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# Micro-Flow based Photoisomerization and In-flow Separation Process

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# Outline

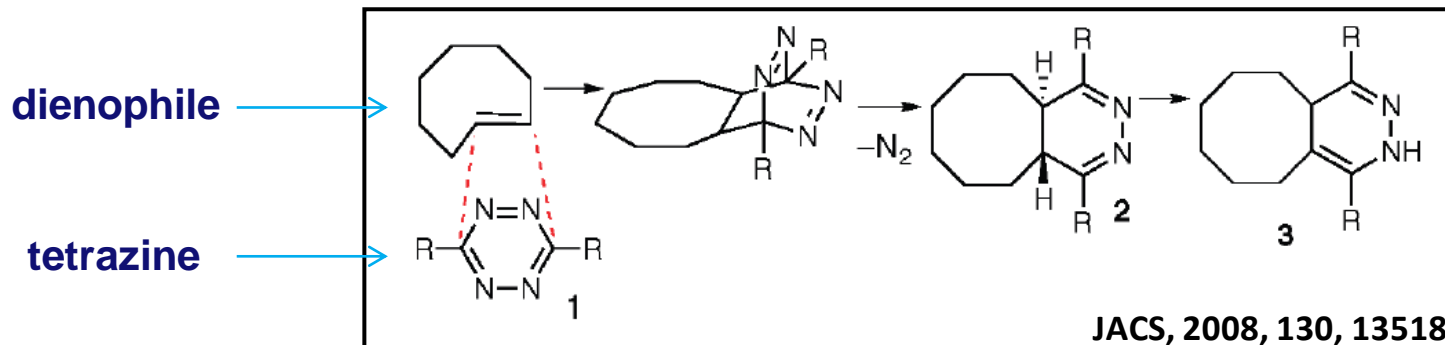
- **Introduction**
- **Motivation**
- **Photo-micro setup**
- **Photo reactor study**
- **Packed bed study**
- **Conclusion & Outlook**



# Introduction: “Click” chemistry project - Pretargeting

The pretargeting approach:

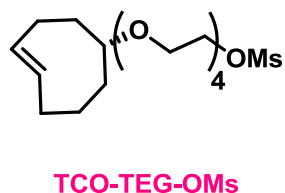
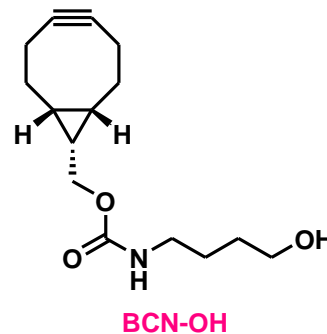
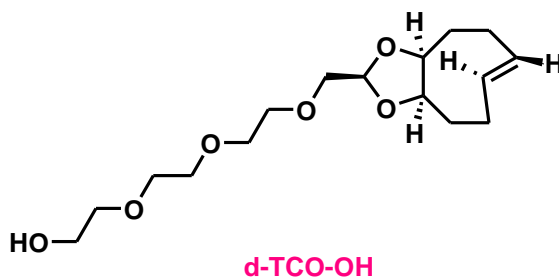
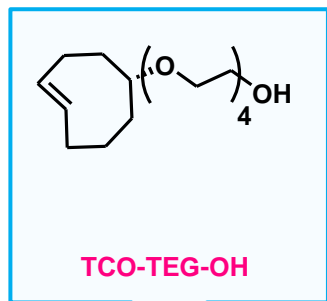
- ❖ Hot-topic in radiopharmaceutical research
- ❖ Approach that allow PET imaging of antibodies radiolabeled with fluorine-18 (antibodies and  $^{18}\text{F}$  are otherwise not compatible in terms of pharmacokinetics)
- ❖ Involves a bioorthogonal reaction (inverse-electron-demand Diels-Alder reaction)



Fast kinetics, highly selective *in vivo*

Radiopharmacy lab of KU Leuven is interested in developing new dienophiles, with favorable *in vivo* properties (see next slide for structures)

