Effect of phase transfer chemistry, segmented fluid flow and sonication on the synthesis of cinnamic esters.

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Introduction and Scope of the Project

Phase-Transfer Catalyst (**PTC**) technology is used in the commercial manufacture of more than $10 billion per year of chemicals, including pharmaceuticals, flavours & fragrances, dyes, additives and polymers.

PTC PROS[1]

- ✓ Improved yield and selectivity
- ✓ Reduced variability
- ✓ Improved Environmental Performance
  - lower organic solvent consumption
  - less by-products
- ✓ Enhanced Safety
  - better control of exothermic reactions
  - use less hazardous reagents
- ✓ Reduced Manufacturing Costs
  - use alternate less expensive or easier to handle raw materials
  - avoid water sensitive reactants

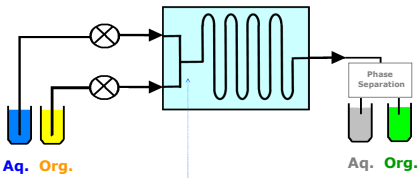
PTC CONS[1]

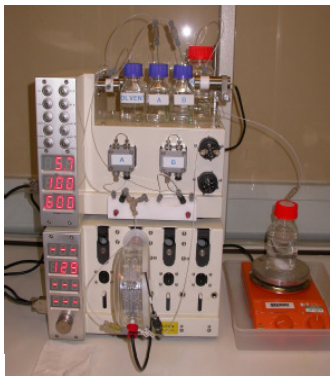
- ✘ Difficult scale up
- ✘ Long reaction time
- ✘ Mixing is crucial
- ✘ Presence of Phase transfer catalyst

FLOW CHEMISTRY PROS[2]

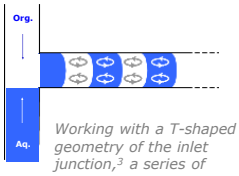
- → Easy scale up
- → Short reaction time
- → High surface-to-volume ratio
- ➢ Precise control of variables (e.g temperature, pressure, concentration, residence time and heat transfer)
- ➢ Superheating
- ➢ Enhanced Safety

Generic scheme of a bi-phasic reaction under flow chemistry conditions.

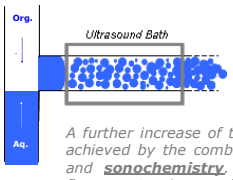




Vapourtec R2-R4 series Flow Reactor

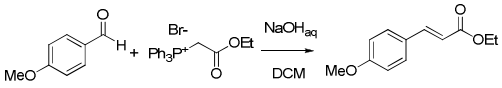


*Working with a T-shaped geometry of the inlet junction,[3] a series of organic-aqueous **segments** is generated.*



*A further increase of the interface area can be achieved by the combination of flow chemistry and **sonochemistry**. Indeed, immersing the flow reactor in an ultrasound bath, irregular sized segments and emulsion are formed.*

Model Reaction and Set-up of optimal conditions



System	Isolated Yield (%)	Reaction time
Flask reaction [4]	55	24 h
Flow system	78	30 min [a] (RT[b]: 5 min)
Flow system without PTC	63	30 min (RT: 5 min)
Flow system without PTC and with sonication	**96**	**30 min (RT: 5 min)**

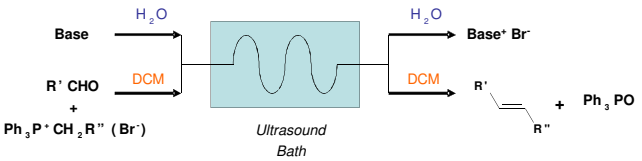
OPTIMAL CONDITIONS:

Reactor volume: **10 ml**
Reagents Flow rate: **1 ml/min**
Residence Time (RT): **5 min**
Temperature: **RT**
Organic solvent: **DCM**
Stoichiometry:
1 eq. aldehyde
2 eq. phosphonium salt
2 eq. base

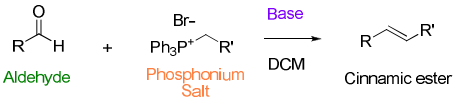
PTC-free
Only E-isomer achieved

[a] *The reaction was performed on the same amount of starting material (1 mmol) as in the flask reaction system*

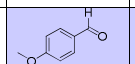
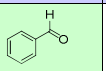
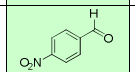
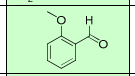
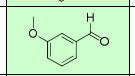
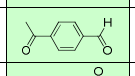
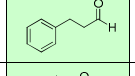
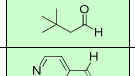
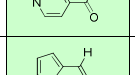
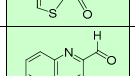
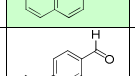
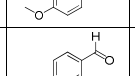
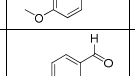
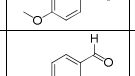
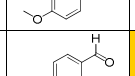
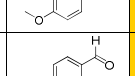
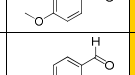
[b] *RT (retention time) = Reactor Volume (ml)/Tot Flow Rate (ml/min)*



Preparation of a set of cinnamic derivatives



- **PTC-free**
- **Only E-isomer achieved**

	Entry[a]	Aldehyde	Phosphonium Salt	Base	Isolated Yield [b,c] (%)
Aldehyde investigation	1			NaOH	96
	2			NaOH	98
	3			NaOH	98
	4			NaOH	83 [d]
	5			NaOH	86
	6			NaOH	37
	7			NaOH	63
	8			NaOH	53
	9			NaOH	75
	10			NaOH	100
	11			NaOH	48
Base investigation	12			LiOH	-
	13			K_2CO_3	98
	14			$NaHCO_3$	78
	15			DMAP	78
Phosphonium salt investigation	16			NaOH	95
	17			NaOH	42[d]
	18			NaOH	48[e]

[a] *Reactor volume: 10 mL; Reagents Flow rate: 1 mL min-1; Temperature : room temperature; Organic solvent: DCM; Molar ratio: aldehyde/ phosphonium salt/ Base=1/2/2 (without PTC).*

[b] *The Z-stereoisomer was not revealed in UPLC-MS analysis.*

[c] *Product purified by flash chromatography on silica gel.*

[d] *E:Z stereoisomers in 6:1 ratio, as determined by ^{1}H-NMR.*

[e] *E:Z stereoisomers in 1.4:1 ratio, as determined by ^{1}H-NMR.*

Conclusions

➢ It has been proved that combination of phase transfer chemistry, flow chemistry and sonochemistry can lead to significant improvements in bi-phasic reactions.

➢ A simple, mild and fast protocol for the synthesis of cinnamic ester derivatives has been developed. This protocol:

- can be **applied** to different aldehydes, alkyl phosponium salts and bases
- avoids phase transfer **catalysts**
- allows short **reaction time** (5 minutes residence time)
- leads to good **yield** and high **E/Z-selectivity**
- allows an easy **scale up**

References

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