2.9	3.8	4.8	6.1	7.6	9.5	11.6	14.1	16.9	20.2	24.0	28.2	33.0
Hexane	2.5	3.1	4.0	5.0	6.1	7.4	9.0	10.7	12.7	14.9	17.4	20.2	23.2	26.5	30.1	34.1
IPA	2.0	2.8	3.8	5.1	6.7	8.7	11.0	13.9	17.2	21.2	25.7	30.9	36.8	43.5	51.0	59.4
MEK	1.9	2.4	3.1	4.0	4.9	6.1	7.5	9.0	10.8	12.8	15.1	17.6	20.4	23.4	26.8	30.5
MeOH	3.3	4.5	6.0	7.9	10.2	13.0	16.5	20.6	25.4	31.1	37.7	45.3	54.0	63.9	75.1	87.7
NMP	0.0	0.0	0.1	0.1	0.1	0.2	0.3	0.4	0.5	0.7	1.0	1.2	1.6	2.0	2.5	3.1
Pentane	5.9	7.3	9.0	10.9	13.0	15.5	18.3	21.4	24.8	28.5	32.7	37.2	42.0	47.3	52.9	59.0
p-Xylene	0.3	0.4	0.6	0.8	1.1	1.4	1.7	2.2	2.7	3.4	4.1	5.0	6.0	7.1	8.4	9.9
t Butyl Alcohol	1.9	2.7	3.6	4.8	6.3	8.1	10.2	12.7	15.6	19.0	22.9	27.3	32.3	37.8	44.0	50.8
THF	2.7	3.5	4.4	5.5	6.9	8.4	10.1	12.2	14.4	17.0	19.9	23.1	26.6	30.5	34.7	39.4
Toluene	0.7	1.0	1.3	1.7	2.2	2.7	3.4	4.2	5.1	6.2	7.5	8.9	10.5	12.3	14.4	16.7
Water	1.0	1.2	1.8	2.6	3.7	5.0	6.6	8.5	10.8	13.5	16.5	20.0	23.8	28.1	32.8	37.9

Flow chemistry – Multi-step reactions



- Intermediate may be
  - Unstable
  - Toxic
  - Air or moisture sensitive
- Used immediately
  - Minimal inventory

Where our Customers apply flow chemistry

- Highly exothermic reactions
- Reactions involving unstable (or toxic) intermediates
- Very rapid reactions (Rt < 1 min)
- Reactions requiring superheating
- One or more very volatile reagents or dissolved gases
- Multi-phase: liquid/liquid, liquid/solid or gas/liquid
- Reactions requiring better selectivity
- Continuous flow photochemistry
- Continuous flow electrochemistry
- Easy scaleup route once reaction is optimized

Catalysis in flow – How to design a reaction

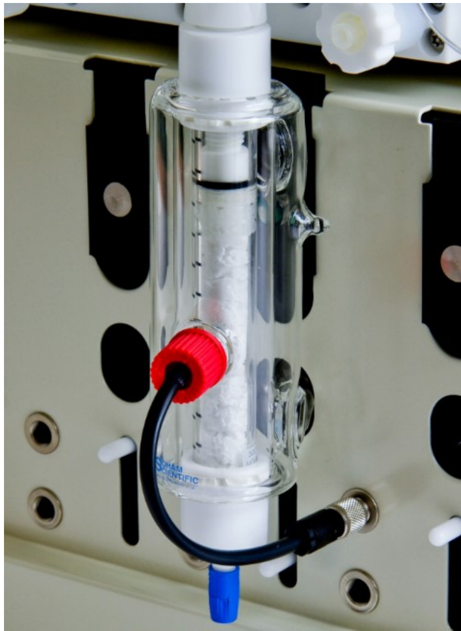
To translate batch catalytic reactions in continuous flow, three questions must be answered:

- Physical form of catalyst? — It will define how the catalyst is handled
- Physical properties of reagents? — It will define how to handle them and reaction parameters
- Thermally or non-thermally mediated reaction? — It will define the type of reactor needed

Catalysis in flow – Physical form of catalyst

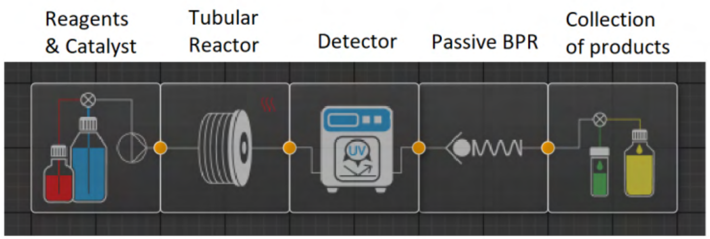
- **Homogeneous catalysts** – Same phase as reagents, usually liquid