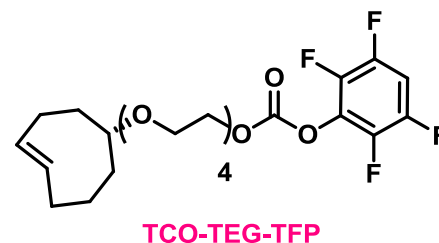
# Introduction: “Click” chemistry project - Pretargeting



precursor for radiofluorination



reference

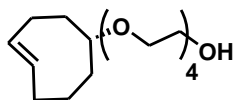


conjugatable derivative

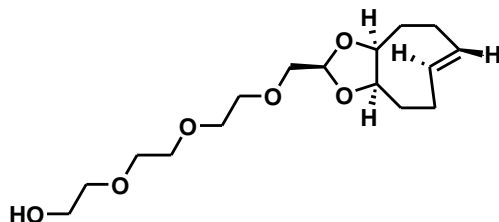
- [<sup>18</sup>F]-dienophile + Tz-biomolecule
- [<sup>18</sup>F]-Tz + dienophile-biomolecule
- [<sup>18</sup>F]AlF-mHEDDA-Tz + dienophile-biomolecule

# Introduction:

## Synthesis of functionalized trans-cyclooctene



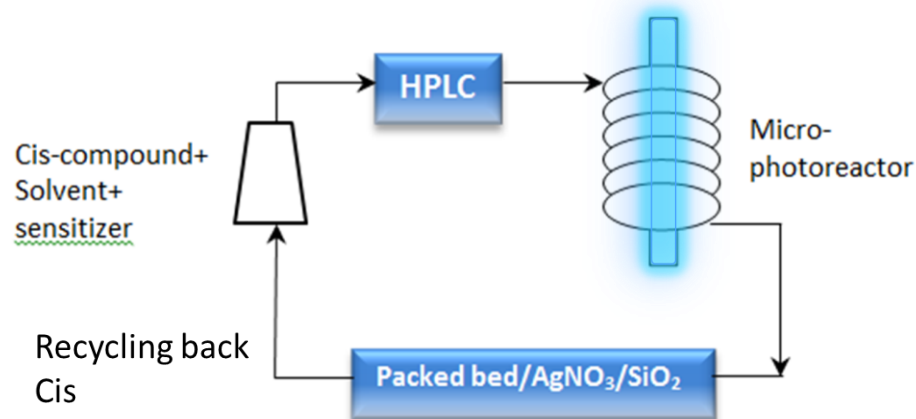
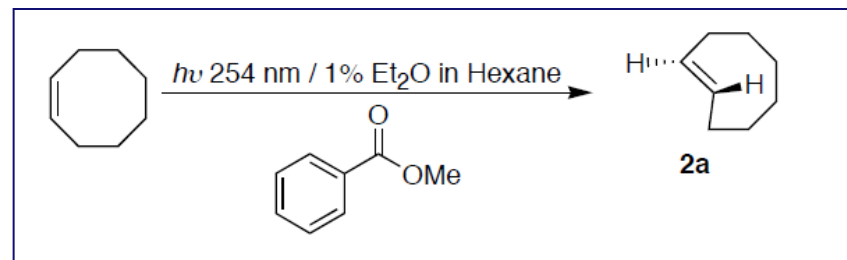
TCO-TEG-OH



d-TCO-OH

*trans* C=C  
→ photoisomerisation step

- Direct method for the synthesis of TCO
- Replacing batch reactor to microreactor
- In-flow separation process based on Ag-complexation to isolate TCO derivatives and push the equilibrium



In collaboration with Dr. Emilie Billaud, Radiopharmacy Lab, KU Leuven

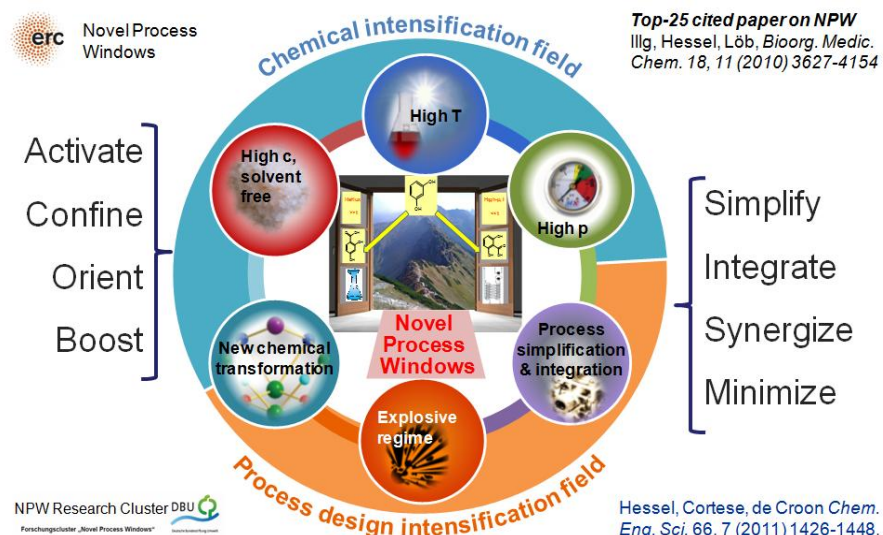
Improvement of the photoreactor setup → microphotoreactor, continuous-flow (at TU Eindhoven)

