

# Benzoic acids and phenols alkylation within microreactor: Toward a selective and continuous multistep process

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ERA Chemistry – 6<sup>th</sup> Flash Conferences  
Roscoff (France)  
28<sup>th</sup> february – 4<sup>th</sup> march 2010

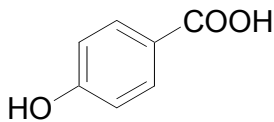


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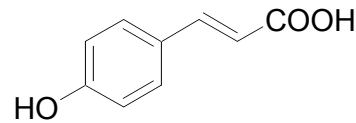
# Selective polyphenol functionalization

Polyphenols are naturally abundant (over 4,000 distinct species)

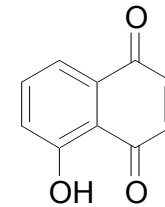
Hydroxybenzoic acids  
(spice, strawberry)



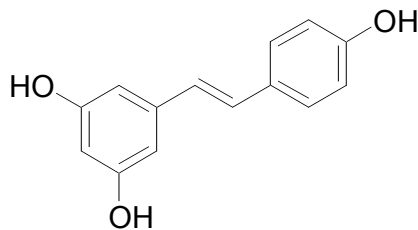
Hydroxycinnamic acids  
(tomatoes)



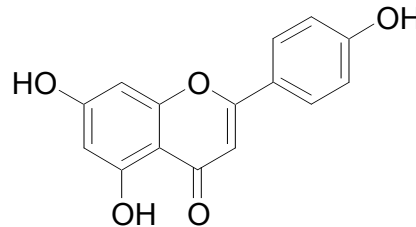
Naphtoquinones  
(walnut)



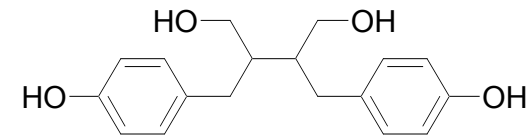
Trans-stilbenes  
(grape)



Flavanoids  
(strawberry)



Lignans  
(wood, intestinal bacteria)



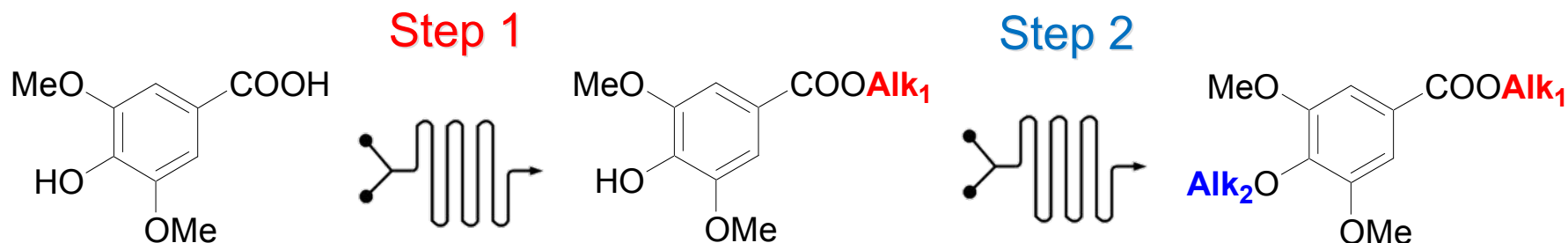
**Green Chemistry (Bioresource)**



**Precursors for Medicinal Chemistry**

# Multistep selective alkylation of polyphenol

## CHALLENGE



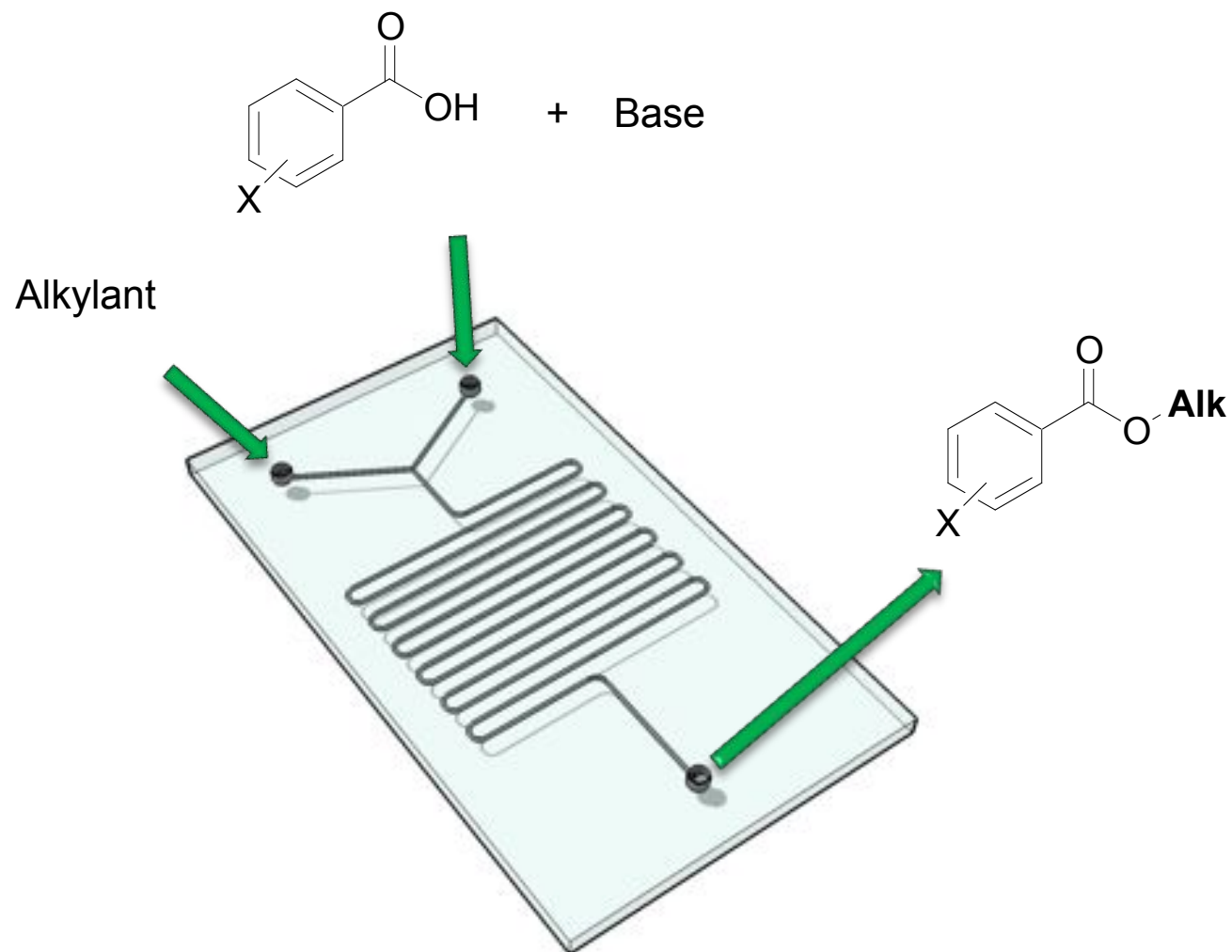
➔ Continuous green process without purification of the intermediate

