SFGP 2019 – 15-17th October 2019

A dual (bio)catalysis approach for the synthesis of 5-HMF from D-glucose

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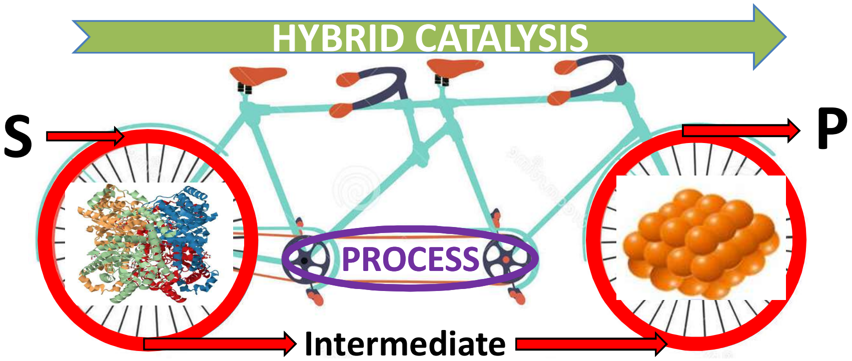
[3] *IFP Energies Nouvelles, Rond-Point de l'Echangeur de Solaize*



Hybrid catalysis ⇔ Extension of chemoenzymatic catalysis which is often a **multisequential approach**

… green synthesis approach
(coexistence of both (bio)catalyst)

CHALLENGES for combining chemo- and biocatalysis :

⇒ **Reciprocal poison, need of co-factor/co-enzyme**
⇒ **Incompatibility in reaction conditions**

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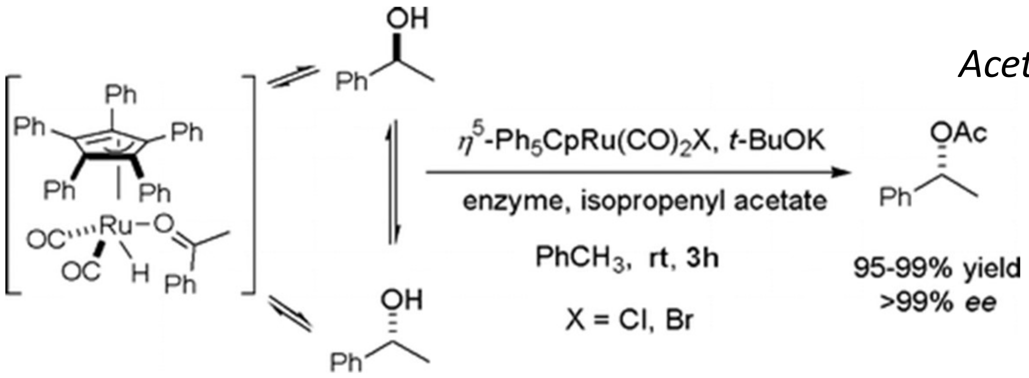
Zeikus J, Jain M, Elankovan P (1999) Appl Microbiol Biotechnol 51(5):545–552

Hybrid catalysis for racemization of secondary alcohols

Pentaphenyl cyclopentadienyl ruthenium complexes

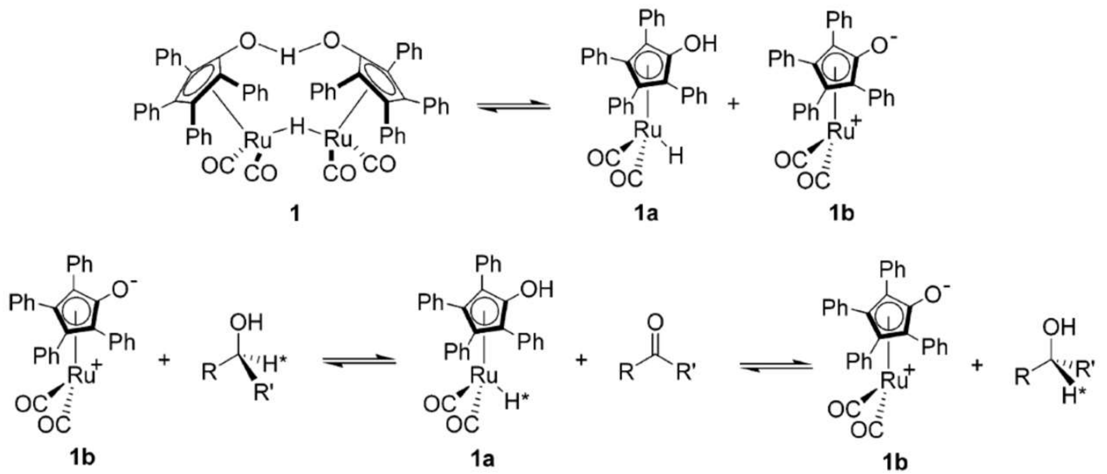


Acetates

Homogeneous Enzyme and Metalcatalyst

Ru complex = hydrogenation by organometallic H transfer
Enzyme (lipase) = acetylation of only one of the enantiomers

Scheme 7. Proposed Mechanism for the Racemization of Alcohols Catalyzed by 1



Racemization mechanism for the Ru catalyst **1**

- Proton abstraction ⇒ ruthenium hydride intermediate **1a + ketone**
- Reduction of ketone by ruthenium intermediate **1a** ⇒ racemic alcohol and the ruthenium species **1b**

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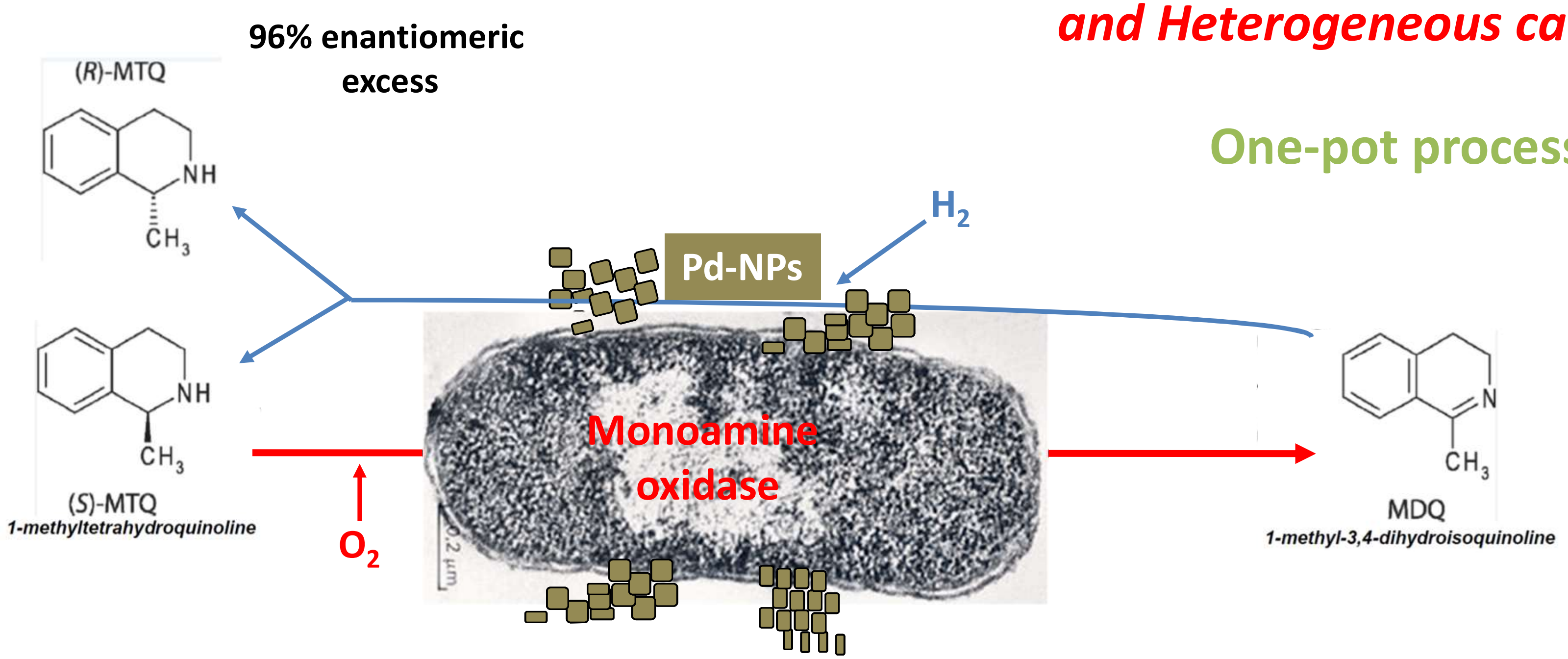
Belén Martín-MatuteMichaela EdinKrisztián BogárF. Betül KaynakJan-E. Bäckvall, J. Am. Chem. Soc.2005 - 127248817-8825
Oscar PàmiesJan-E. Bäckvall, Combination of Enzymes and Metal Catalysts. A Powerful Approach in Asymmetric Catalysis, Chem. Rev.2003 - 10383247-3262