# NOVEL PROCESS WINDOWS



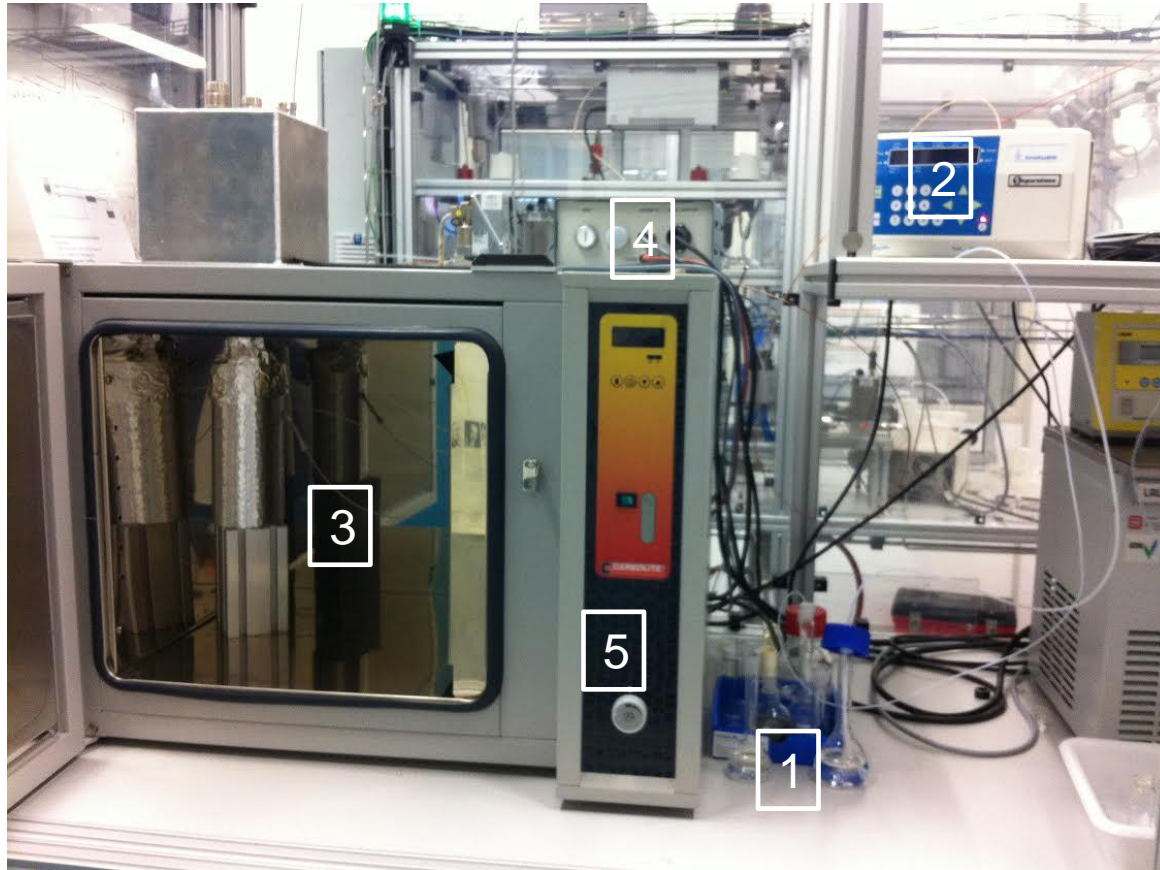
- ❑ **Process design intensification** slow process. Thus, chemical intensification through photo-flow processing and removal of the trans isomer out of the equilibrium are required.
- ❑ **Transport intensification** a photo micro-flow process design with minute-range processing time and an in-flow separation process based on Ag-complexation to isolate TCO derivatives after their manufacture has been developed.

