

# *Enzymes as Green Catalysts in Pharma Industry*

Workshop on Biocatalysis in Pharmaceutical Industry

*27<sup>th</sup> Sept 2018, Hotel Avasa, Hyderabad.*

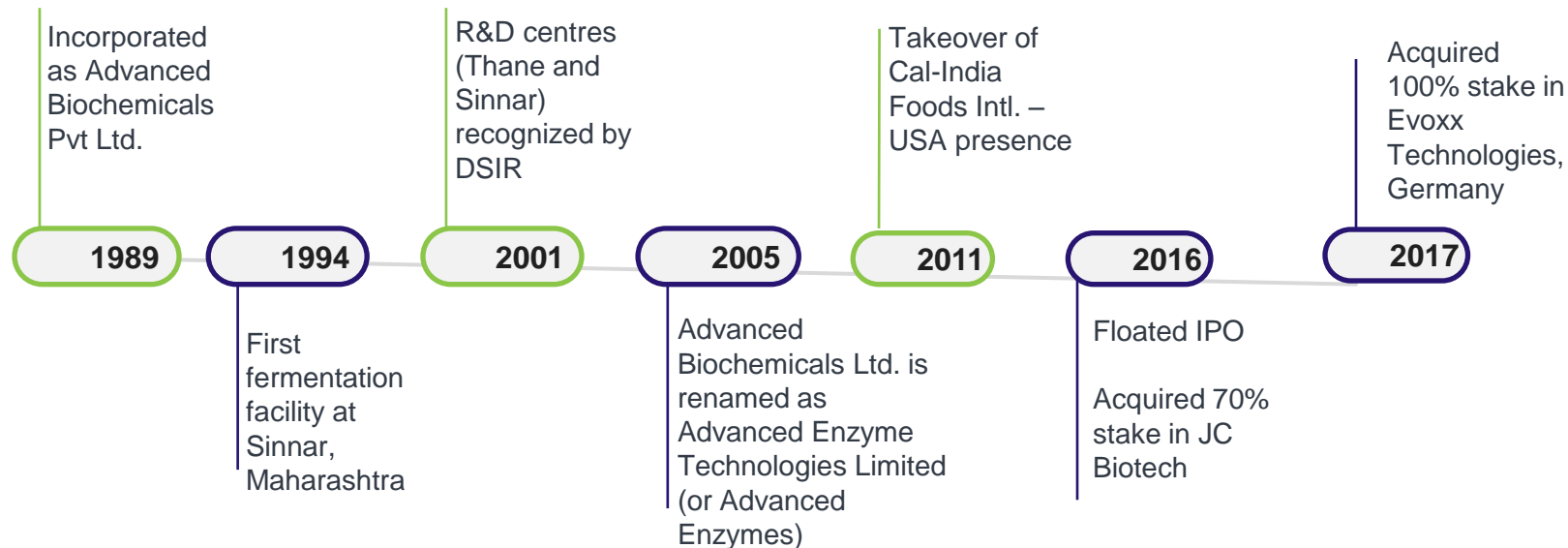


**Suresh Kumar Kannapogu**  
Project Leader- Technical

# Outline

- Advanced Enzyme Technologies in brief
- What are enzyme
- Applications in Pharma Industry
- What we offer

# Brief History and Evolution



# Advanced Enzyme in brief

**Advanced Enzymes is a research driven company with global leadership in the manufacturing of enzymes producing a wide range of enzymes that helps customers produce more from less**



**Manufacturing Units – 7**

India - 5    USA - 2



**R&D Expense – 4%**

R&D Strength – 60+



**23+**

Years of  
Fermentation  
Experience



**400+**

Proprietary  
Products



**700+**

Customers  
Worldwide



**45+**

Countries  
Worldwide  
Presence



**28**

Registered  
Patents



**420**

m<sup>3</sup> Fermentation  
Capacity



**550+**

Employees



**68+**

Enzymes  
& Probiotics

# Global Footprint

## International Presence

### Manufacturing Facilities – 8

#### INDIA

Thane	1
Nasik	2
Indore	1
Ongole	1

#### USA

Chino	2
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#### GERMANY

Monheim	1
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### R&D Centres - 6