Development of hybrid catalysis with physical separation of (bio)catalysts → Enzyme in microorganism

Homogeneous Enzyme and Heterogeneous catalyst

One-pot process



1. Non selective hydrogenation by Pd-NPs on the cell surface = production of the 2 enantiomers *(S)*- and *(R)*-MTQ
2. *E. Coli* cells coated with Pd-NPs expressing a monoamine oxidase (enzyme engineering) which catalyzes the deracemization of *(S)*-MTQ to the substrate MDQ
3. H_2/O_2 cycles for process implementation with the two catalysts present simultaneously

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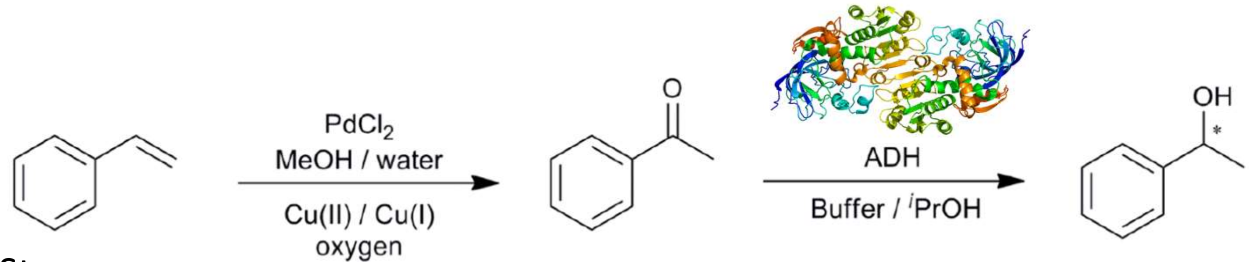
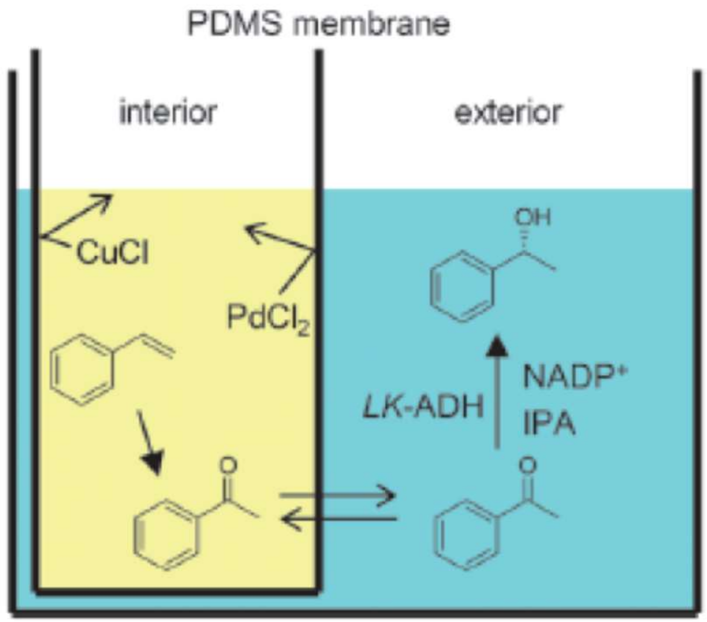
Joanne M., Foulkes, Kirk J. Malone, Victoria S. Coker, Nicholas J. Turner, Jonathan R. Lloyd ACS Catal.2011, 1, 11, 1589-1594

Development of hybrid catalysis with physical separation of (bio)catalysts

Membrane separation



Styrene



Separation of the catalysts by PDMS membrane

1. **Reactions conducted in aqueous media = enzyme deactivation by Cu ions**
2. **Reactions conducted through compartmentalization**
3. **Polydimethylsiloxane porosity enables diffusion of only the organic substrate and product into the exterior where the enzymatic catalysis takes place**

One-pot process

Homogeneous Enzyme and Metalcatalyst

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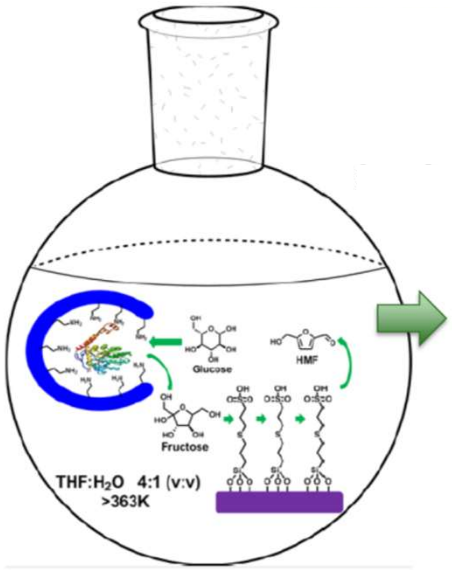
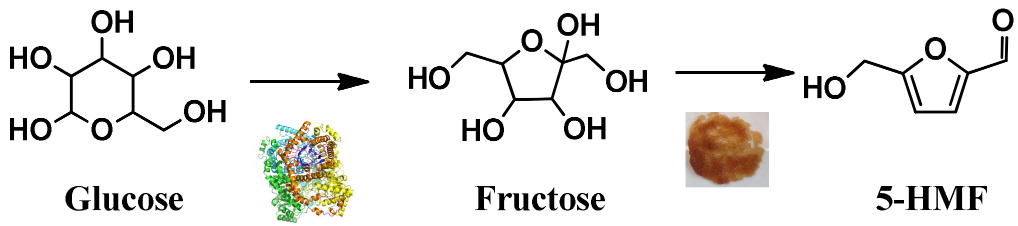
Sato H, Hummel W, Gröger H. Angew Chem Int Ed Engl. 2015 Apr 7;54(15):4488-92