- **Heterogeneous catalyst** –Different phase as reagent, usually solid

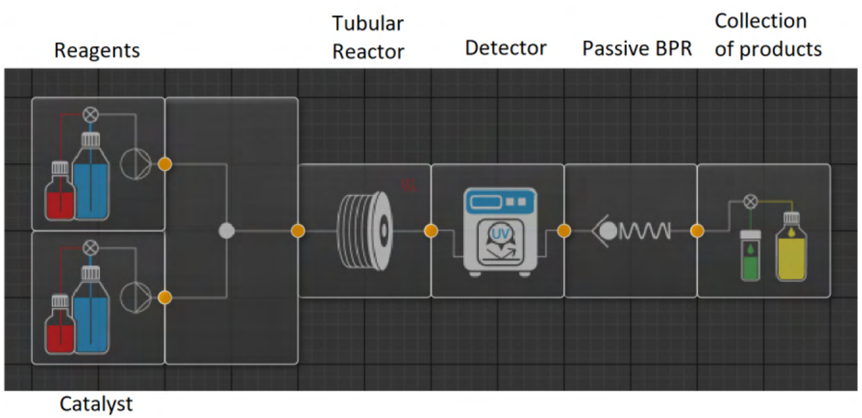


Catalysis in flow – Homogeneous catalysis

- Catalyst and reagent premixed in the same solution
  - Simple approach
  - Fixed stoichiometric ratios per solution

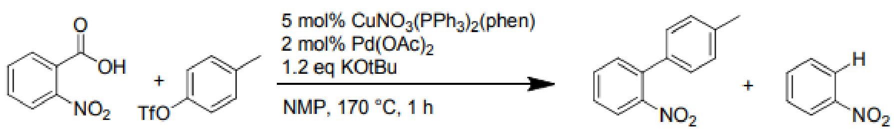


- Catalyst and reagent prepared in different solutions
  - Multi-channel approach
  - Tunable stoichiometric ratios with the same solutions

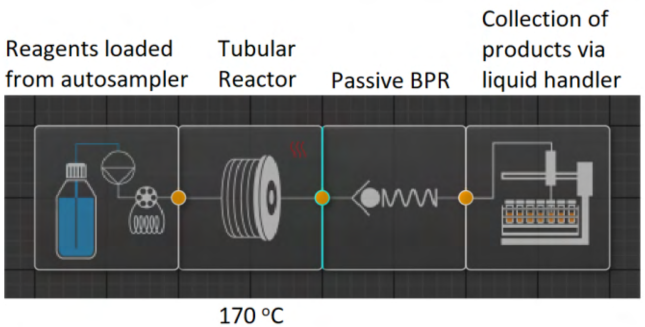


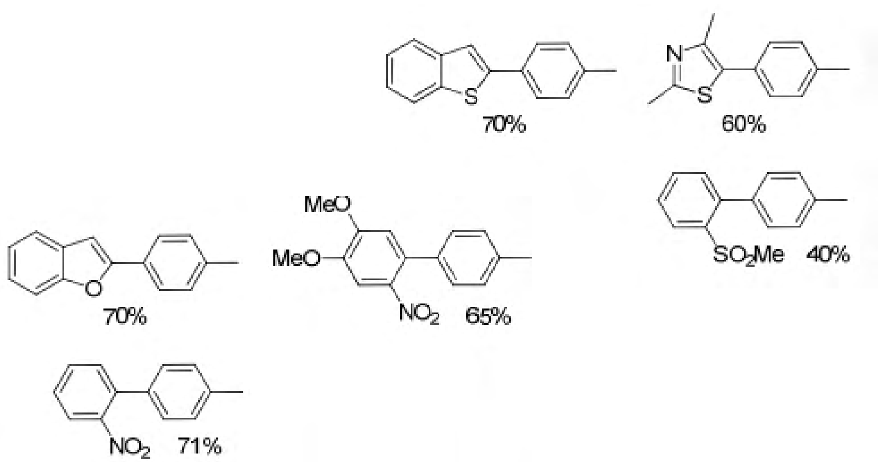
Catalysis in flow – Homogeneous catalysis

Decarboxylative cross coupling – Substrate scope*



Batch	7 %	37 %
Flow	71 %	0 %





Vapourtec Application Note 27 : Decarboxylative Cross-Couplings with a Soluble Catalyst System

