



## How the chemists integrate Enzymes and Renewable Resources in their development strategy



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## A skillful expertise for APIs and intermediates

### MINAKEM Group's brands

**MINAKEM**  
France

FDA audited for APIs  
Solids management

Chemical expertise:

- Cyanidation
- Hydrogenation
- Carbonylation
- Boronic acids
- C-C coupling
- Lithiation
- Thio chemistry

**CHEMTEC LEUNA**  
Germany

FDA audited for an API  
Liquids management

Chemical expertise:

- Hydrazine chemistry
- Acetylene use
- Phosgene use
- Protecting chemistry
- Continuous process
- DiBoc in solution

**PENNAKEM**  
USA, China

Fufural, furanes  
Methyl THF, THF

Chemical expertise:

- Renewable resources
- Hydrogenation (Vapor)
- Distillation
- Friedel & Craft
- Decarbonylation
- Amination

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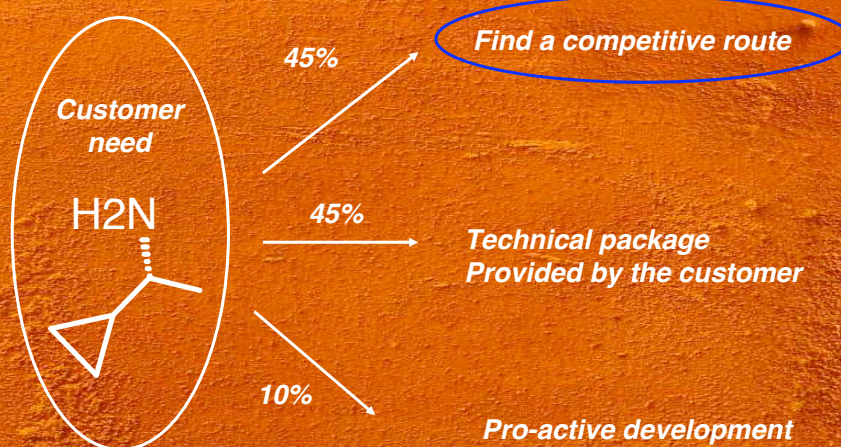
## Overview of the chiral approach ?

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## Custom synthesis – our job

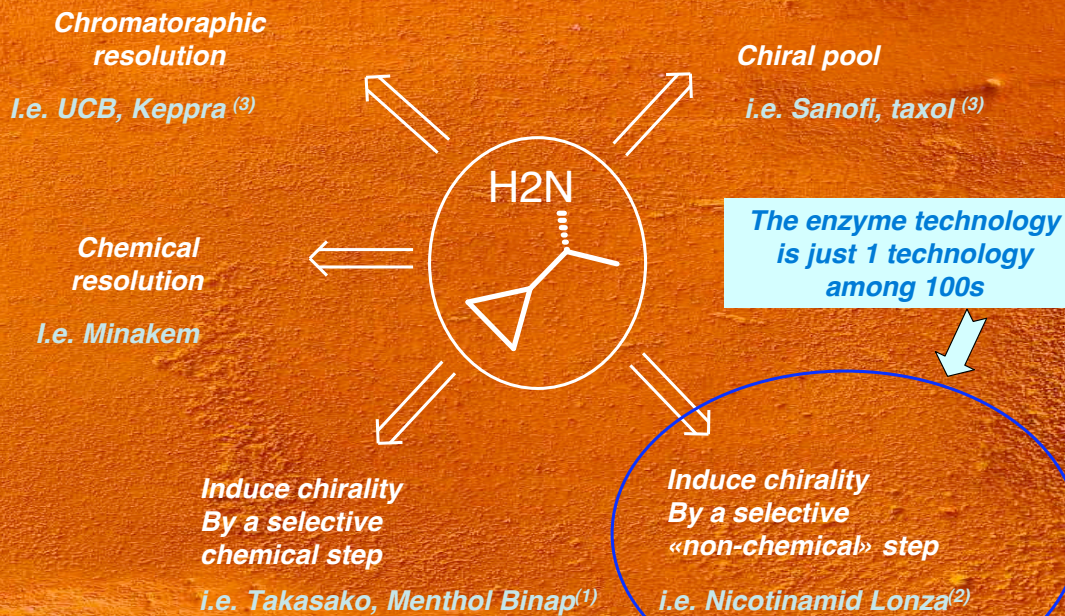


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# Chirality – numerous technologies