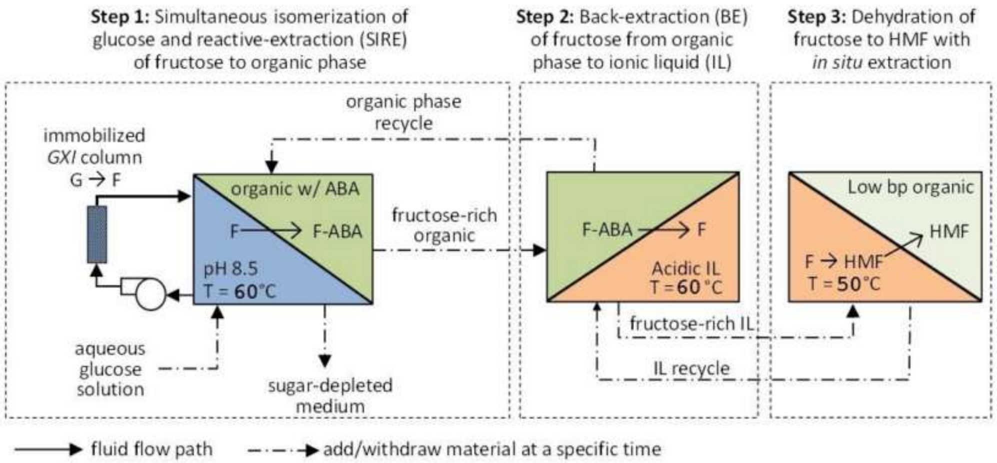
Limits : 1. Formation of humins

2. Inactivation of the isomerase by organic solvent even protected in the silica

3. Product recovery ?

⇒ Physical separation of (bio)catalyst - COMPARTMENTALIZATION

Hua Huang et al., ACS Catalysis, 4(7), 2165-2168



Sequential approach

⇒ SIMULTANEOUS approach

Chheda, J. N., Dumesic, J. A. Catal. Today 123, 59–70 (2007)

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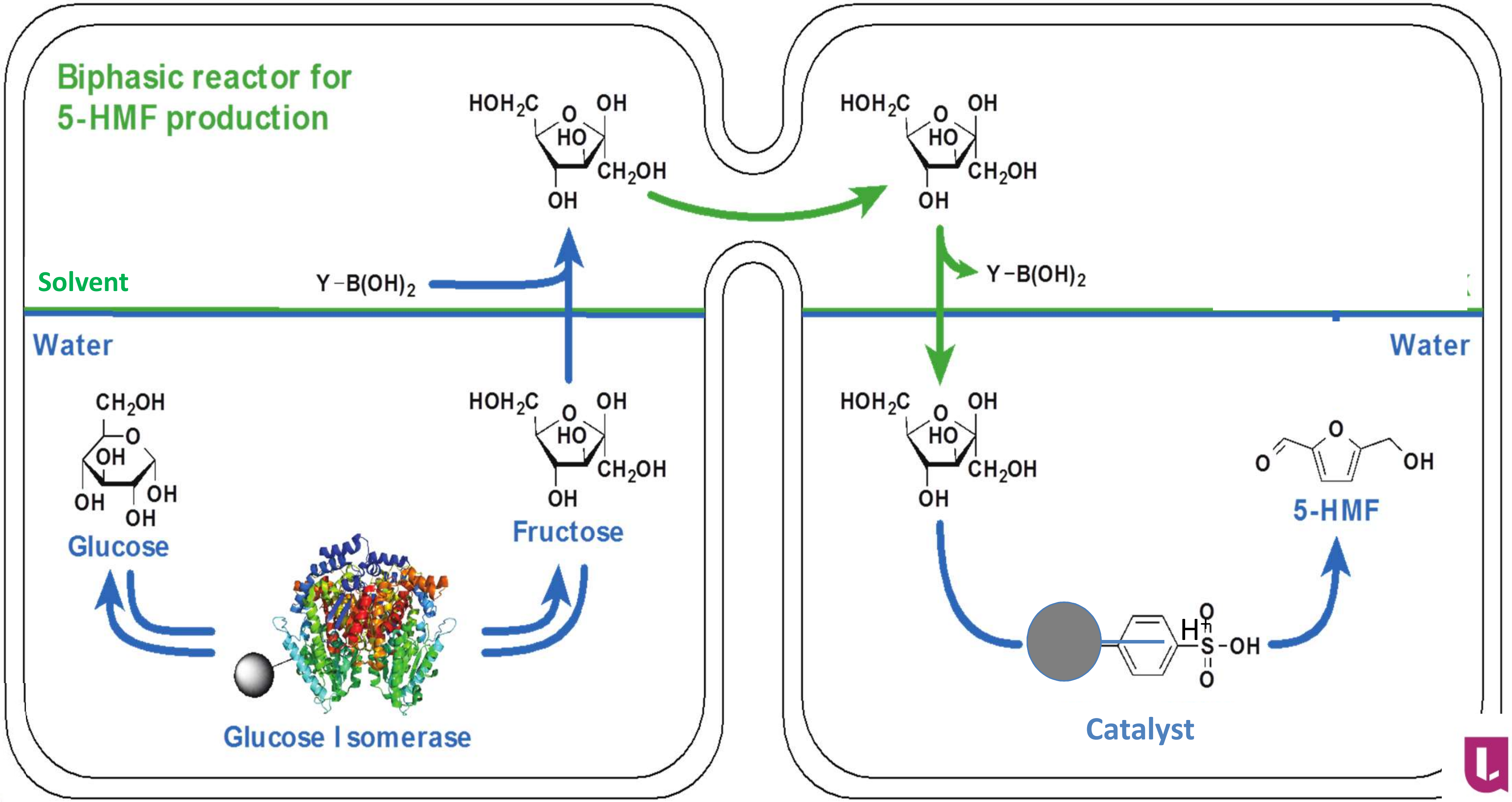
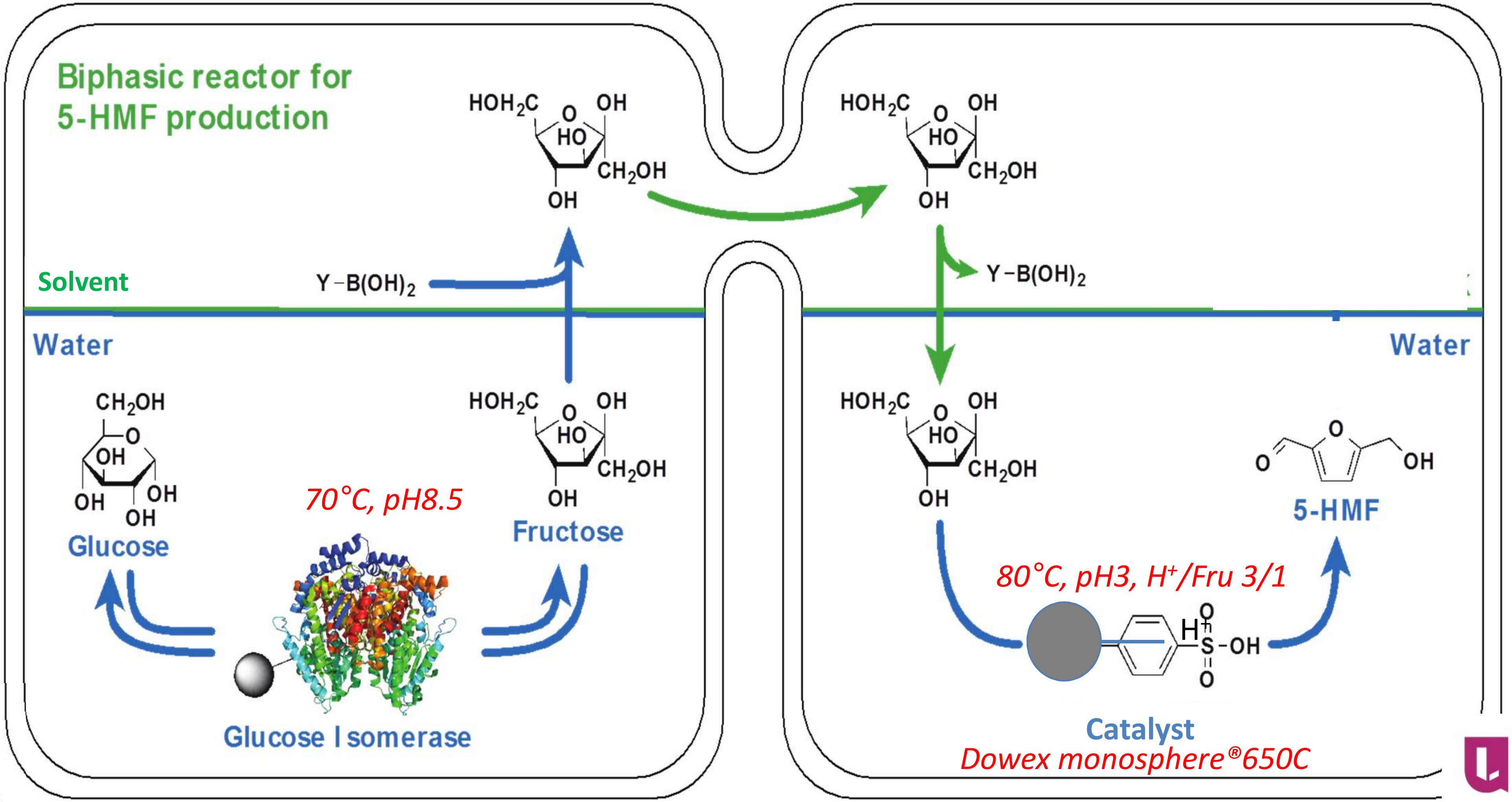
OUR GOAL...HYBRID CATALYSIS IN DESIGNED « H » REACTOR