Catalysis in flow – Heterogeneous catalysis

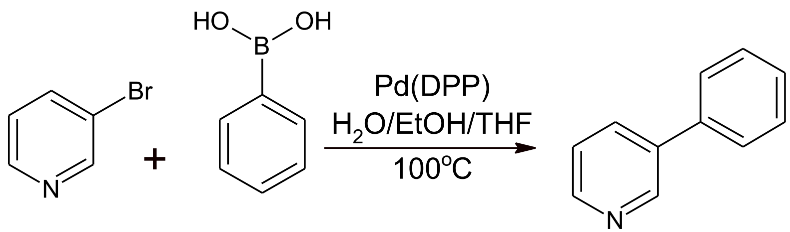
- **Fixed bed reactor** – Solid catalyst packed in a column, reagents flow through (*i.e. immobilized enzymes, Raney-Ni catalyst, etc.)*

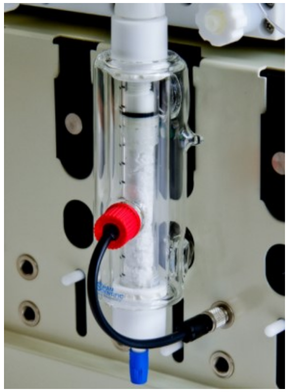
- **Solid catalyst pumped as slurry** – Some catalysts can be pumped as slurry (*i.e. Pd/C, TiO_2, etc.)*

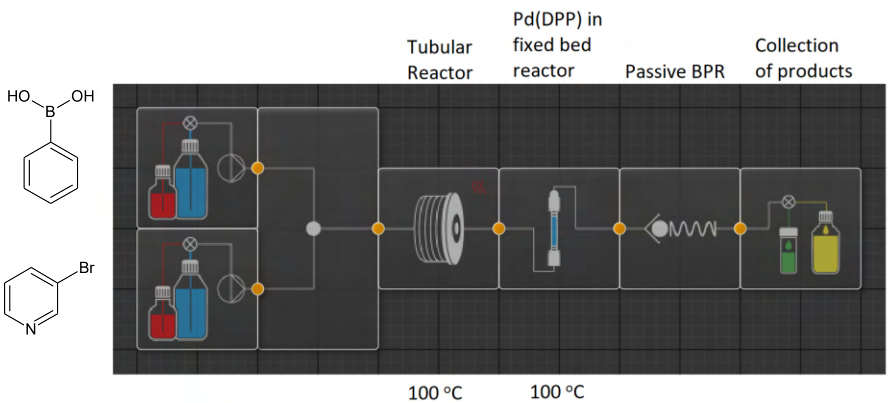
- **Catalytic reactors** – The reactor itself is the catalyst (*i.e. Copper reactor*)