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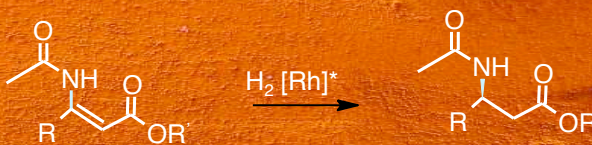
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(1) – wikipedia (2) Biocatalysis. Andreas S. Bommarius and Bettina R. Riebel ISBN: 3-527-30344-8 (3) public information

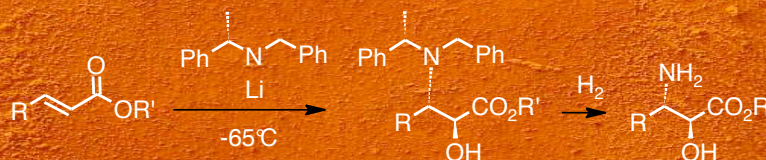
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# Chirality at Minakem 1/2

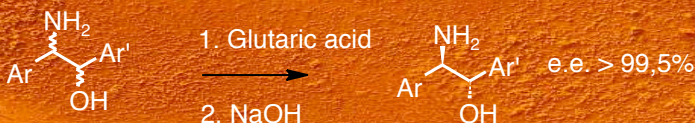
Asymetric hydrogenation



\*Collaboration with Prof. Dixneuf (Univ. Rennes, F)



Chemical resolution



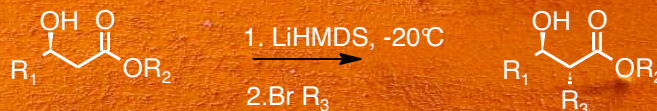
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## Chirality at Minakem 2/2

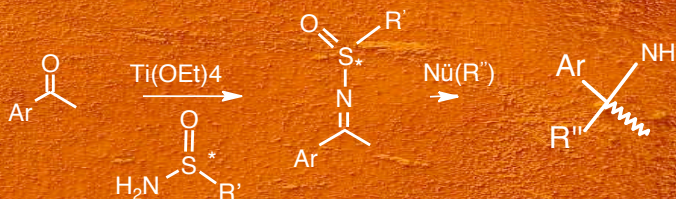
Aryl / alkyl coupling



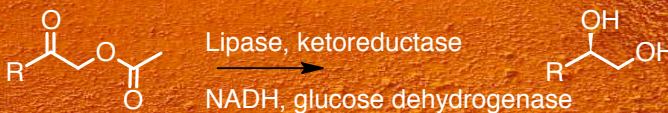
Sulfinamide

To induce chirality

To bypass an unstable imine



Enzymatic reduction



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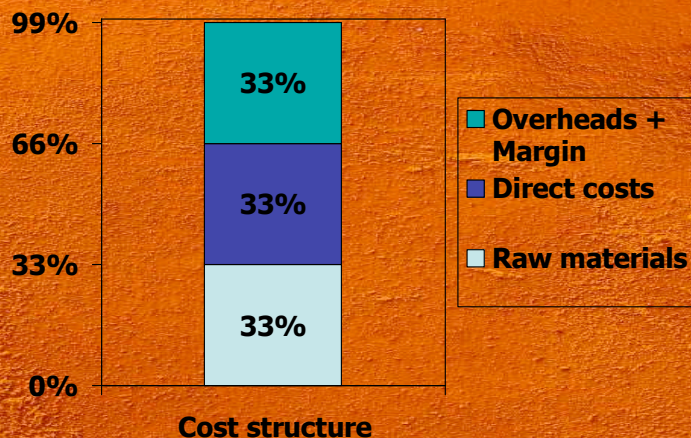
How to integrate enzymes  
in our toolbox of technologies ?