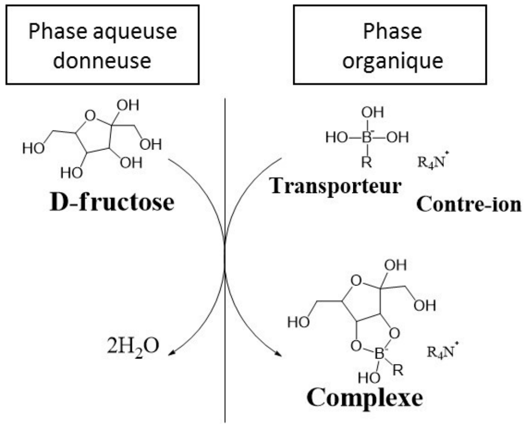
Alexandra Gimbernat et al. 2017, ChemCatChem, 9, 2080 – 2084



Alexandra Gimbernat et al. 2017, ChemCatChem, 9, 2080 – 2084

Extraction of fructose

Development of liquid membrane

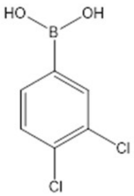


- Solvent

MIBK

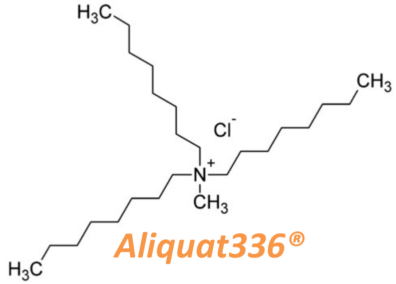
4-methylpentan-2-one (MIBK)

- Carrier (T)



34-DCPBA

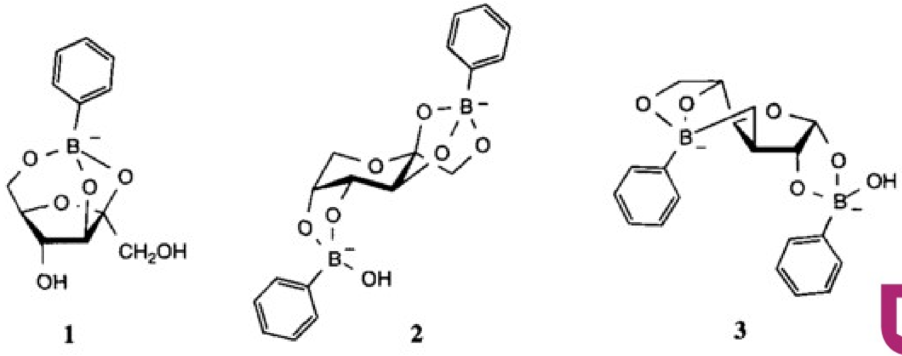
23-DCPBA	35-DCPBA	3-TFMPBA	2-NNPBA
34-DCPBA	3-NPBA	4-B1nPBA	32-carboPBA
35-BTFMPBA	24-DCPBA	4-M21HPBA	
4-TFMeOPBA	2-TFMPBA	2-T5PBA	



Aliquat336®

Glucose and fructose adducts formed with boronic acids
Affinity $(34\text{-DCPBA})_{Fru}$ >> $(34\text{-DCPBA})_{Glc}$
This complex induces the negative ion on the bore

Ionic interaction with the couterion **Aliquat336®**
Formation of a lipophilic complex
Extraction in MIBK solvent