Catalysis in flow – Heterogeneous catalysis

Suzuki-Miyaura coupling*





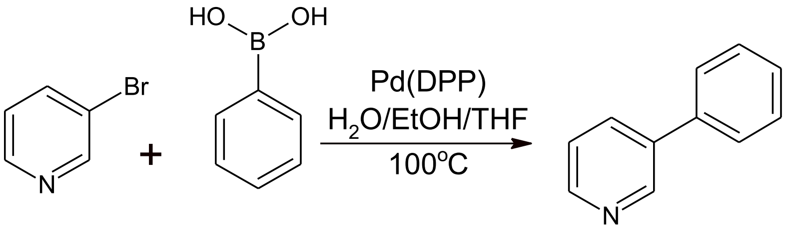


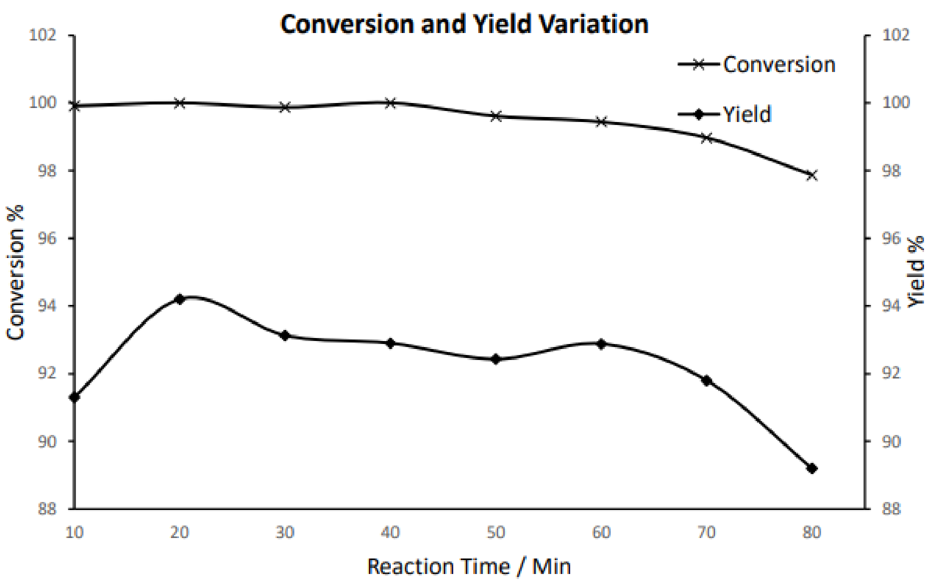
Temperature	Rt	Starting material	Product
70 °C	2.85 min	1.8 %	82.9 %
70 °C	5.00 min	0.2 %	93.3 %
100 °C	1.00 min	3.2 %	88.7 %
100 °C	1.25 min	3.6 %	85.7 %
100 °C	1.50 min	3.2 %	89.6 %

Vapourtec Application Note 49 – Suzuki Coupling with SiliaCat DPP-Pd Heterogeneous Catalyst

Catalysis in flow – Heterogeneous catalysis

Suzuki-Miyaura coupling*

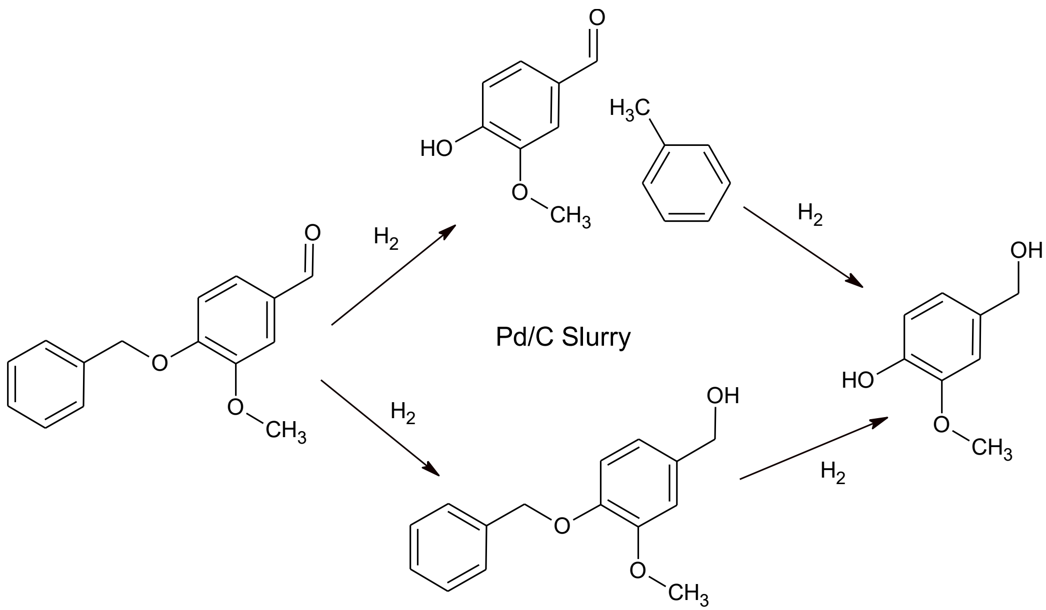




Vapourtec Application Note 49 – Suzuki Coupling with SiliaCat DPP-Pd Heterogeneous Catalyst