- ❑ **New chemical transformation**  
New TCO derivatives can be made by this process for in vivo pretargeted imaging





# Photo-micro setup



**1- Inlet and outlet of the microreactor**

**2- HPLC pump**

**3- Light source surrounded with microreactor, covered with aluminum sheet**

**4- light source power supply**

**5- Micro-photoreactor safety oven**





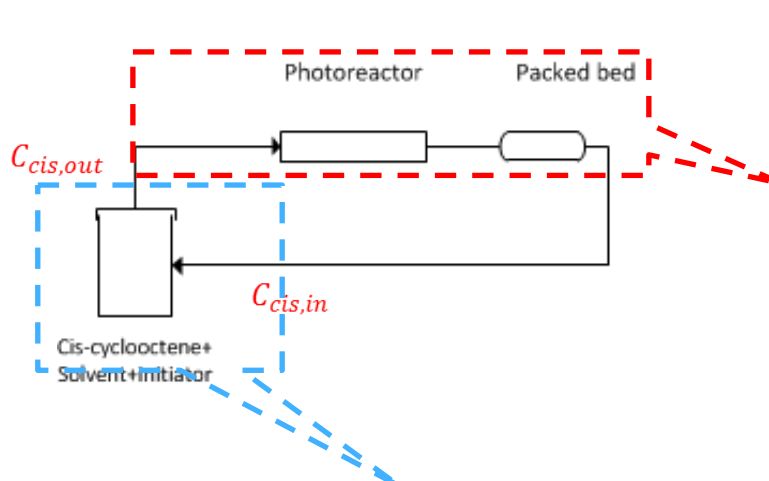
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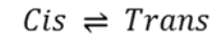
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# Modeling

- In order to improve the flow setup, it is important to study photoreactor and packed bed.



One pass without considering the packed bed:



$$r_{Cis} = k_1 \times C_{cis} - k_2 \times C_{trans}$$

$$C_{trans} + C_{cis} = C_t$$

$$r_{Cis} = (k_1 + k_2) \times C_{cis} - k_2 \times C_t$$

$$-\frac{dC_{cis}}{dt} = r_{Cis}$$

$$-\frac{dC_{cis}}{dt} = (k_1 + k_2) \times C_{cis} - k_2 \times n/V$$

$$\text{at } t = 0 \quad C_{cis} = \text{const.}$$

CSTR tank:

Accumulation = Input mole - Output mole

$$[n_{cis}]_{t+\Delta t} - [n_{cis}]_t = \dot{n}_{cis,in} \times \dot{n}_{cis,out}$$

$$[n_{cis}]_{t+\Delta t} - [n_{cis}]_t = Q \times C_{cis,in} \times \Delta t - Q \times \frac{n_{cis,out}}{V} \times \Delta t$$

$$\frac{[n_{cis}]_{t+\Delta t} - [n_{cis}]_t}{\Delta t} = \left( Q \times C_{cis,in} - Q \times \frac{n_{cis,out}}{V} \right)$$

$\lim \Delta t \rightarrow 0$

$$\frac{dn_{cis}}{dt} + \frac{Q}{V} n_{cis} = Q \times C_{cis,in}$$

# Modeling

- **1 set of ODE:**

$$-\frac{dC_{cis}}{dt} = (k_1 + k_2) \times C_{cis} - k_2 \times \frac{n_{cis}}{V}$$