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## Cost structure of a molecule in the fine chemical industry



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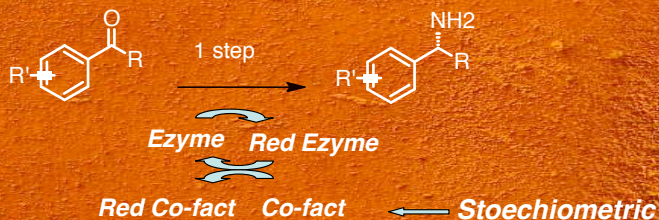
## Benchmarking enzymatic route vs chemical route

### Minakem route



Cost production basis 100

### Enzymatic route



In 1 week, conversion obtained >30%, e.e. >=99%

Cost production estimation 400 with an optimized yield (conversion 100%) including 200 for the co-factor used at stoichiometric amount

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## Chiral technologies – criteria of choice

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- *provide a competitive advantage*
- *ability to quickly check 'proof of concept' in the lab*
- *get a quick cost estimation at production scale*
- *ability to scale-up*
- *long term commitment of suppliers*

## Driven factors for the enzymes

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- *Good selectivity / substrate*
- *High conversion rate*
- *Low dilution rate (target 15%)*
- *Cost effectiveness of the system (incl. co-factors)*
- *Industrial availability of the enzyme (2-3 months)*
- *IP free enzyme, if possible*

## Minakem strategy

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- *Focus on ketoreductase and aminoreductase to reduce the number of chemical steps*
- *Make a first cost evaluation to benchmark enzymes vs traditional chemical route*
- *Partnership with Libragene signed in 2007*
- *In contact with main enzymes suppliers to evaluate them on specific subject*

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## Risk assesment to choose enzymes

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- *Integrate enzymes as an option in the culture of the chemists*
- *Find a chemist internally to support the project*
- *Availability of samples (2-3 weeks)*
- *Get a price at industrial scale far beyond its achievment*
- *Find a supplier able to commit on the long term run*
- *Find a supplier able to optimize the enzyme*

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## How to earn money with enzymes ?

### Main issues

- *Catalytic quantity but no precious metal to earn on*
- *1 fee, difficult to ask for royalties*

### Different business model has been set-up

- *IP owned, royalties but not accepted by the industry*
- *Acquisition of fine chemical players (low probability to succeed)*
- *R&D on major molecules (generics) and exclusive partnership with a fine chemical sub-contractor*

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## Conclulsion about enzyme technology

*Good technology with daily improvements*

*But it has to overcome key issues:*

- *Enzyme is just an additional tool to generate chirality*
- *It has to be competitive versus traditional technologies*
- *The supplier needs to have a long term commitment*
- *Inability of suppliers to earn money does not help to build trust and long term collaboration*
- *“Old chemists” (R&D leaders) often does not want to think enzymes*

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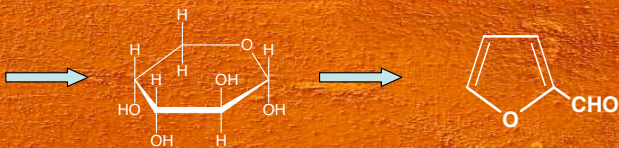
# How to get access to downstream renewable raw materials ?