➔ High structural diversity

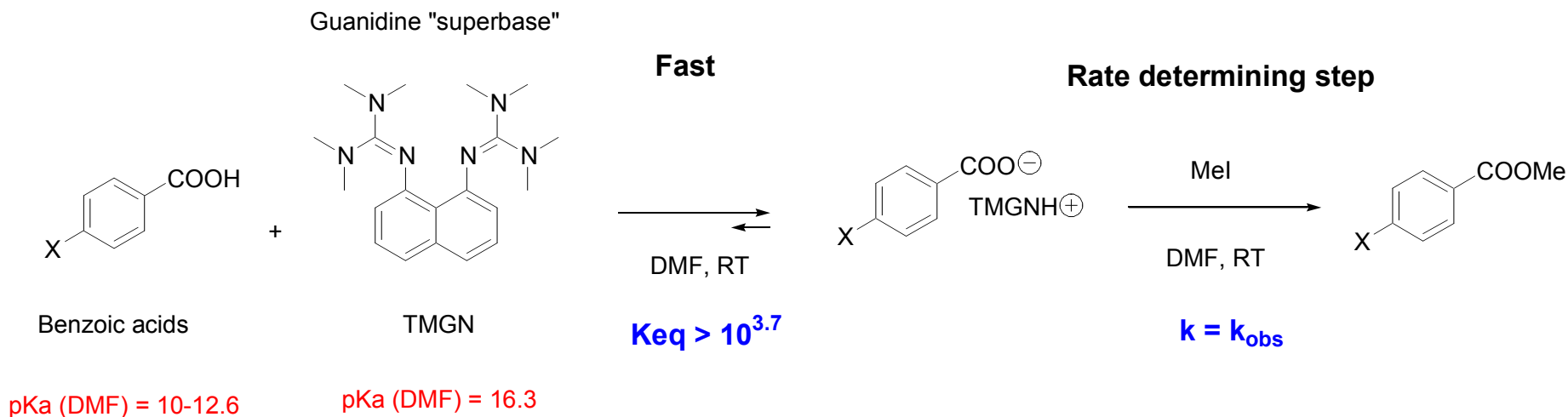
Strategy: 1) Optimisation of the two steps separately  
2) Connection of the two steps

# First step: Benzoic acid alkylation within microreactor

Azarmidokht Gholamipour-Shirazi (PhD)



# Benzoic acid alkylation in the presence of a superbases



[Benzoic acid]<sub>0</sub> : 0.2 mol.L<sup>-1</sup>

➔ **NMR kinetic study:** The reaction is complete after 2 minutes

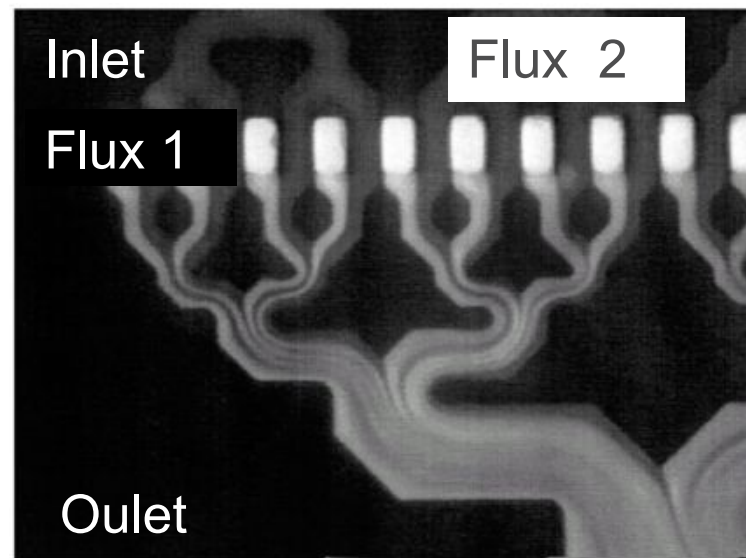
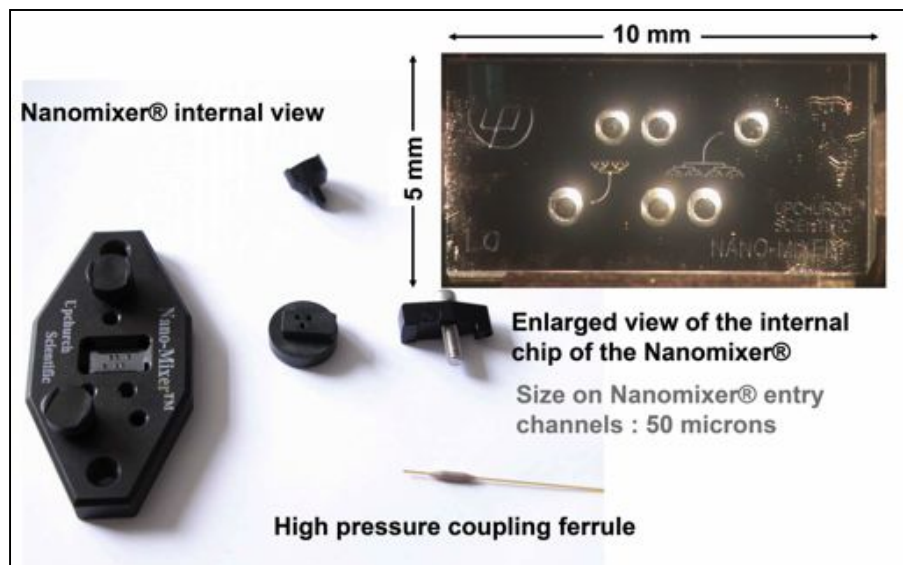
➔ **Flash reaction**