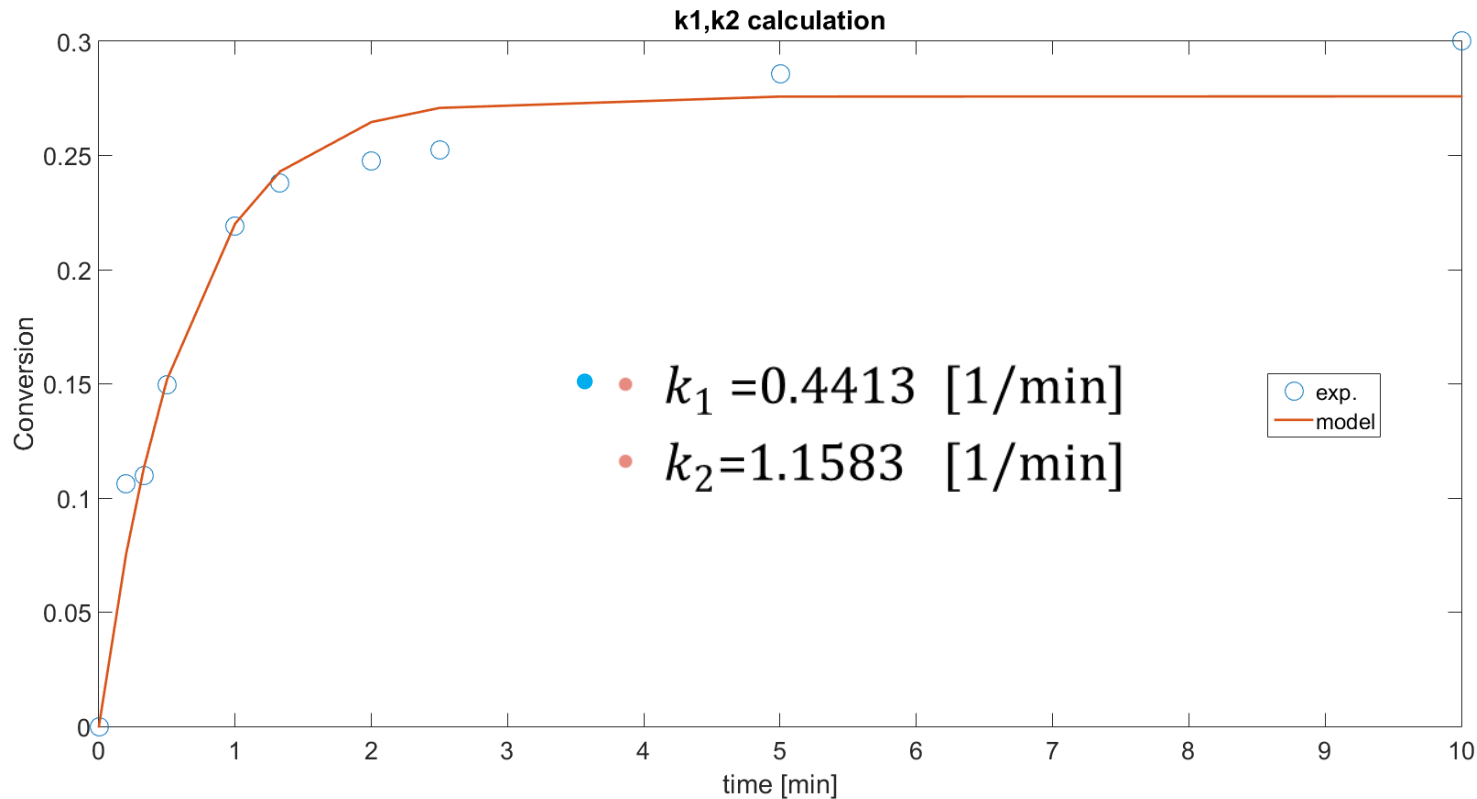
$$\frac{dn_{cis}}{dt} + \frac{Q}{V} n_{cis} = Q \times C_{cis}$$

$$\text{At } t=0 \quad n_{cis} = \frac{C_0}{V}$$

$$\text{At } t=0 \quad C_{cis} = C_0$$

In order to solve this set we need to know  $k_1, k_2$ .