Fructose Adducts

Glucose Adduct

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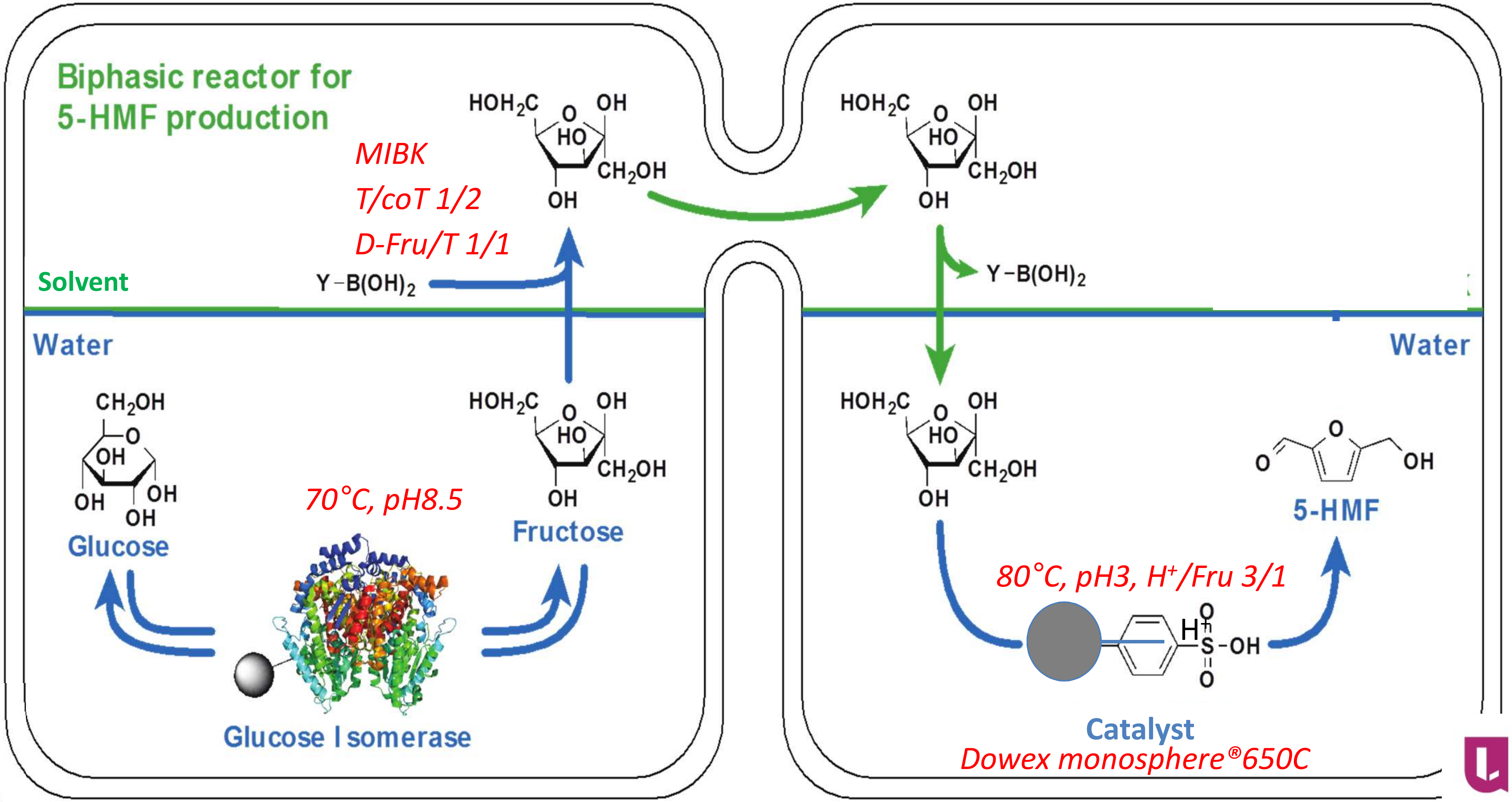
Westmark, P. R., Gardiner, S. J., Smith, B. D. J. Am. Chem. Soc. 118, 11093–11100 (1996).
Takeuchi, M., Koumoto, K., Goto, M., Shinkai, S. Tetrahedron 52, 12931–12940 (1996).

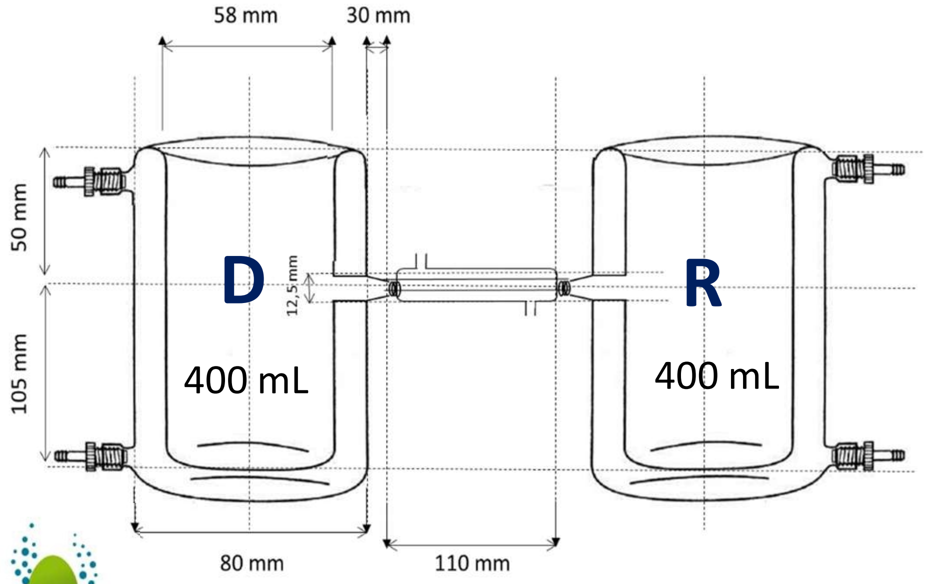


Alexandra Gimbernat et al. 2017, ChemCatChem, 9, 2080 – 2084

Transport of fructose:

Reactor configuration

Reactor « H »:
- Bicompartmentalized
- Symmetrical
- Thermostated
- Insertion of stirring blade



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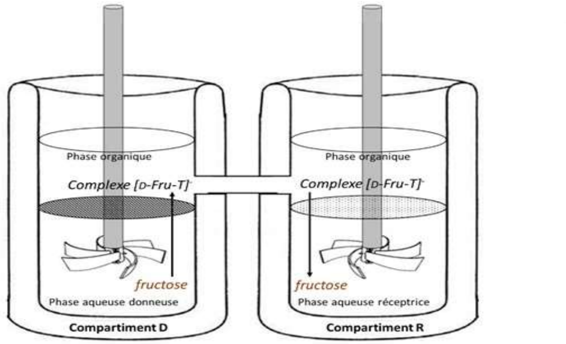
Patents

FR3077221 « Réacteur en forme de H comprenant des déflecteurs"

FR1755668 "Procédé de production de 5-hydroxymethylfurfural à partir d'hexoses"

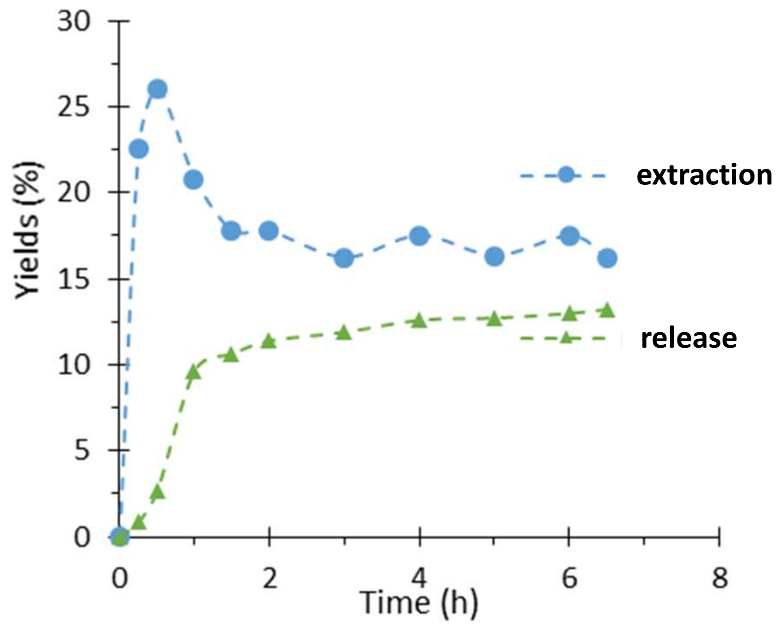
Transport of fructose:

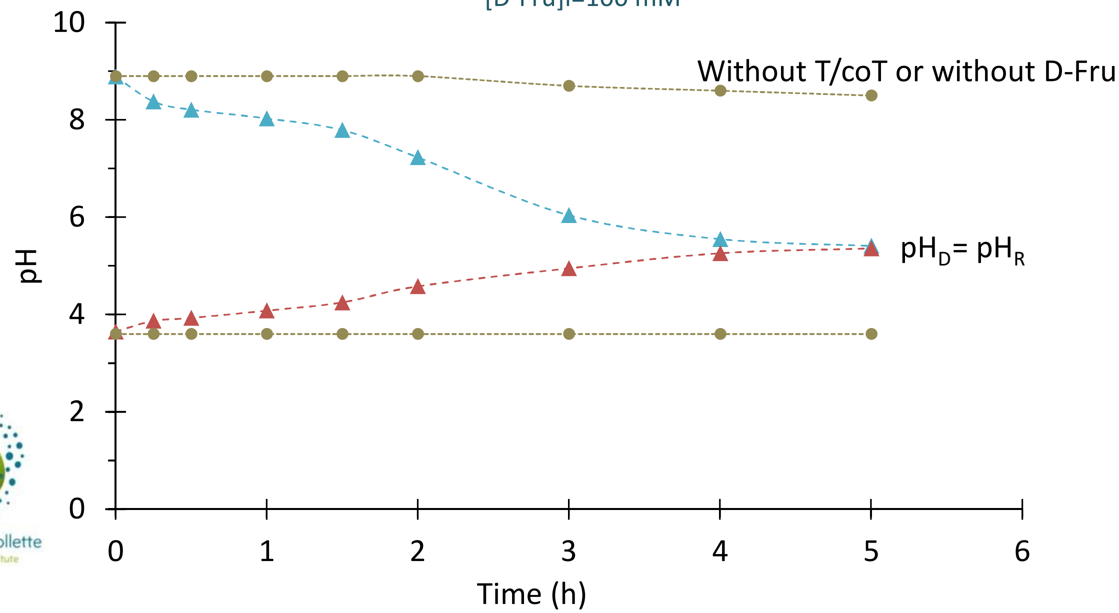
200 mL MIBK, 70,°C
[34-DCPBA]=100 mM
[Aliquat336®]=200 mM



Compartment D:
V=200 mL
Tris-HCl 100 mM
pH 8.5
[D-Fru]i=100 mM

Compartment R:
V=200 mL
Citrate buffer
100 mM pH 3



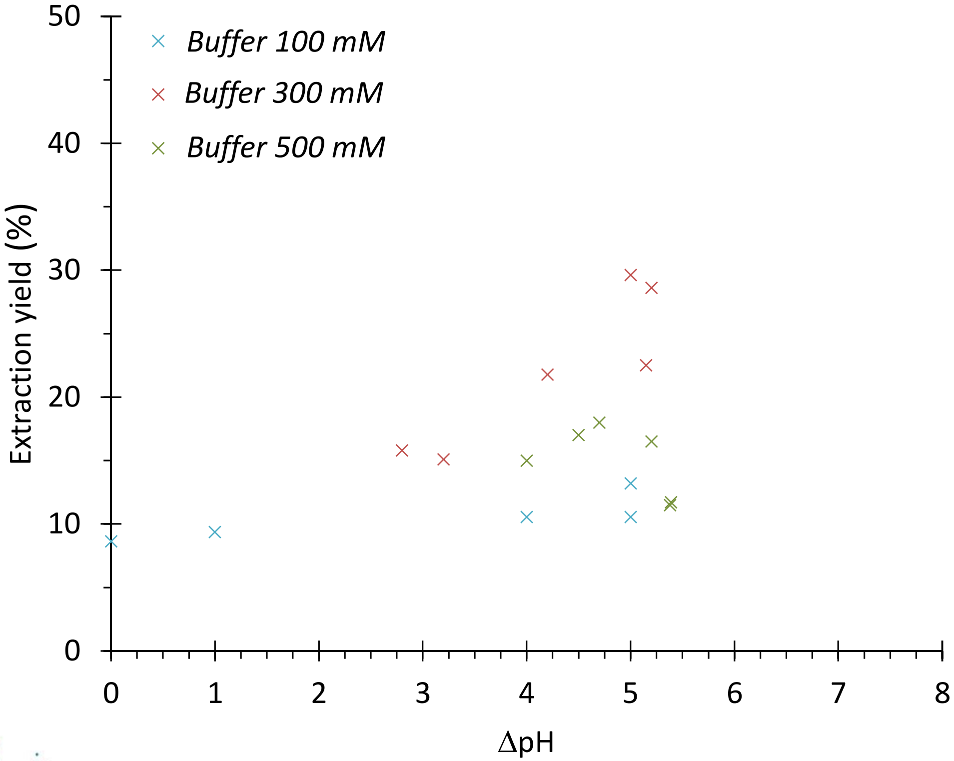


➡ pH unstable during the simultaneous process

→ Control of pH

Transport of fructose:

- Influence of ΔpH and **ionic strength** of the buffer solutions on **extraction yields**:



200 mL MIBK, 70,°C
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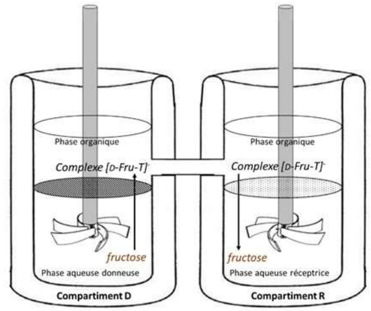

Compartment D:
V=200 mL
Tris-HCl X mM
pH 8.5
[D-Fru]i=100 mM

Compartment R:
V=200 mL
Citrate buffer
300 mM pH 3

$\Delta pH = pH_D - pH_R \approx 4.5 - 5$

Need to control the pH in continuous during the process

$Y_{extraction}$ (500 mM) < $Y_{extraction}$ (300 mM)