➔ The reaction can be easily transposed under microflow

# Experimental setup for benzoic acid alkylation

Mixing device : Nanomixer® from Upchurch Scientific

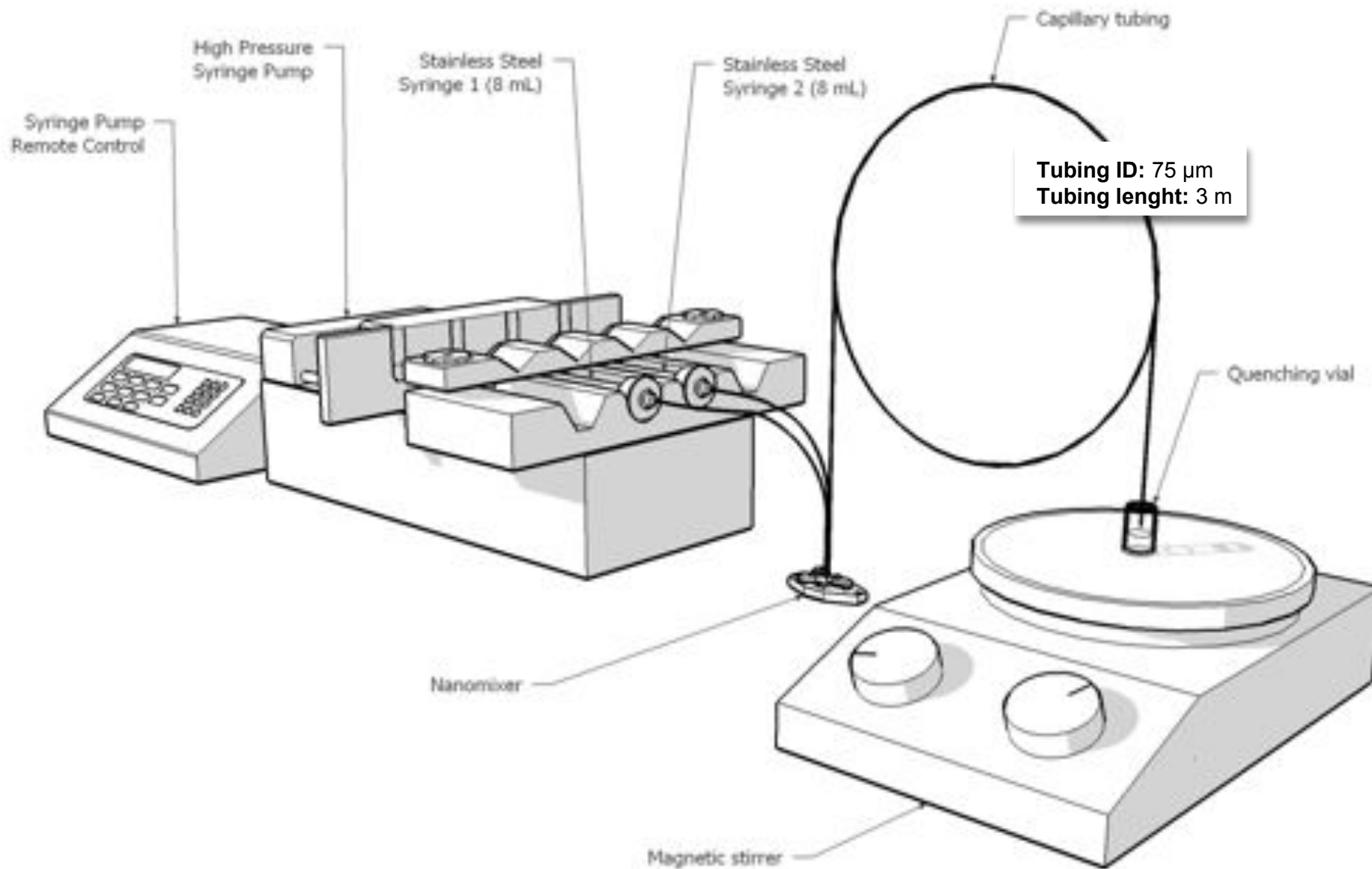


➔ Multilaminating mixer

➔ Fast mixing by diffusion

➔ Fast & Selective deprotonation of most acidic position

# Experimental setup for benzoic acid alkylation



High pressure drop induced by the Nanomixer®

# Parameters to control

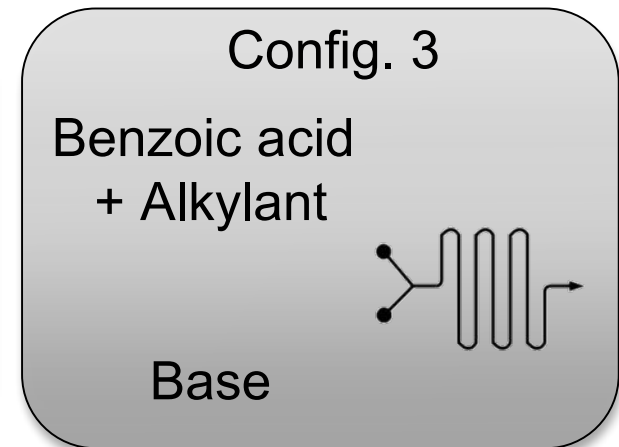
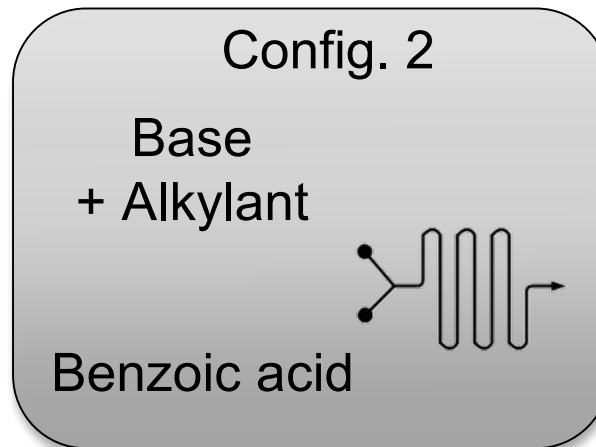
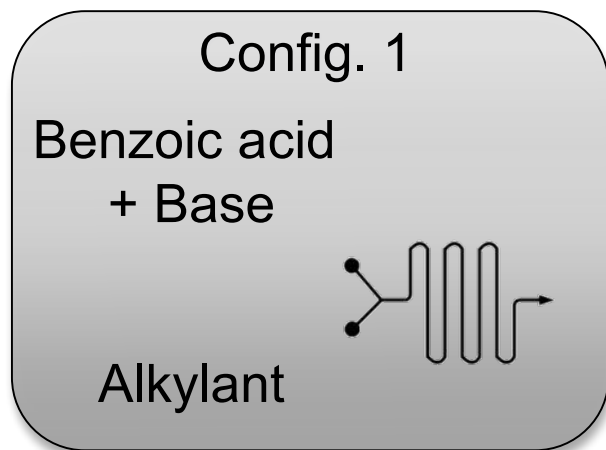