# $k_1, k_2$ calculation



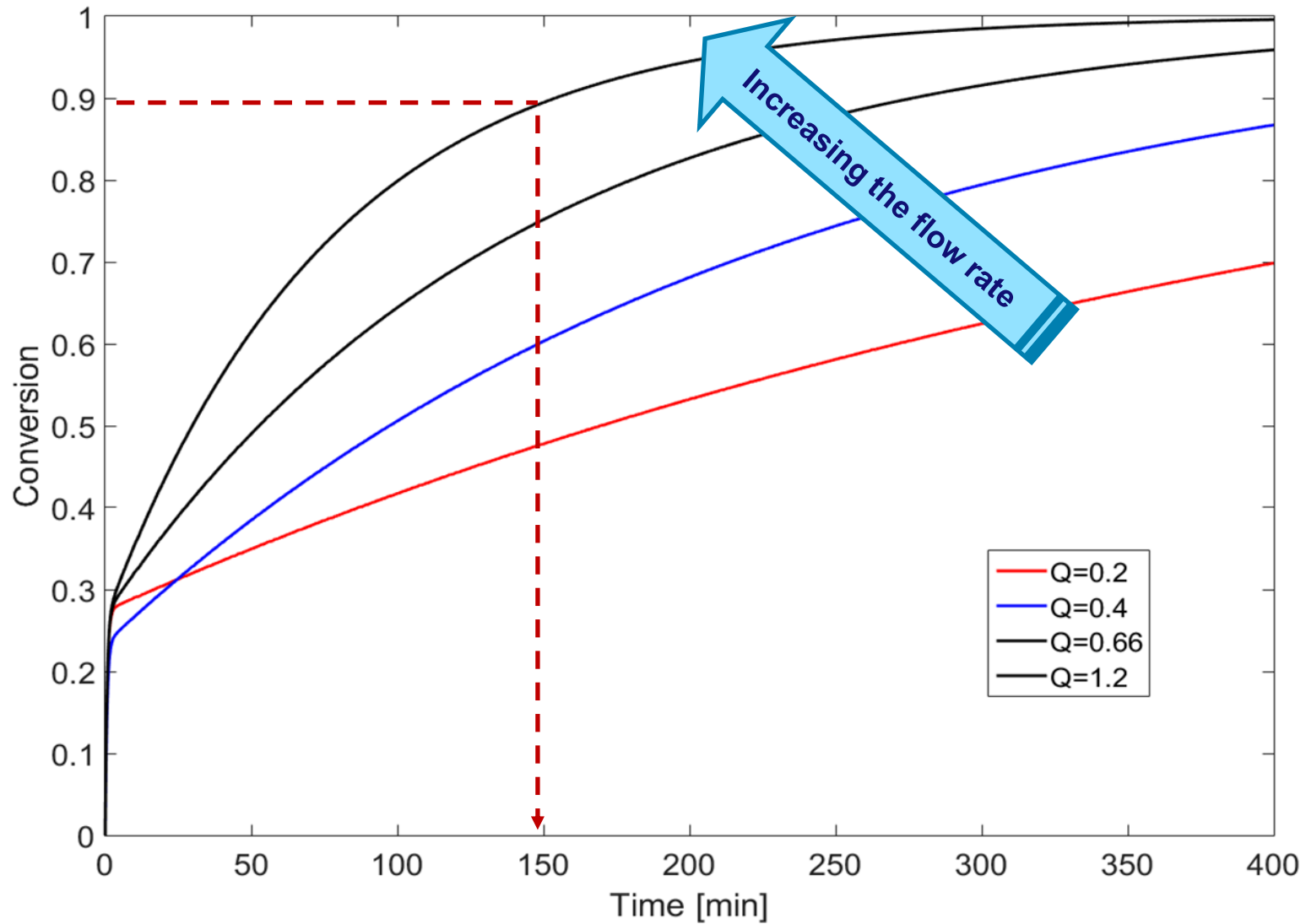
$$-\frac{dC_{cis}}{dt} = (k_1 + k_2) \times C_{cis} - k_2 \times C_t$$

at  $t = 0$        $C_{cis} = 0.02$  M



$$X = 1 - \left[ \frac{1}{k_1 + k_2} (k_1 e^{-t(k_1 + k_2)} + k_2) \right]$$

# Solving the ODE



# Photoisomerization

- In order to design the photoisomerization setup, we chose as a case study to first focus on cis to trans cyclooctene since cis-cyclooctene is available commercially.