Catalysis in flow – Heterogeneous catalysis

Palladium on Charcoal Slurries with H_2 Gas*

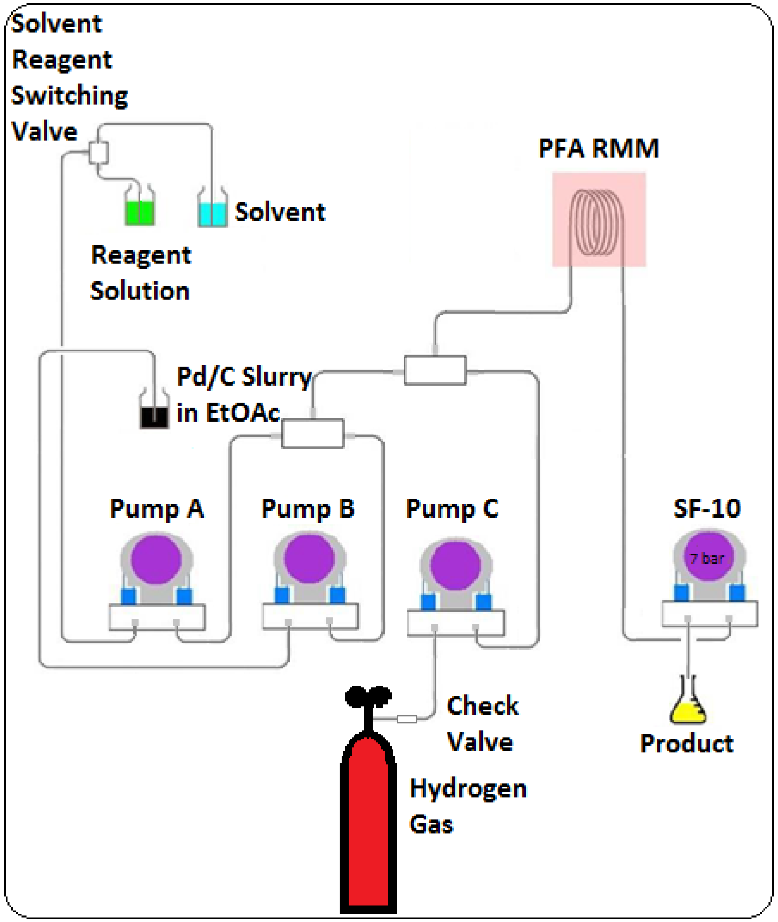


- Pd/C 5 and 10 %
- Up 100 mg/ml
- Pressure with peristaltic BPR
- H_2 using same pump type
- 16 experiments in under 12 h
- Selectivity

Catalysis in flow – Heterogeneous catalysis

Palladium on Charcoal Slurries with H_2 Gas*

- Reagents prepared in a single reservoir
- Pd/C suspended in EtOAc on a stirrer plate – prevents settling
- Peristaltic V-3 is able to pump the slurry directly
- T-piece arranged so that the slurry doesn't change direction
- Peristaltic BPR makes it possible to use the slurry at pressures up to 10 bar

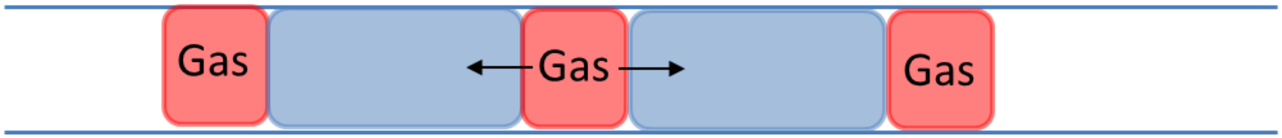


Vapourtec Application Note 54 – Selective hydrogenation of O-benzyl vanillin using hydrogen gas and a palladium on charcoal slurry

Catalysis in flow – Heterogeneous catalysis

Palladium on Charcoal Slurries with H_2 Gas*

- Pumping slurries of up 100 mg/ml 5 and 10% palladium on charcoal **under pressure** continuously
- 3-phases in flow
- Avoids pressure limitations of packed beds
- **81%** isolated yield - **selective** between products
- Use of the V-3 pump to control back pressure
- Versatile ability to optimise catalyst conditions
- Over **6 g/h** of an API intermediate from a 1 mm bore reactor

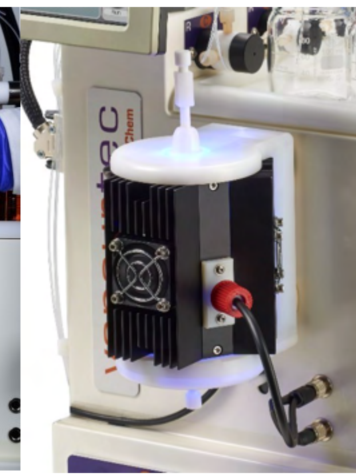


**Vapourtec Application Note 54 – Selective hydrogenation of O-benzyl vanillin using hydrogen gas and a palladium on charcoal slurry*

Catalysis in flow – Novel reaction pathways

What happens when the reaction is not thermally mediated?