Classical parameters :

1. Concentration
2. Flow rate
3. Residence time (Internal diameter & length of the microsystem)



3 possible configurations



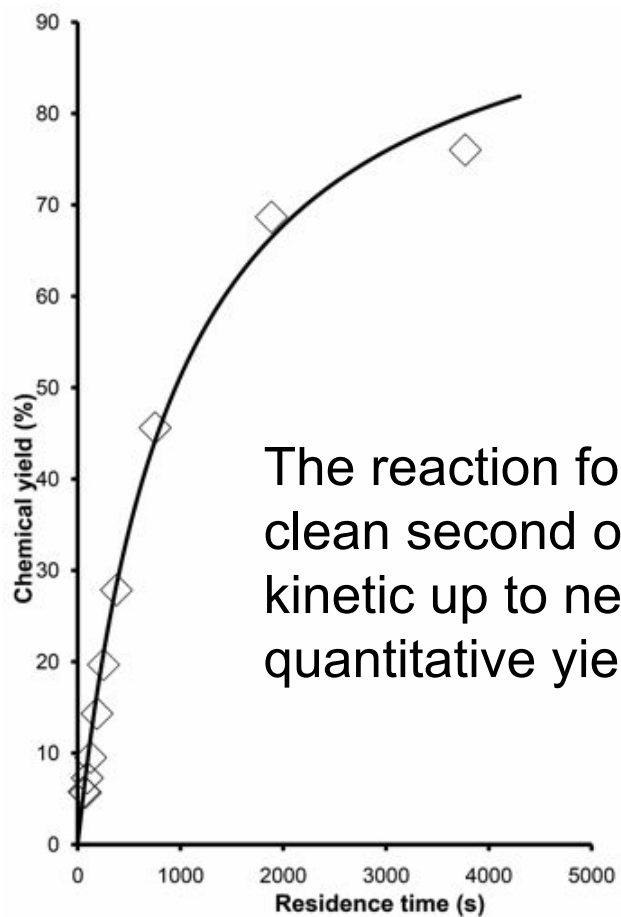
Comparison with batch

### Config. 1

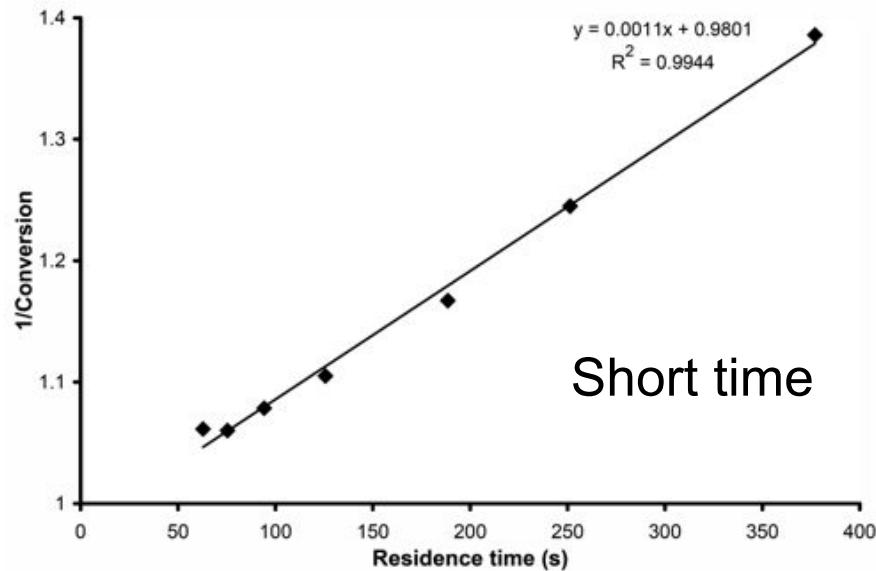
Benzoic acid  
+ Base  
Alkylant



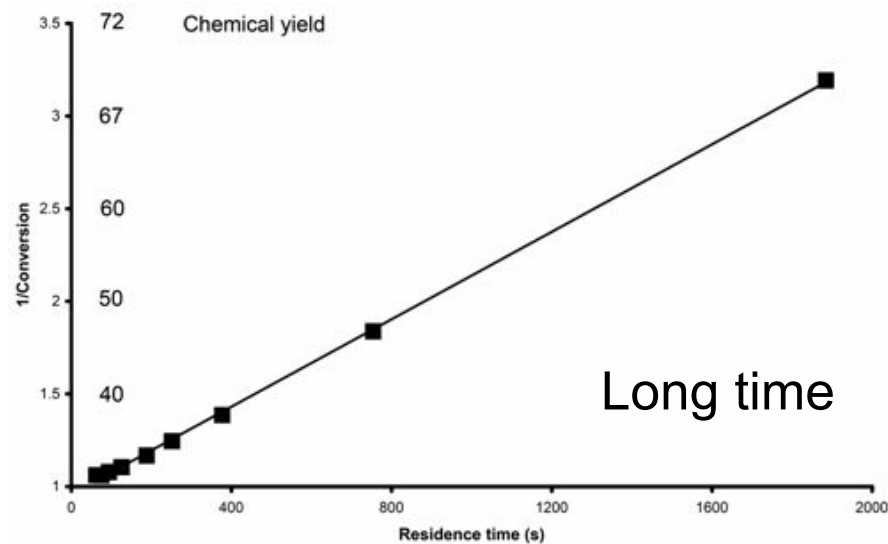
$[\text{Benzoic acid}]_0 : 0.002 \text{ mol.L}^{-1}$