## Different designs

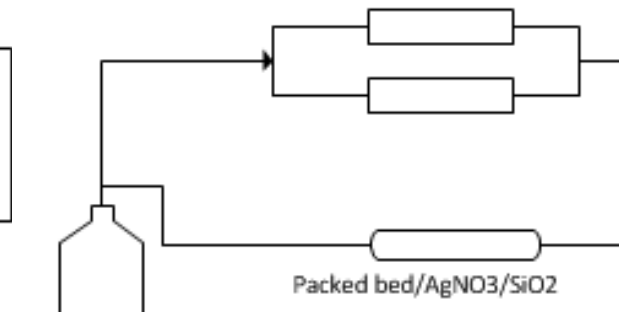
### Design 1

Photoreactor



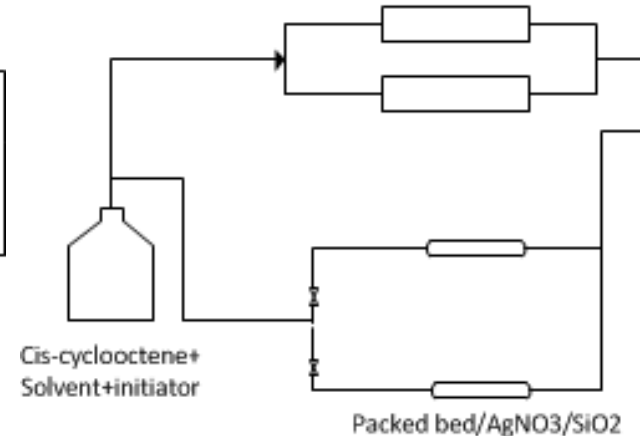
### Design 2

Photoreactor: 2  
in parallel



### Design 3

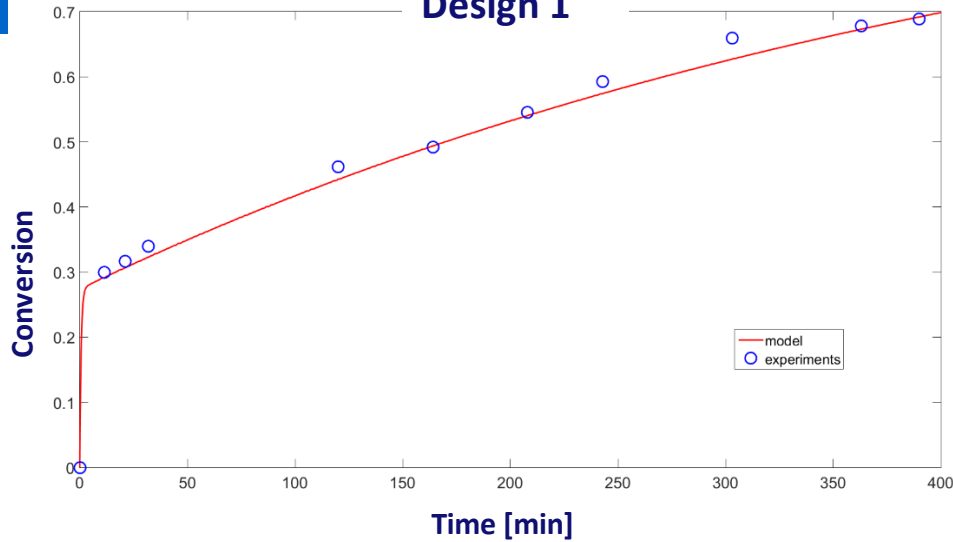
Photoreactor: 2  
in parallel



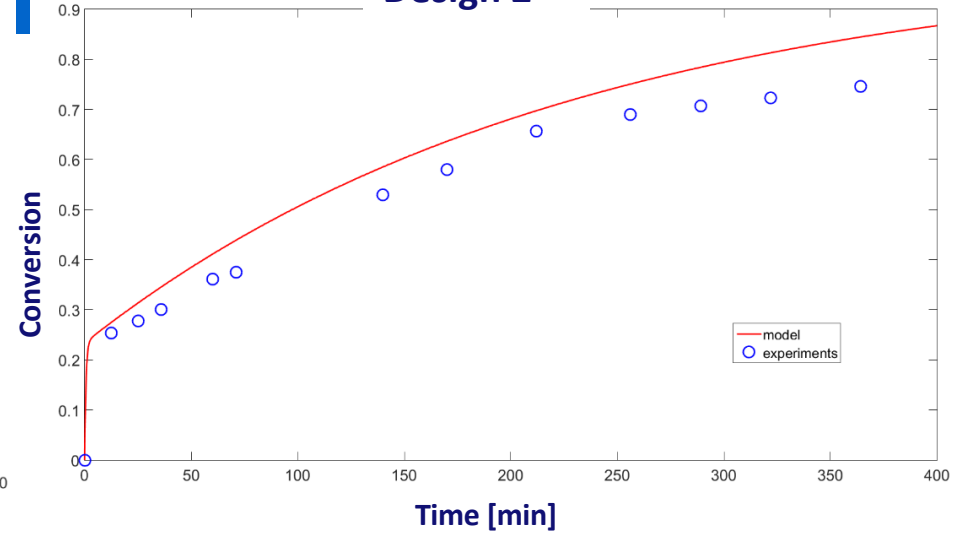


# Solving the ODE

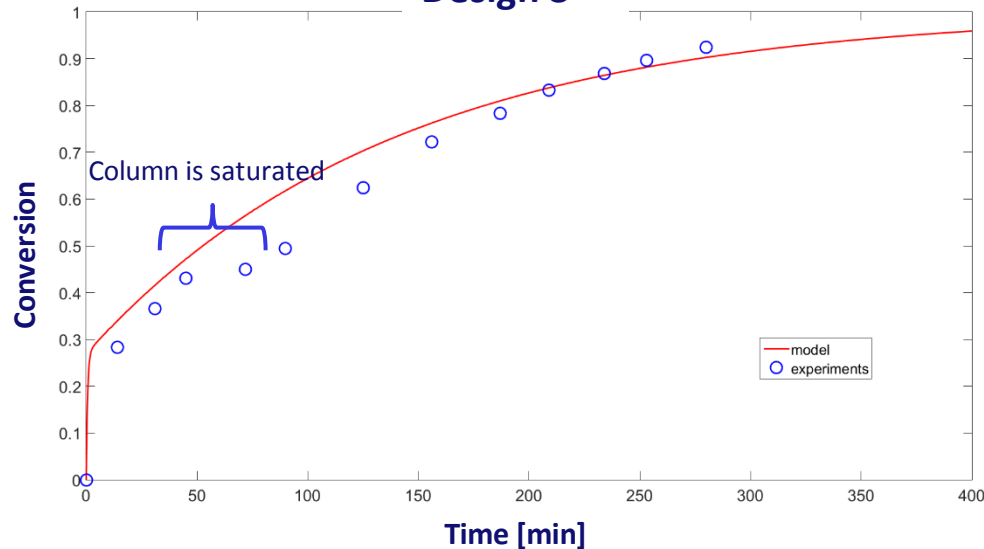
## Design 1



## Design 2



## Design 3



- In order to complete the design it is important to know about the saturation time of the packed bed.



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# Packed bed: Breakthrough curve

Model

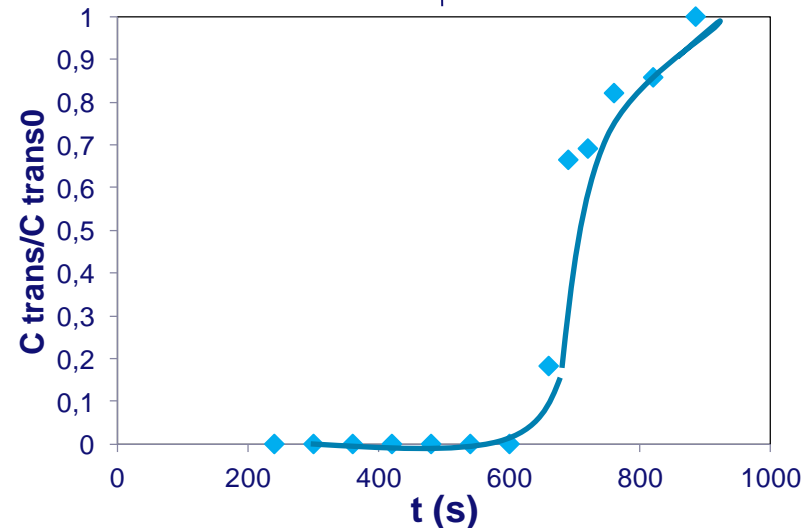
Experiment

We could prove that mass transfer limitation is negligible : Intrinsic process

$$\frac{1}{k_{ads}} \gg \frac{1}{k_{mass\ transfer} \cdot a}$$

- **Local equilibrium theory:** This model is based on the equilibrium between solid and fluid concentration (Langmuir isotherm).

- **Local kinetic theory:** This model is based on the non-equilibrium surface reaction.



- Flow rate = 1 (ml/min)
- $AgNO_3$  = 200 (mg)

# Conclusion & outlook

- ✓ Above **90%** conversion could be achieved within **less than 3 hrs.** In batch process 66% conversion was achieved within 12 hrs [\*].
- ✓ Process integration and chemical intensification (NPW): By theoretically studying and modelling the whole process and validating with the experimental results with different process conditions, it is possible to give a methodology for scaling up the photo-microreactor with in-flow separation process.
- ✓ We already have made similar study (separation in flow) for high temperature for acid base resin (kilo-lab process) [\*\*].

[\*] M. Royzen, G. P. A. Yap & J. M. Fox, J. Am. Chem. Soc. 2008, 130, 3760-37

[\*\*] E. Shahbazali, M. Spapen, T. Noel, V. Hessel, Chem. Eng. J. 2018, 281, 144-154

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[e.shahbazali@tue.nl](mailto:e.shahbazali@tue.nl)



**Thank you**

# Backup slide

- **Local equilibrium theory:**