- Photocatalysts need of photons to promote reactions
- Electrocatalysts need of electrons to promote reactions



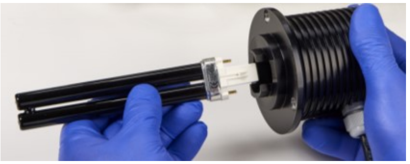
- These reactions are traditionally difficult in batch due to:
  - Non-homogeneous radiation field
  - Hot-spots
  - …

Catalysis in flow – Photocatalysis

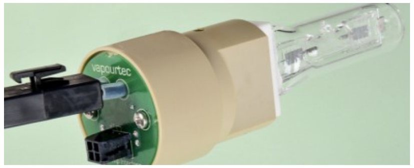
Different photocatalysts require of different wavelengths

- TiO_2, TBADT ~365 nm
- 4CzIPN ~ 420 nm
- $[Ir(dFCF3ppy)_2(5,5'\text{-}dCF_3bpy)](PF_6)$~450 nm

Low pressure mercury - 3 options:
- 254 nm
- 310 nm
- 370 nm



Medium pressure mercury:
220 nm to 600 nm
filters to select desired wavelength

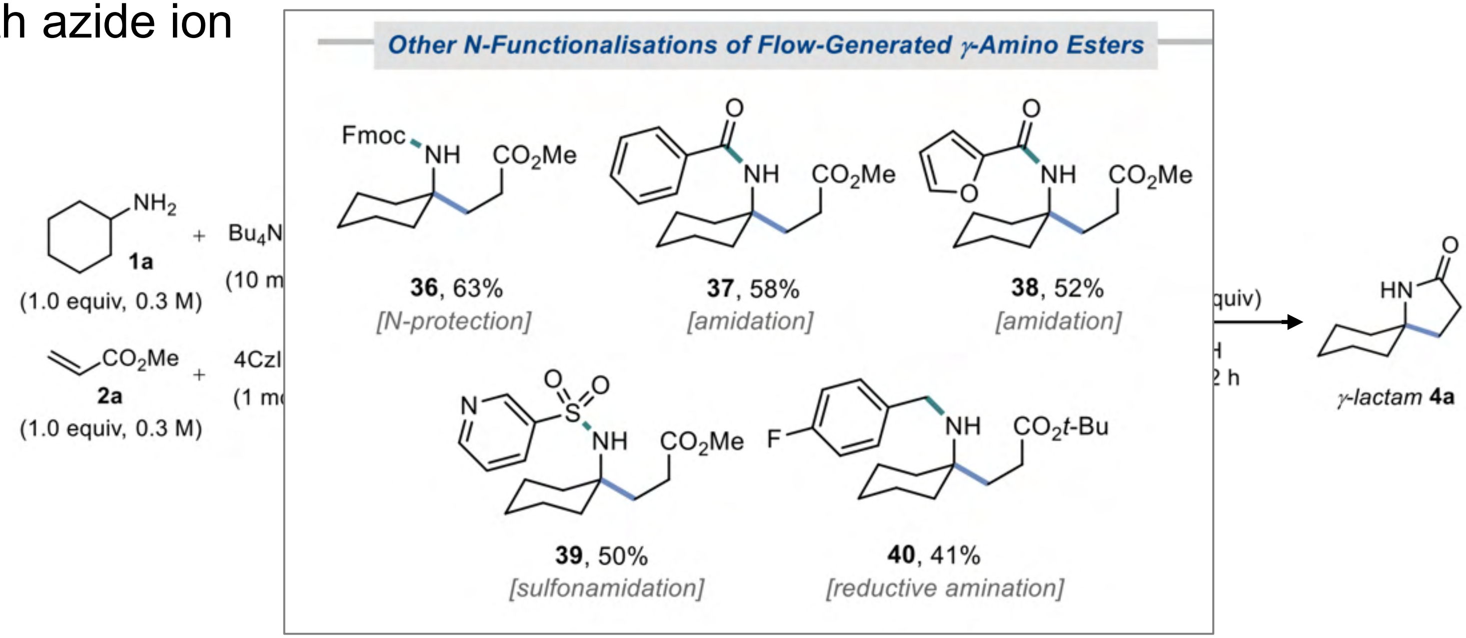


LEDs:
a range of precise wavelengths 365-700 nm
60 or 150 W input power

Catalysis in flow – Photocatalysis

Photocatalytic synthesis of γ-lactams*

- Simple and direct synthesis of γ-lactams and α-tertiary amine derivative
- (HAT) catalyst - using a cheap organic photocatalyst (4CzIPN) in combination with azide ion