The reaction follows a clean second order kinetic up to near quantitative yield



Short time



Long time

# Kinetic results summary



$$k = 0.311 \text{ mol}^{-1} \cdot \text{L} \cdot \text{s}$$

Config. 1

Benzoic acid  
+ Base  
Alkylant



$$k = 0.349 \text{ mol}^{-1} \cdot \text{L} \cdot \text{s}$$

Config. 2

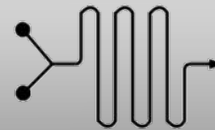
Benzoic acid  
Alkylant + Base



$$k = 0.373 \text{ mol}^{-1} \cdot \text{L} \cdot \text{s}$$

Config. 3

Benzoic acid  
+ Alkylant  
Base

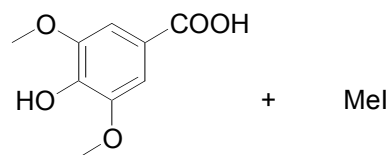


$$k = 0.521 \text{ mol}^{-1} \cdot \text{L} \cdot \text{s}$$



Slight increase of the kinetics within microreactor  
Configuration 3 is the fastest

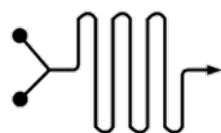
# Preparative study – First results



Syringic Acid

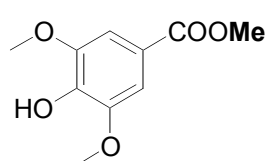
3 possible products

40 s

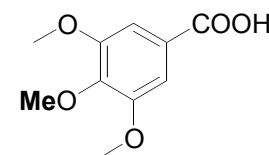


20  $\mu\text{L}\cdot\text{min}^{-1}$

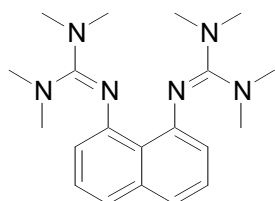
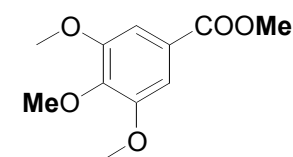
Ester (A)



Ether (B)



Ester-Ether (C)