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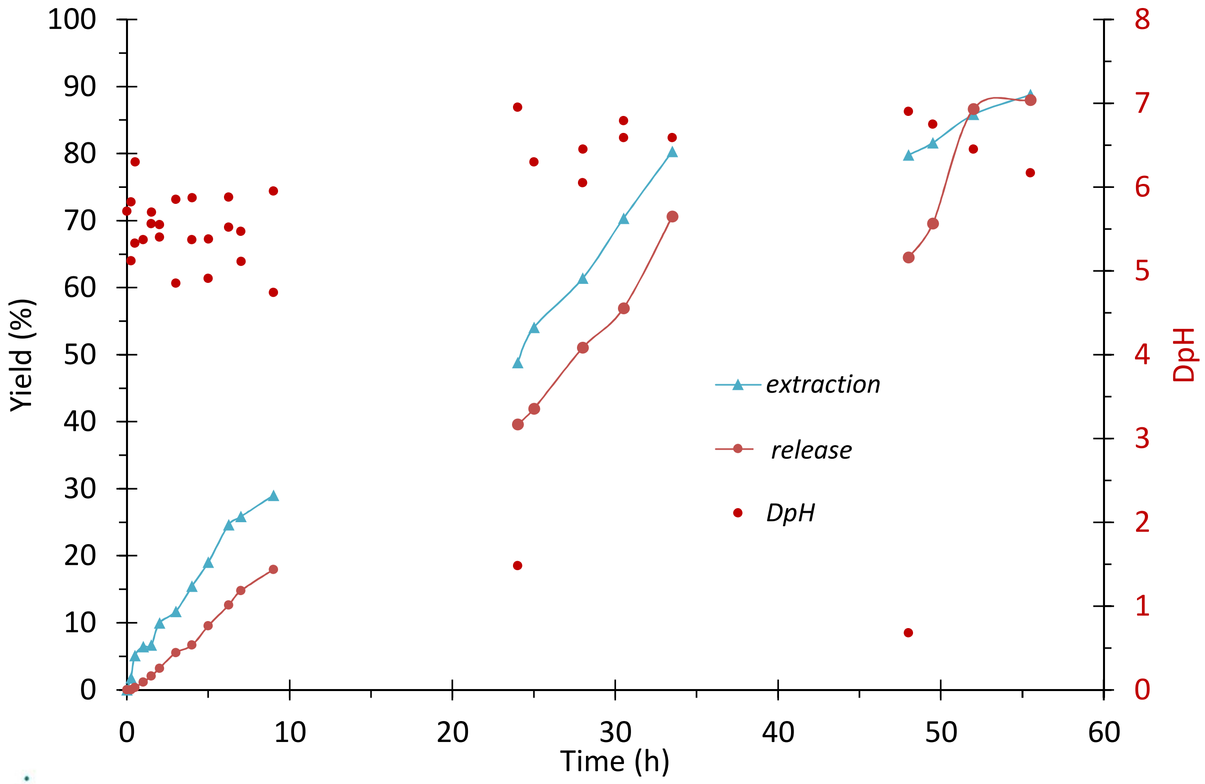
Transport of fructose:

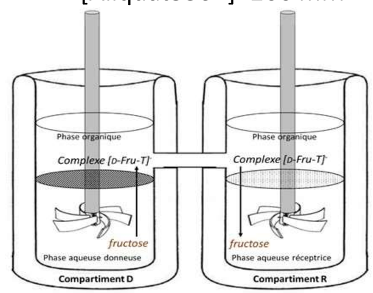
- Cycles of 34-DCPBA / Aliquat336® :



Y_{ext}= 89%
Y_{rel}= 88%
30 regulated hours

$n_{D\text{-}Fru}/n_T$ = 1/0.25

200 mL MIBK, 70,°C
[34-DCPBA]=100 mM
[Aliquat336®]=200 mM



Compartment D:
V=200 mL
Tris-HCl 300 mM
pH 8.5
[D-Fru]i=100 mM

Compartment R:
V=200 mL
Citrate buffer
300 mM pH 3

Amount of fructose extracted > Amount of fructose that could be extracted during 1 extraction cycle

⇒ **34-DCPBA - Aliquat336® pair is recycled during the experiment**

⇒ **This turnover also highlights the movement of the 34-DCPBA (T) and Aliquat336® (coT) molecules in both directions**

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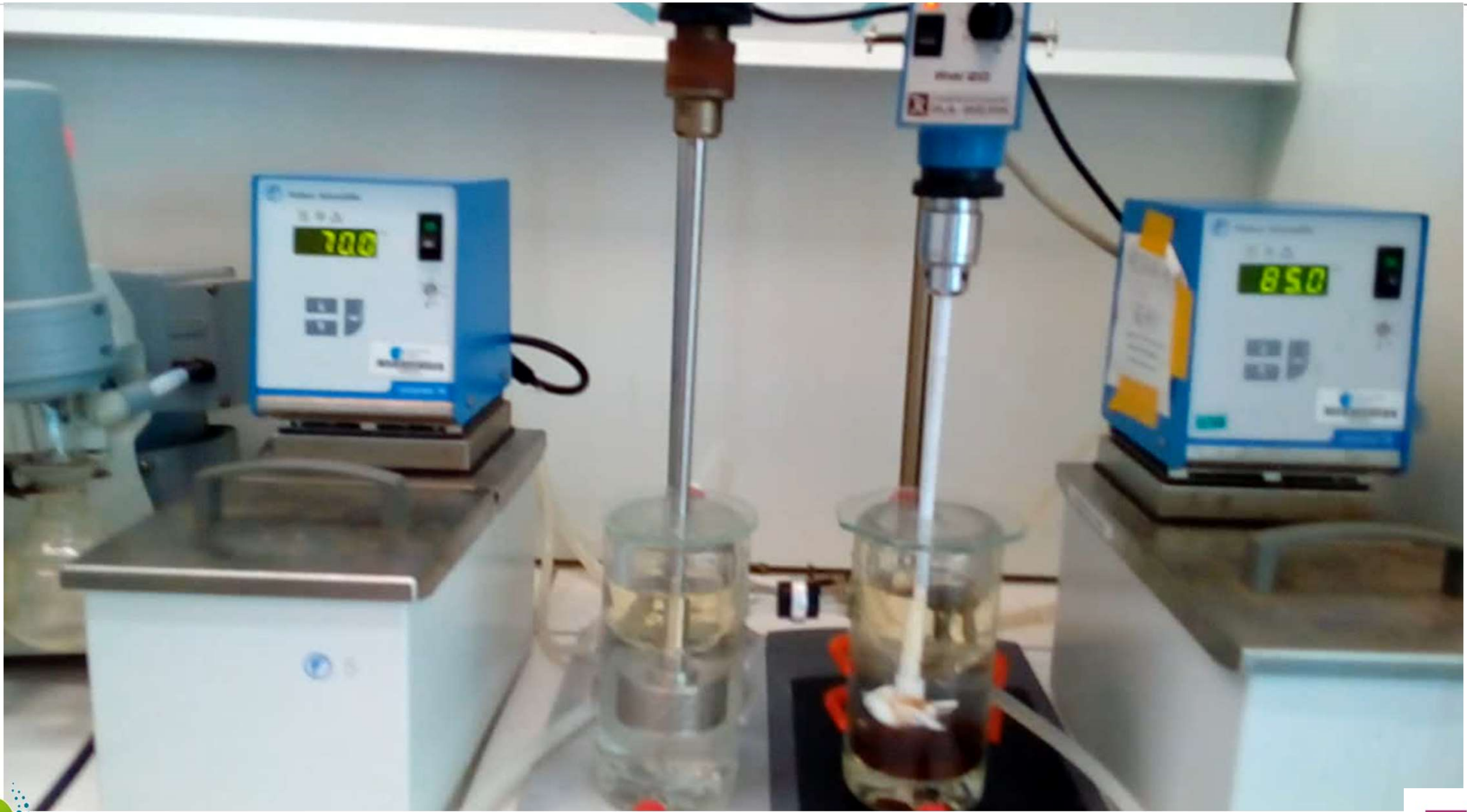