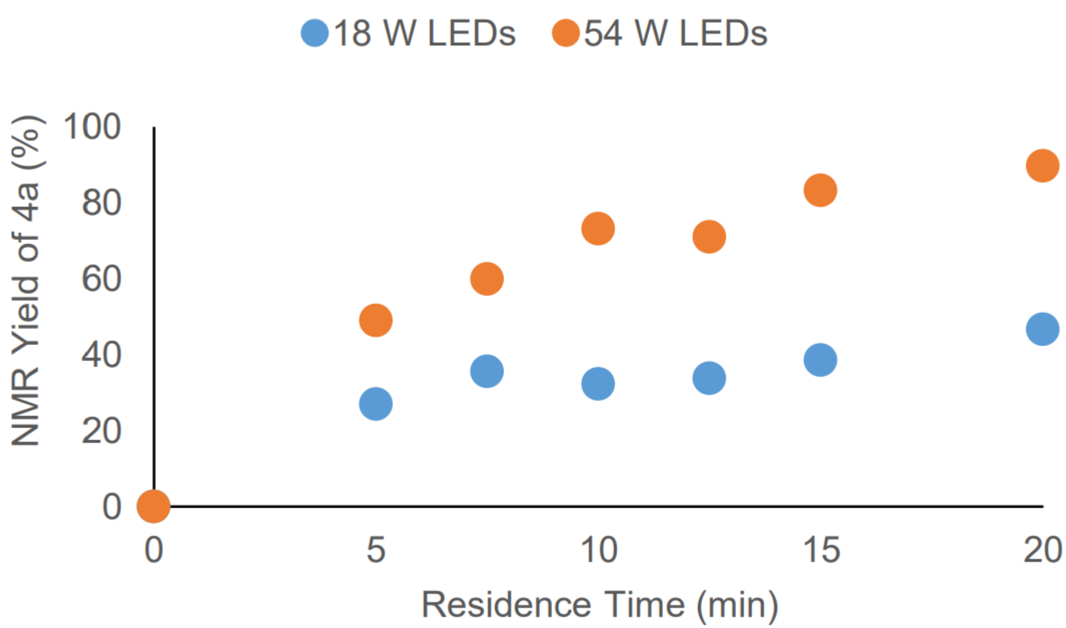


*1. Vapourtec Application Note 68: Photocatalytic Synthesis of γ-Lactams and α-Tertiary Amine Derivatives in Continuous Flow

*2. A. S. H. Ryder et al. Angew. Chem. Int. Ed., 2020

Catalysis in flow – Photocatalysis

Photocatalytic synthesis of γ-lactams – Effect of photonic loading*

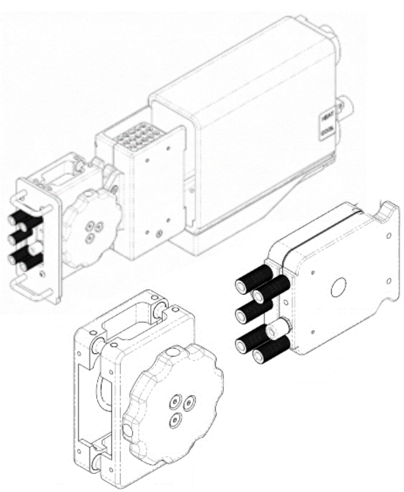


*1. *Vapourtec Application Note 68: Photocatalytic Synthesis of γ-Lactams and α-Tertiary Amine Derivatives in Continuous Flow*

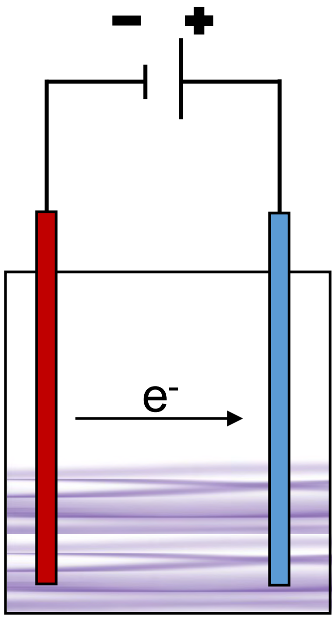
*2. *A. S. H. Ryder et al. Angew. Chem. Int. Ed., 2020*

Catalysis in flow – Electrocatalysis

- Integrated or stand-alone versions
- Working temperatures: from -10 °C to 100 °C
- Limit pressure up to 5 bar, allowing to work above solvent's boiling point and with gas mixtures
- Vapourtec supplies 20 different electrodes