#### INDIA

Thane	2
Nasik	1
Ongole	1

#### USA

Chino	1
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#### GERMANY

Monheim	1
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### Offices - 4

#### INDIA

Thane	1
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#### USA

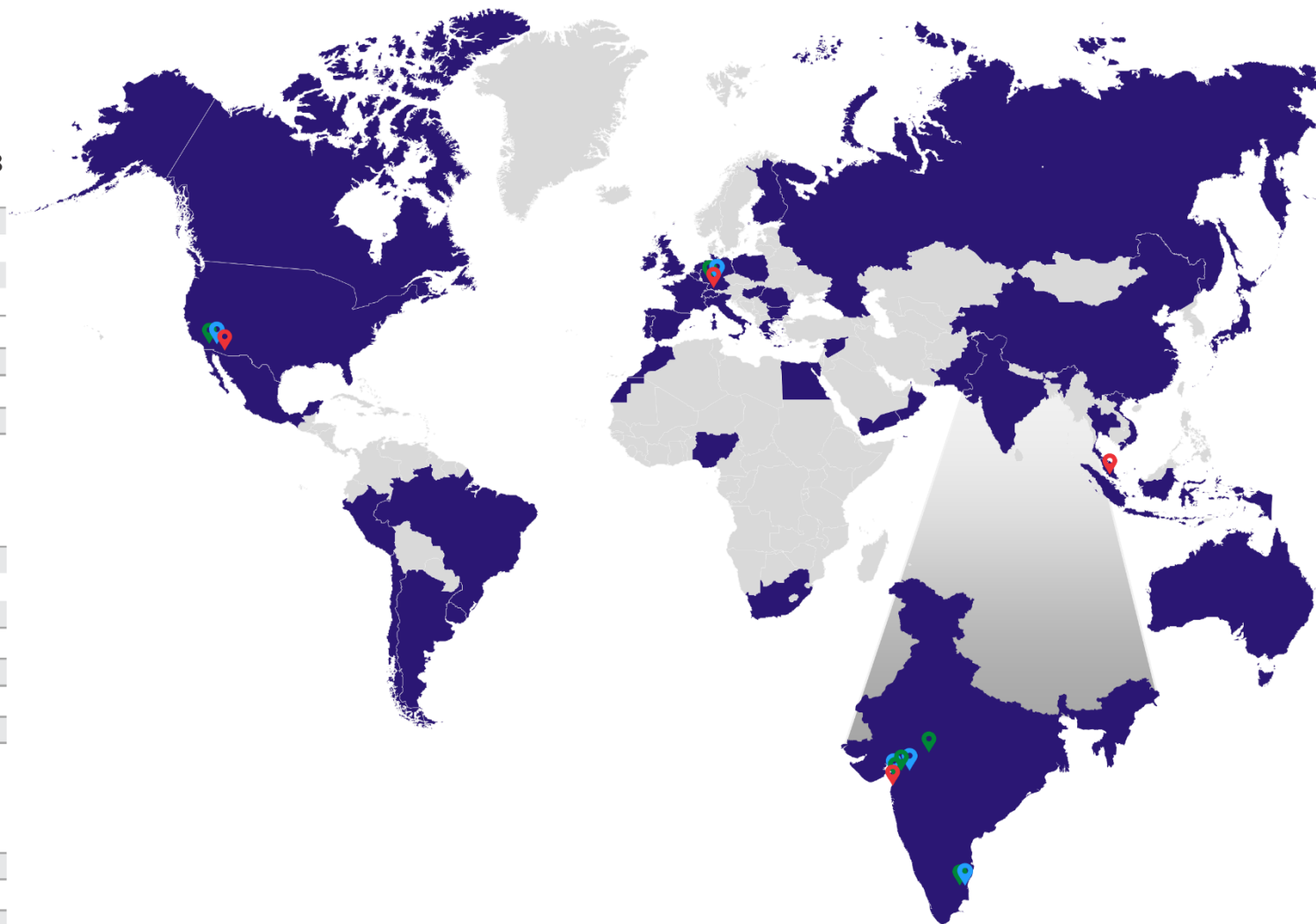
Chino	1
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#### GERMANY