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## Furfural – from renewable resources Lower indexation with Oil Price



Five carbon sugars

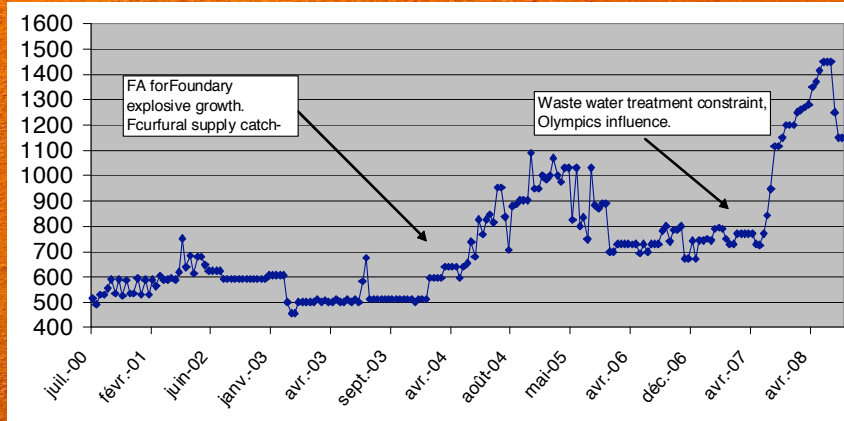
Furfural

Furfural is produced from agricultural waste by-products,  
not from food products

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# Fufural is not linked to oil price evolution

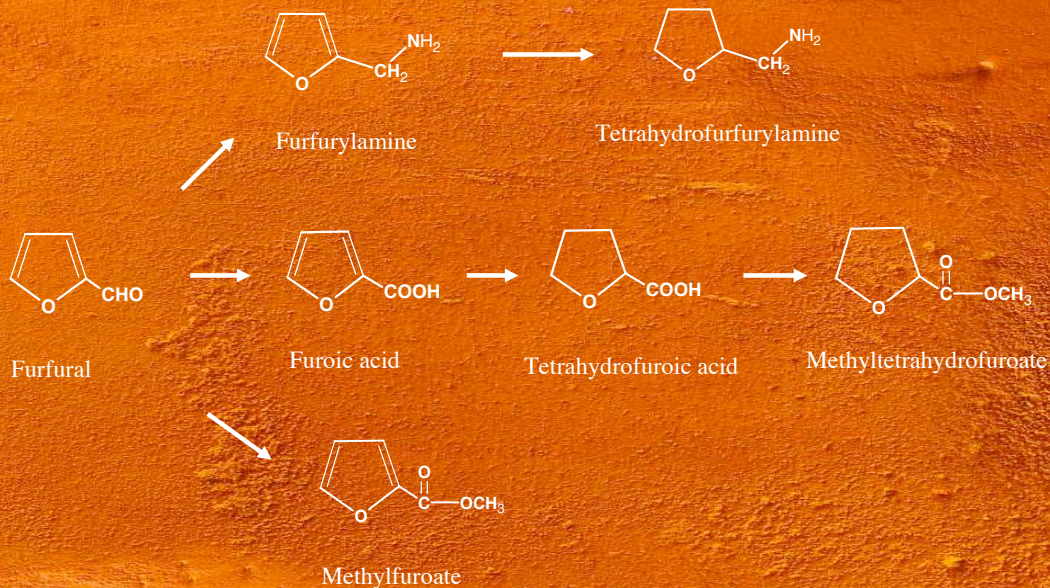


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# Fufural as a building block