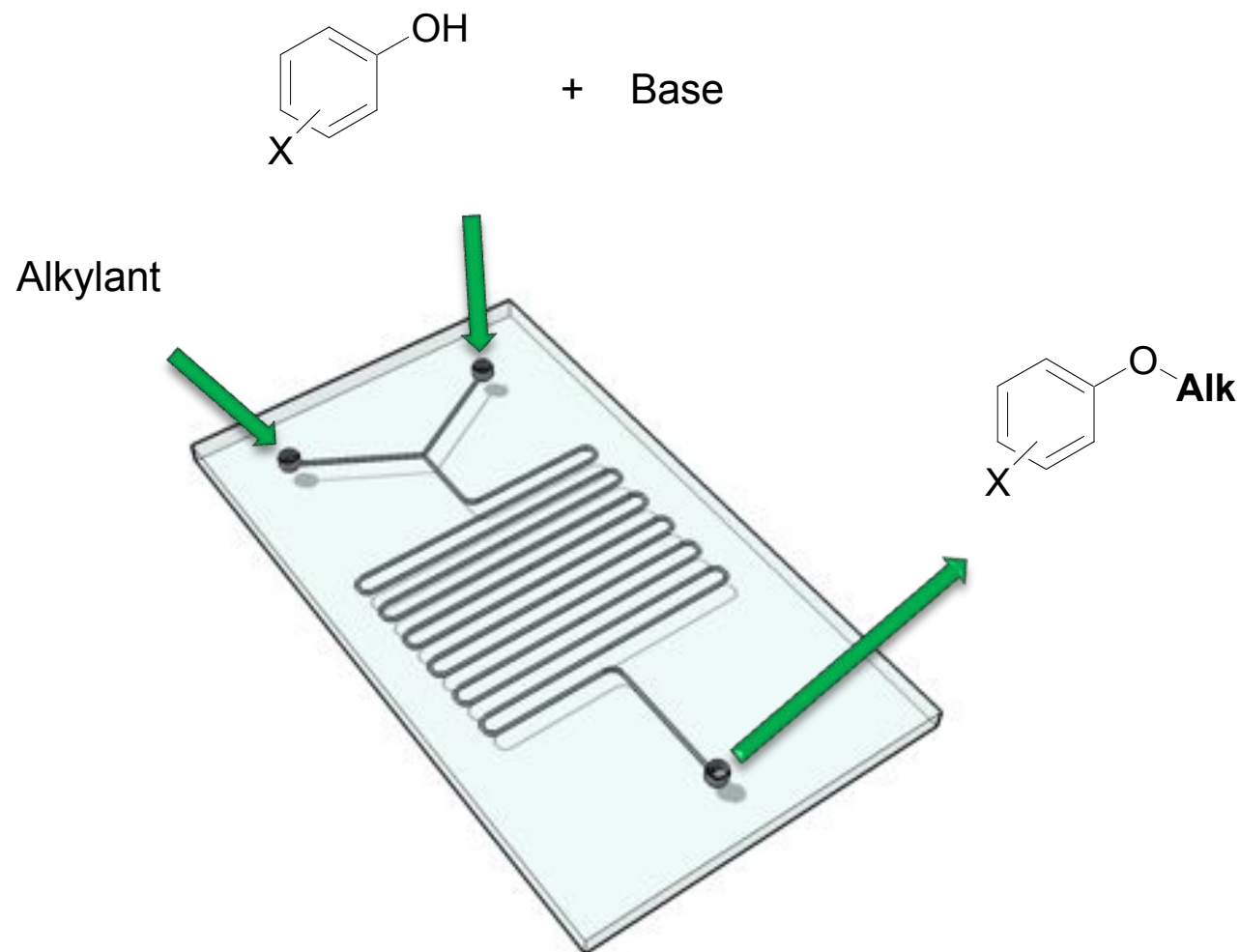
TMGN

Syringic	MeI	TMGN	A	B	C
1	1	1	77%	-	-
1	1.5	1.5	92%	-	8%

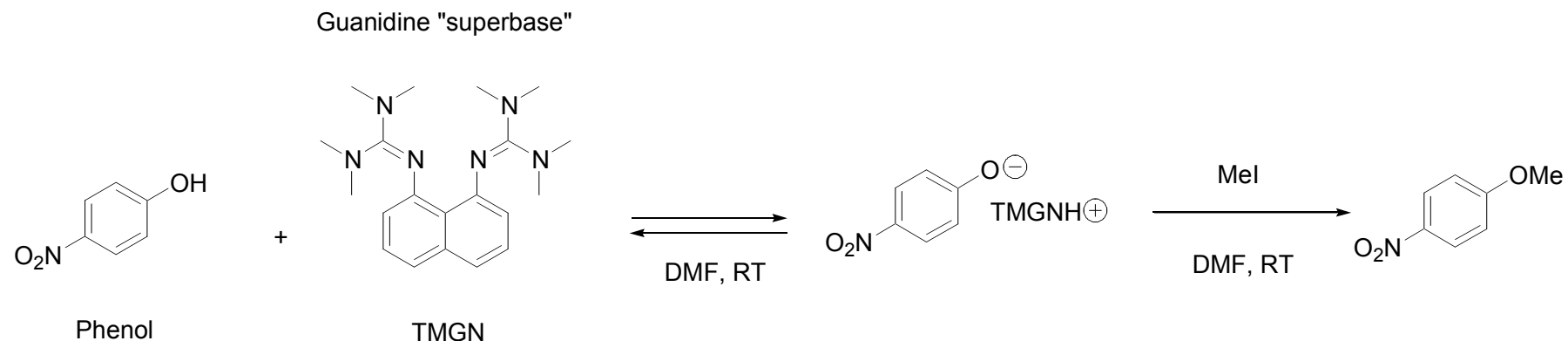
[Syringic Acid] = 0.1 mol.L<sup>-1</sup>

## Second step: Phenol alkylation within microreactor

**Kepka Cédric (PhD)**  
**Vambesien Théodore (Trainee)**



# Phenol alkylation in the presence of a superbase



pKa (DMF) = 10.8

pKa (DMF) = 16.3

[Phenol]<sub>0</sub> = 0.4 mol.L<sup>-1</sup>

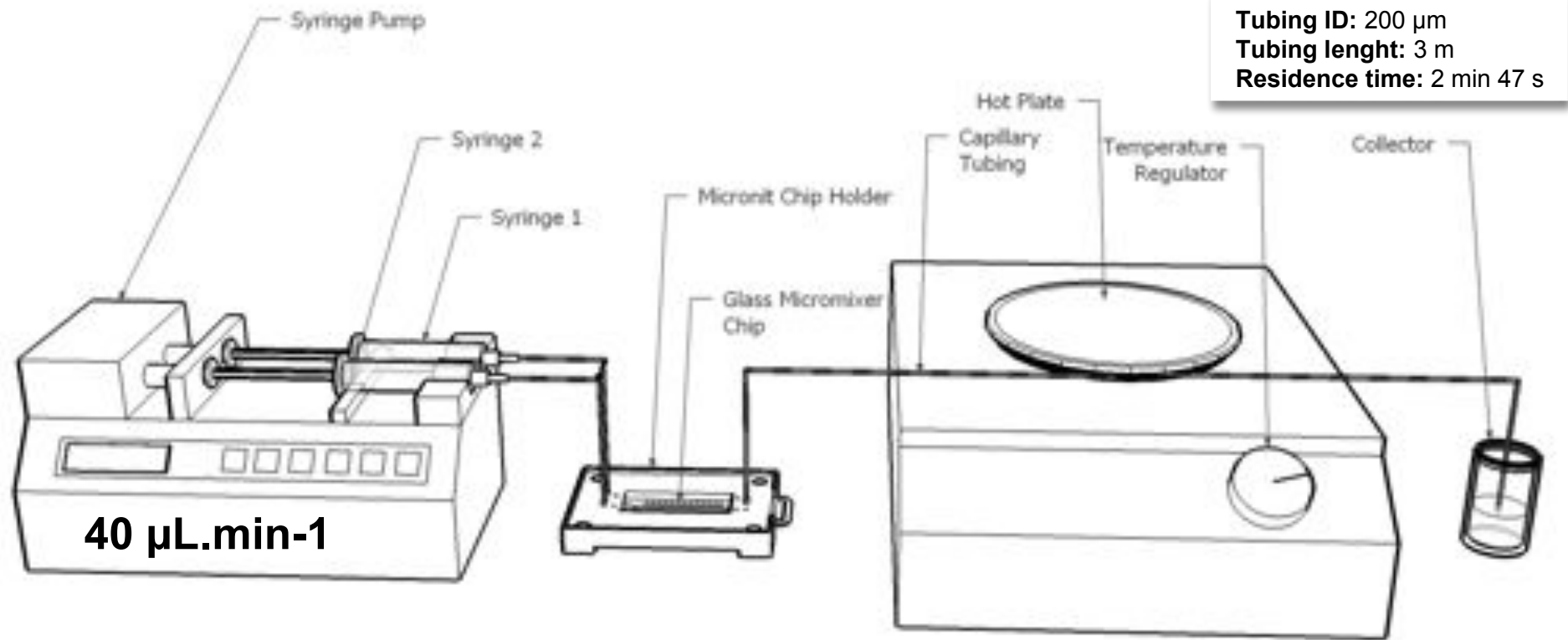
➔ **NMR kinetic study** : The reaction is slow at room temperature

➔ **Transposition within microreactors requires high residence time**

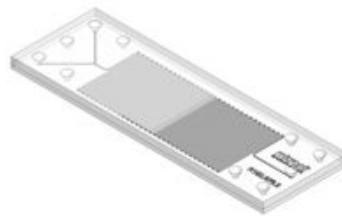


➔ **Effect of the temperature ???**

# Experimental Setup



3 different glass micromixer chips from Micronit



**Y mixer**  
(parallel mixing)



**Tear Drop mixer**  
(Split and recombine mixing)

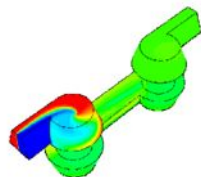


**Swirl mixer**  
(Vortex mixing)

# Phenol alkylation within microreactor

Swirl

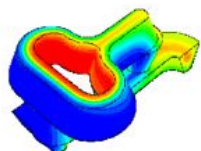
Vortex



Base	DBU	TBD	nBu4NOH
Conversion (25°C)	5	6	3
Conversion (110°C)	60	67	88

Tear Drop

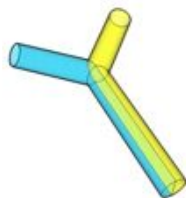
Split and recombine



Base	DBU	TBD	nBu4NOH
Conversion (25°C)	6	13	3
Conversion (110°C)	60	73	88

Y

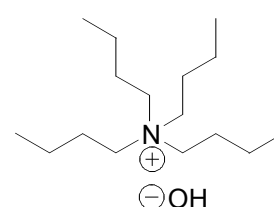
Parallel



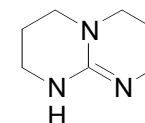
Base	DBU	TBD	nBu4NOH
Conversion (25°C)	8	2	1
Conversion (110°C)	59	70	90