Catalysis in flow – Electrocatalysis



Electrochemistry – Basic principles

- Reactions carried on an electrolytic cell
- Flow of electrons drives non-spontaneous redox reactions
- Working in batch held back electrosynthesis…

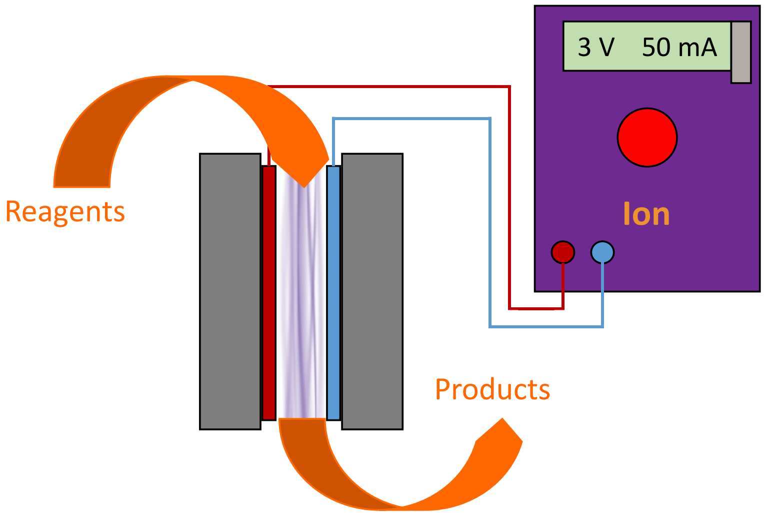
Non-homogeneous electric field
Need of electrolyte
Hot-spots on solution media

Low efficiency and/or difficult purification

Catalysis in flow – Electrocatalysis

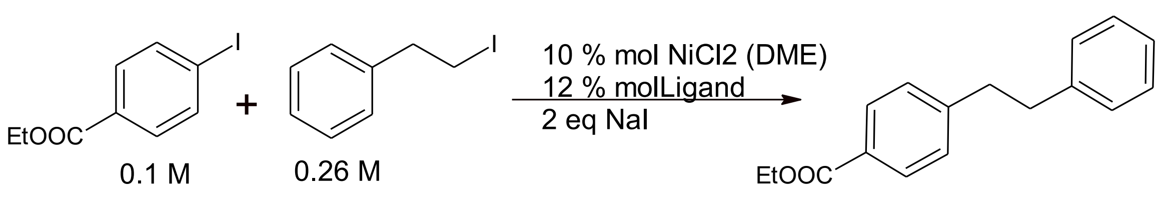
New opportunities in flow

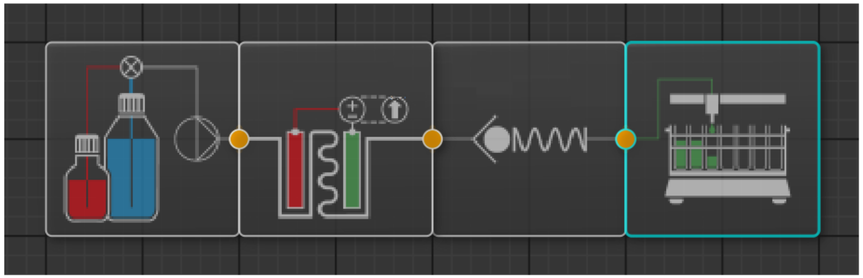
- By flowing reagents through a microreactor you can overcome batch issues
  - Homogeneous electric field
  - Electrolyte is now an option
  - Homogeneous temperature
- Why to switch from organic oxidants?
  - Non-hazardous reagents
  - Selectivity based on current



Catalysis in flow – Electrocatalysis

Electrochemical Csp2-Csp3 cross coupling of organic halides*





Entry	Temperature	Flow rate	Rt	Ligand	SM	TM
1	30 °C	0.06 ml/min	10 min	Dtbbpy	38 %	18 %
2	30 °C	0.03 ml/min	20 min	Dtbbpy	5 %	40 %
3	50 °C	0.06 ml/min	10 min	Dtbbpy	9 %	38 %
4	50 °C	0.03 ml/min	20 min	Dtbbpy	0 %	50 %
5	50 °C	0.06 ml/min	10 min	L1	5 %	55 %
6	**50 °C**	**0.03 ml/min**	**20 min**	**L1**	**0 %**	**81 %**

**Application Note 63: Electrochemical pathway for cross coupling of organic halides - Csp2-Csp3 bonding*

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