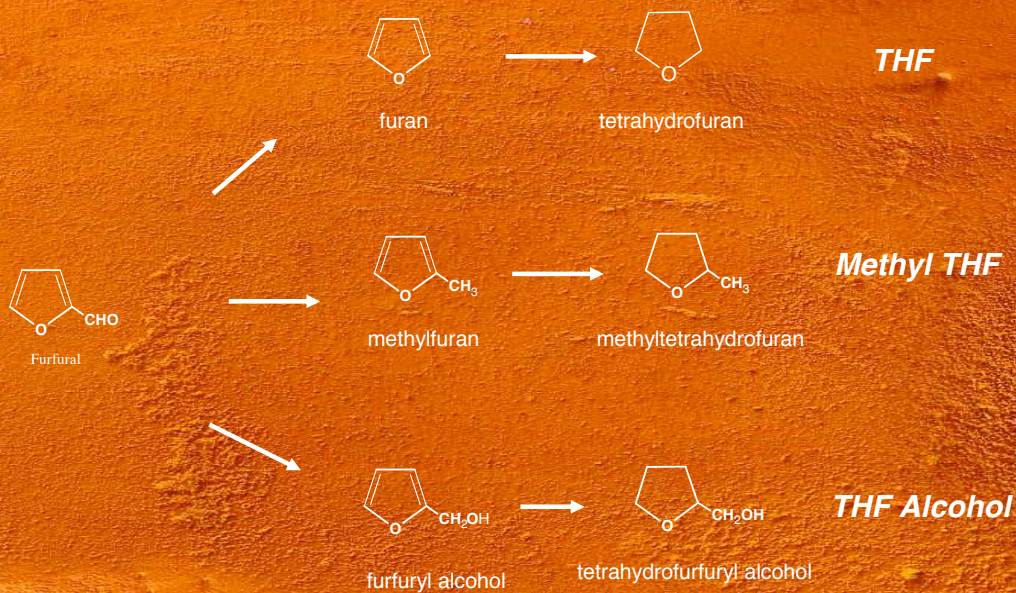


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PENNAKEM  
Renewable Resource Chemistry

## A range of green solvents



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## Methyl THF A Greener Solvent...



...with  
Process and Cost Advantages  
for organometallics

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## Why Methyl THF is growing so fast ?

- MeTHF offers an opportunity to reduce costs (yield, productivity)
- MeTHF is more stable than THF (less solvent required)
- MeTHF follows the growing demand on organometallic chemistry
- MeTHF enables long term competitive advantage through process innovation on existing process
- The MeTHF of PennAkem is not a petro-chemical derivative

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## Scope of reactions benefiting from MeTHF properties

MeTHF is a versatile solvent

1. Grignard
2. Lithiation
3. Hydride based reduction
4. Organopalladium
5. Organozinc
6. Biphasic reactions

*B. Comanita; D. Aycocq, Industrie Pharma Magazine, No.17, 2005, 54-56  
D. Aycocq, Org. Process Res. Dev., 11 (1), 156 -159, 2007*

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## > 14 % Higher yield in Grignard formation

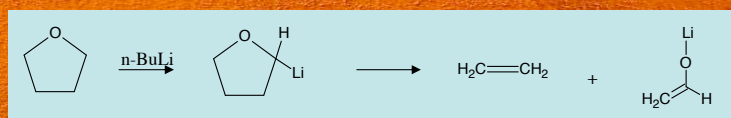
#	Reagent	Solvent	Organomagnesium Yield	MeTHF Yield Improvement
1	benzyl chloride	THF	85%	<b>14%</b>
		MeTHF	99%	
2	benzyl bromide	THF	83%	<b>15%</b>
		MeTHF	98%	
3	o-methylbenzyl chloride	THF	78%	<b>19%</b>
		MeTHF	97%	
4	o-chlorobenzyl chloride	THF	20%	<b>66%</b>
		MeTHF	86%	
5	allyl chloride	THF	73%	<b>16%</b>
		MeTHF	89%	

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## 7 time more stable with nBu-Li vs THF

THF reacts with n-butyllithium



The reaction of n-butyllithium with MeTHF is considerably slower

Compound	Half life at 35°C minutes
THF	10
MeTHF	70

 X 7

R. Bates, J. Org. Chem. (1972) 37(4), p560.

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## Physical properties benefits

- MeTHF is the solution to THF's shortcomings:
  1. MeTHF is not miscible with water
    - No need for a second solvent or use of saline solutions (productivity)
    - Clean phase separation with no emulsions & rag layers
  2. MeTHF gives better extraction yields
    - Reduced number of extraction steps
    - Less solvent volumes
  3. MeTHF forms azeotrope like toluene
    - Easy to dry
    - Easy to recycle and reuse

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## Increased Solubility of Various Grignard Reagents

Reagents	% Sol. In MeTHF	% Sol. In THF
MeMgBr	35%	15%
EtMgBr	40%	10%
PhMgBr	45%	15%
EtMgCl	30%	25%

*P. Rüttmeyer et al., Chemetall DE 19808570*

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