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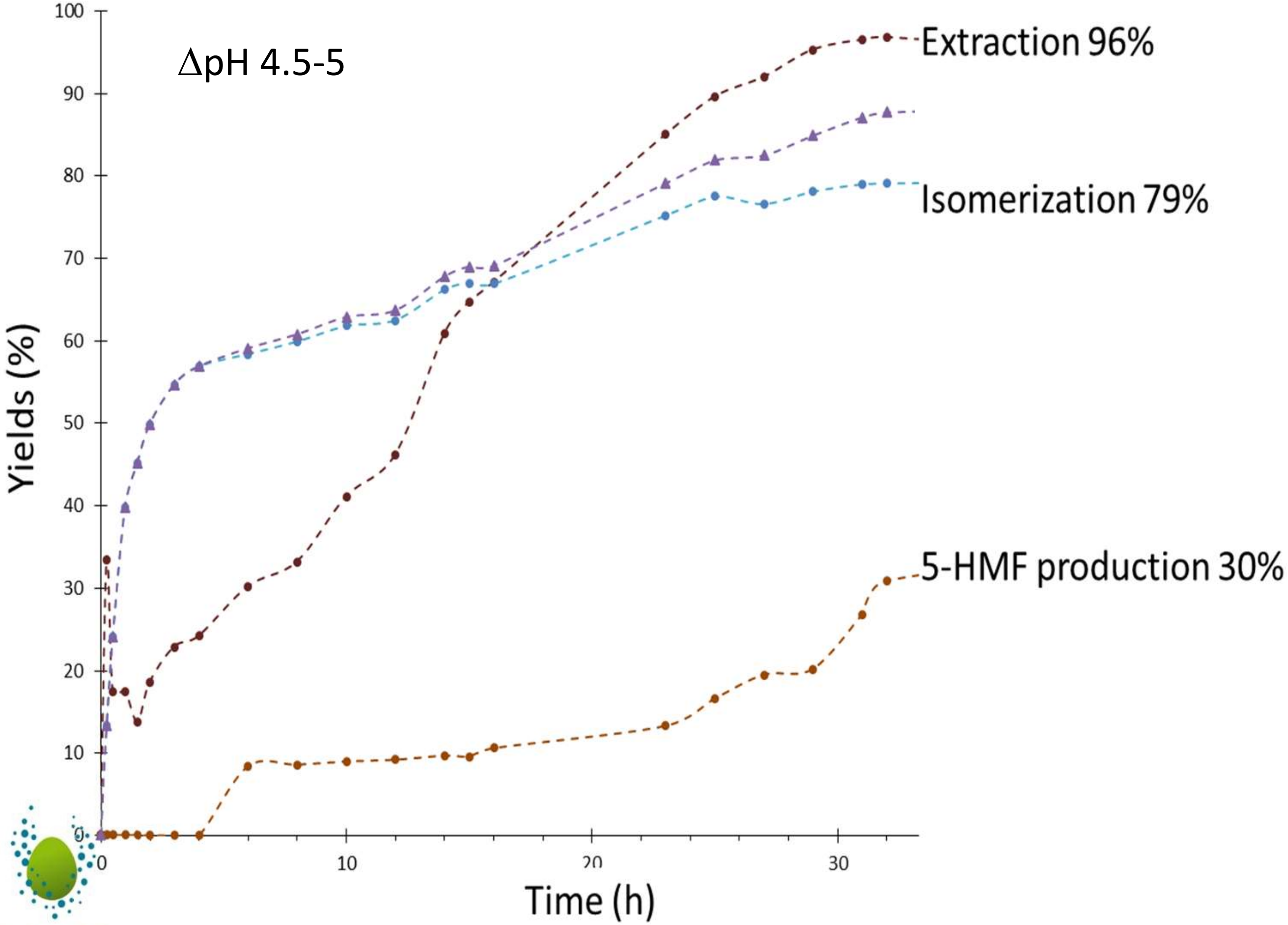
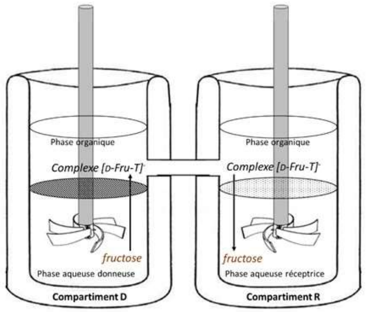
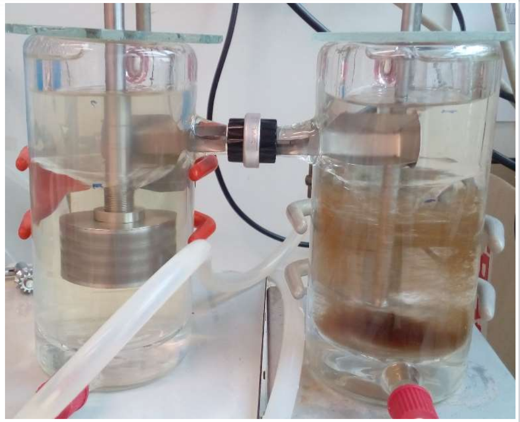
Hybrid catalysis process implementation

- Implementation of simultaneous catalysis in the « H » reactor:



200 mL MIBK, 70,°C
[34-DCPBA]=100 mM
[Aliquat336®]=200 mM





Compartment D:
V=200 mL
Tris-HCl 300 mM
pH 8.5
[D-Fru]i=100 mM

Compartment R:
V=200 mL
Citrate buffer
300 mM pH 3

$Y_{5\text{-}HMF}$=30% at 32h
Conversion*=90%
$Yield_{isomerization}$=79% (55% at thermo. equil.)

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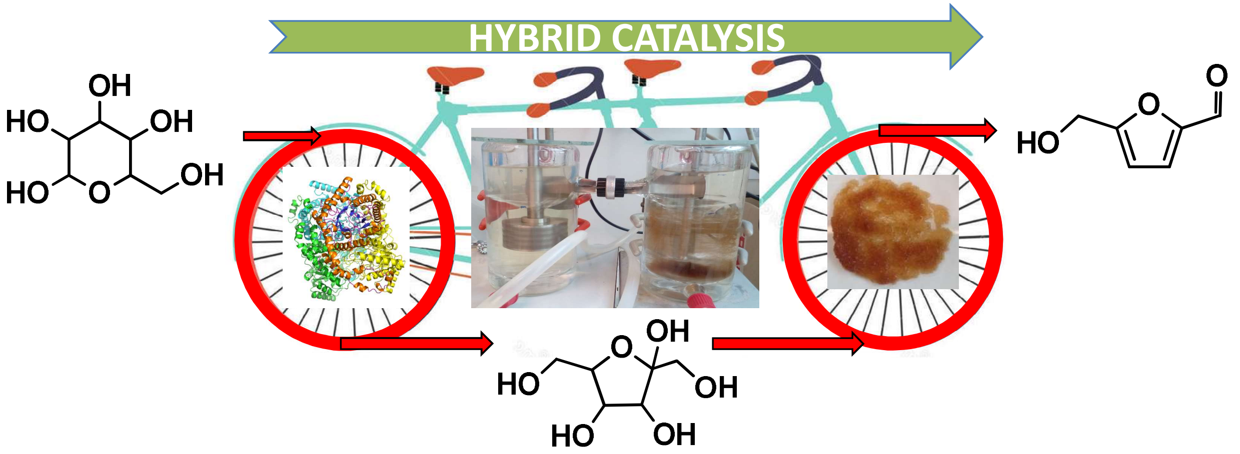
Summary



- Simultaneous (bio)catalytical reactions
- Shifting of isomerization thermodynamic equilibrium (25%)

- Study of reactions in sequential approach
- Design of the reactor « H »
- Optimization of D-Fru transport
- Implementation of (bio)catalysis in tandem in the « H » reactor

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REALCAT — Brings catalysis over lightspeed

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Mickael CAPRON
Franck DUMEIGNIL
Sébastien PAUL

IFP Energies nouvelles

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Nicolas LOPES-FERREIRA
Damien DELCROIX

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A dual (bio)catalysis approach for the synthesis of 5-HMF from D-glucose

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