## Bases

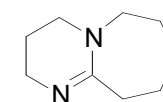
*n*-Bu<sub>4</sub>NOH



TBD



DBU



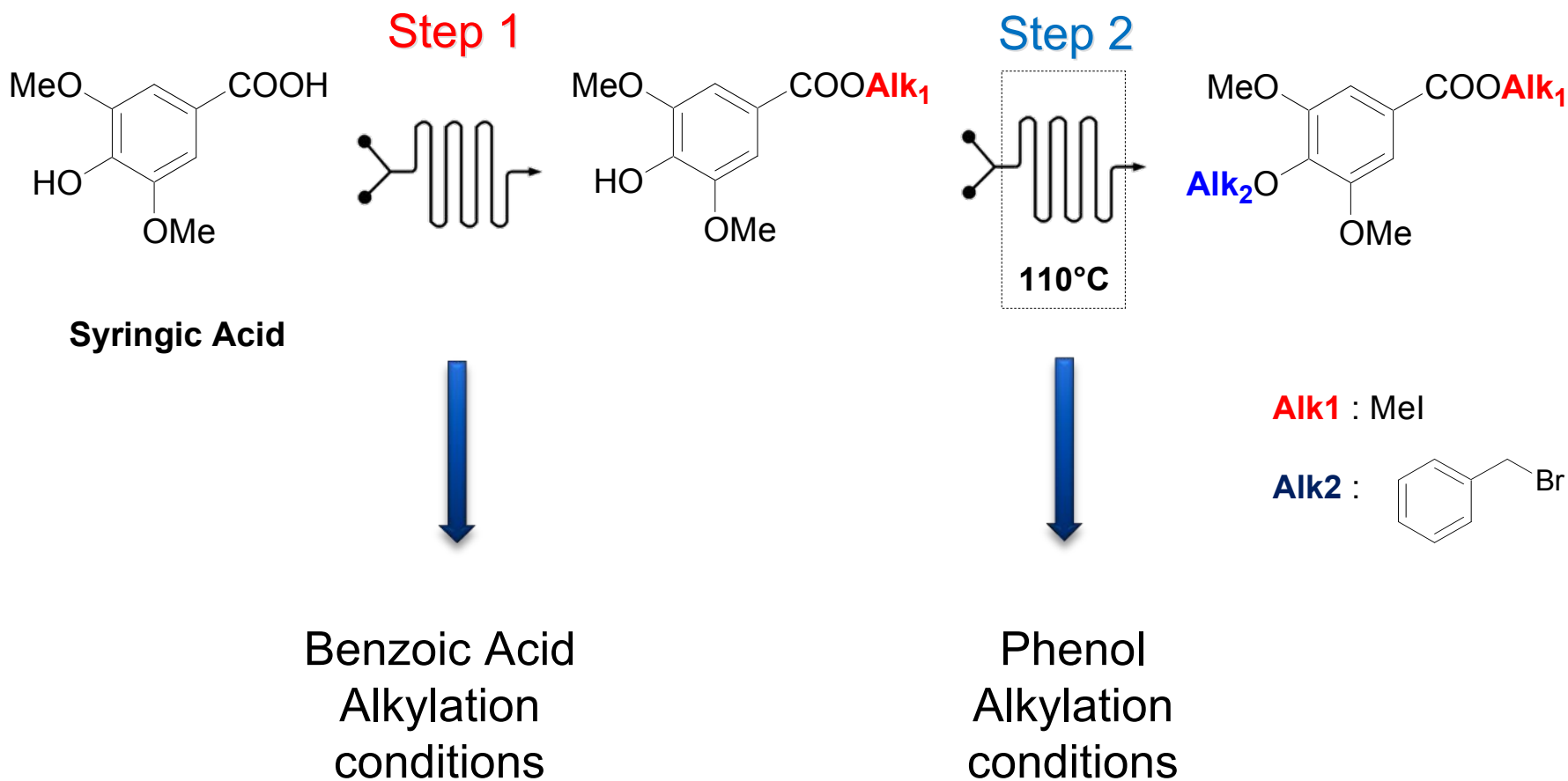
➔ *n*-Bu<sub>4</sub>NOH > TBD > DBU

➔ No effect of the mixer

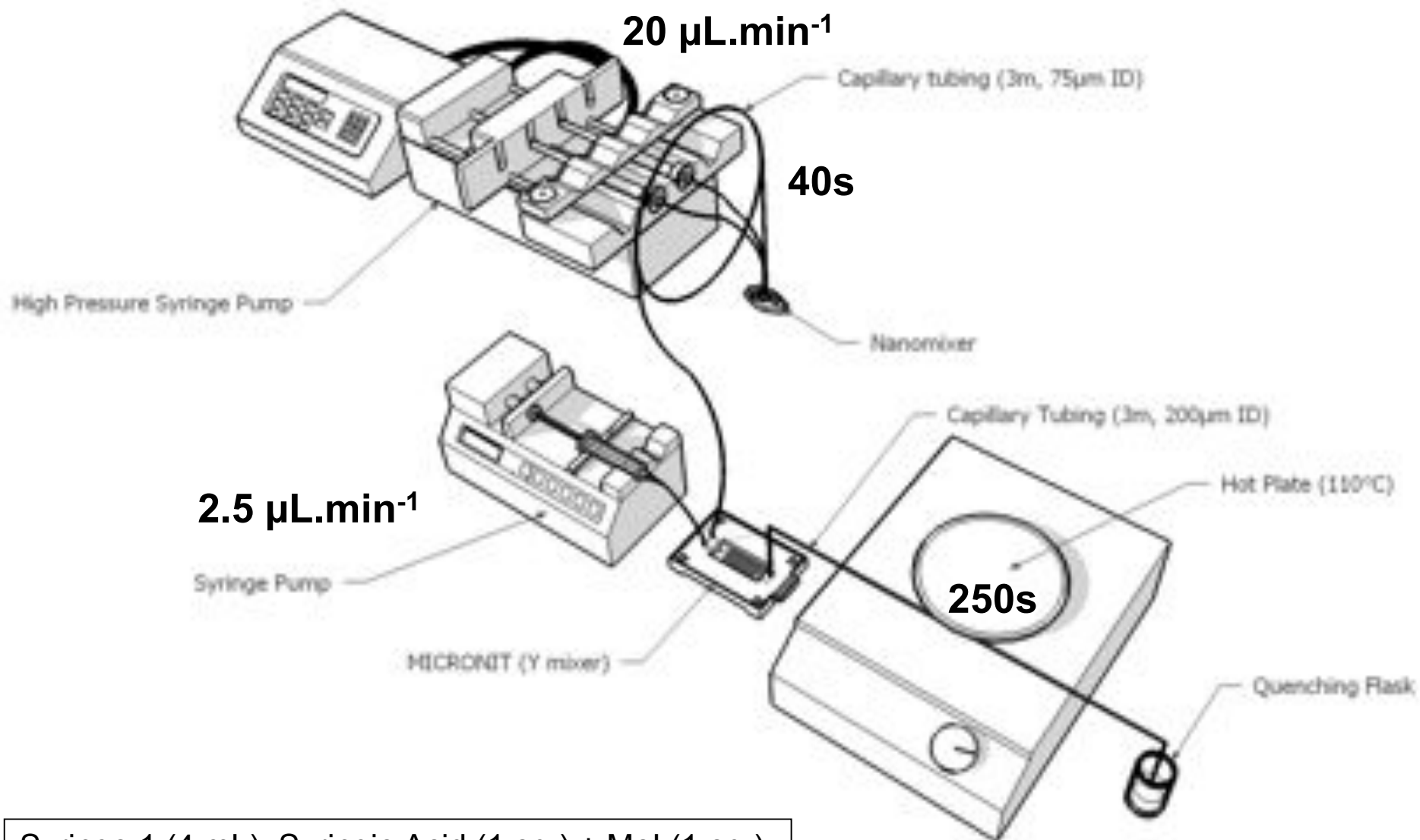
➔ High effect of the temperature

# Selective multistep alkylation within microreactor

Thijs Janssens (trainee)

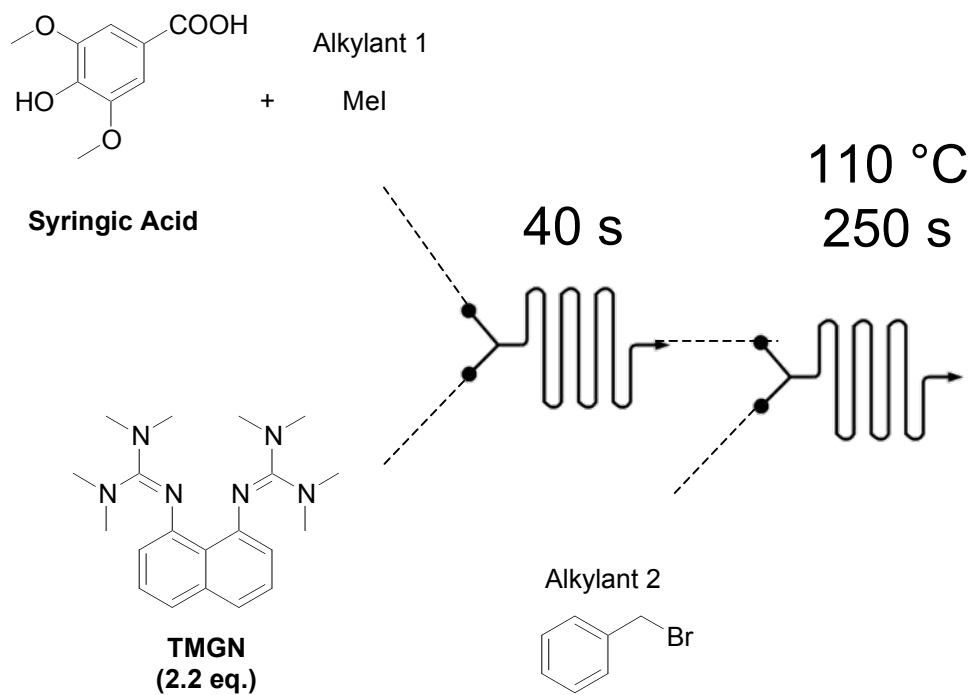


# Selective multistep alkylation within microreactor



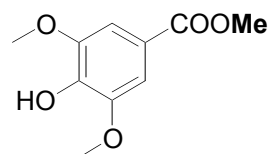
Syringe 1 (4 mL): Syringic Acid (1 eq.) + MeI (1 eq.)  
Syringe 2 (4 mL): TMGN (2.2 eq.)  
Syringe 3 (1 mL): Benzyl Bromide (1 eq.)

# Preparative study – First result



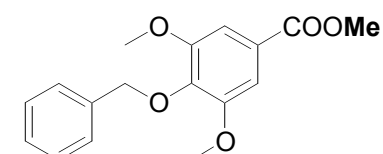
NMR study of the crude mixture: 2 main products

Ester (A)



1/3

Ester-Ether (B)



2/3

+ traces of side-products

(degradation during the purification)

[Syringic Acid]<sub>0</sub> = 0.1 mol.L<sup>-1</sup>

## Conclusion and perspective

- ➔ **Benzoic acids alkylation in the presence of TMGN can be done easily within microreactor**
- ➔ **Phenols alkylation within microreactor is more problematic and presently require heating activation**
- ➔ **Milder and faster conditions for phenols alkylation are highly required - Stronger bases ???**
- ➔ **First result from multistep experiment is very promising.**
- ➔ **Production of mg quantities appropriate for biological tests**
- ➔ **Scaling-up requires larger channels and parallelization**

# Aknowledgments

## Leaders:

Dr. Christian Rolando  
Pr. Didier Barbry

## Students:

Azarmidokth Gholamipour-Shirazi (Benzoic acid alkylation within microreactor)  
Thijs Janssens (Multistep process)  
Cédric Kepka (Phenol alkylation with TMGN)  
Theodore Vambesien (Phenol alkylation under microflow)

## Sponsors:

CNRS, University of Lille 1, OSEO, CPER Nord-Pas de Calais

**THANK YOU FOR YOUR ATTENTION**

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**Because Thierry Henry is presently improving his famous technique**