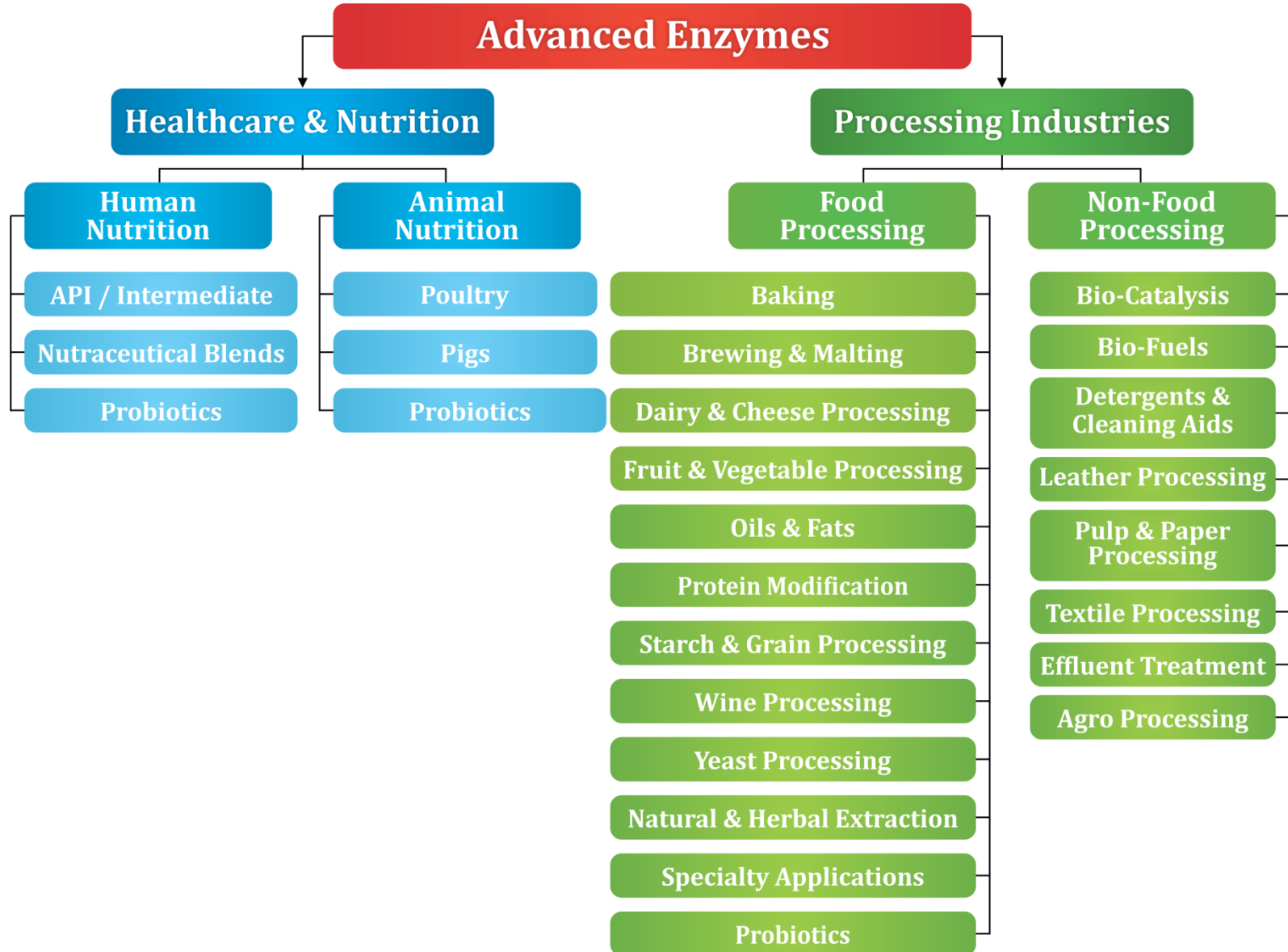
Monheim	1
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#### MALAYSIA

Kuala Lumpur	1
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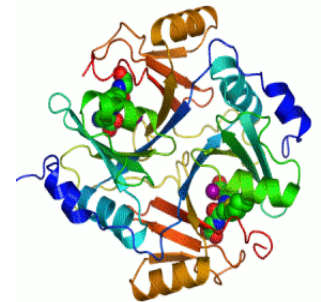


# Business Segments



# What are Enzymes ?

- Enzymes are biological catalyst(made of proteins) which accelerates chemical reaction without being consumed or changed.
- Biocatalysis can be described as the application of nature's catalysts (enzymes) to industrial processes .
- Nature boasts of having a variety of enzymes which can catalyst variety of reactions.
- With the advent of Genetic Engineering other technology advancement enzymes are further tailored for a particular reaction.



# Enzyme Applications

Enzymes are used in several commercial applications.

Pharmaceuticals

Fine chemicals

Foods and beverages

Cosmetics

Textile & Detergents

Paper

Leather

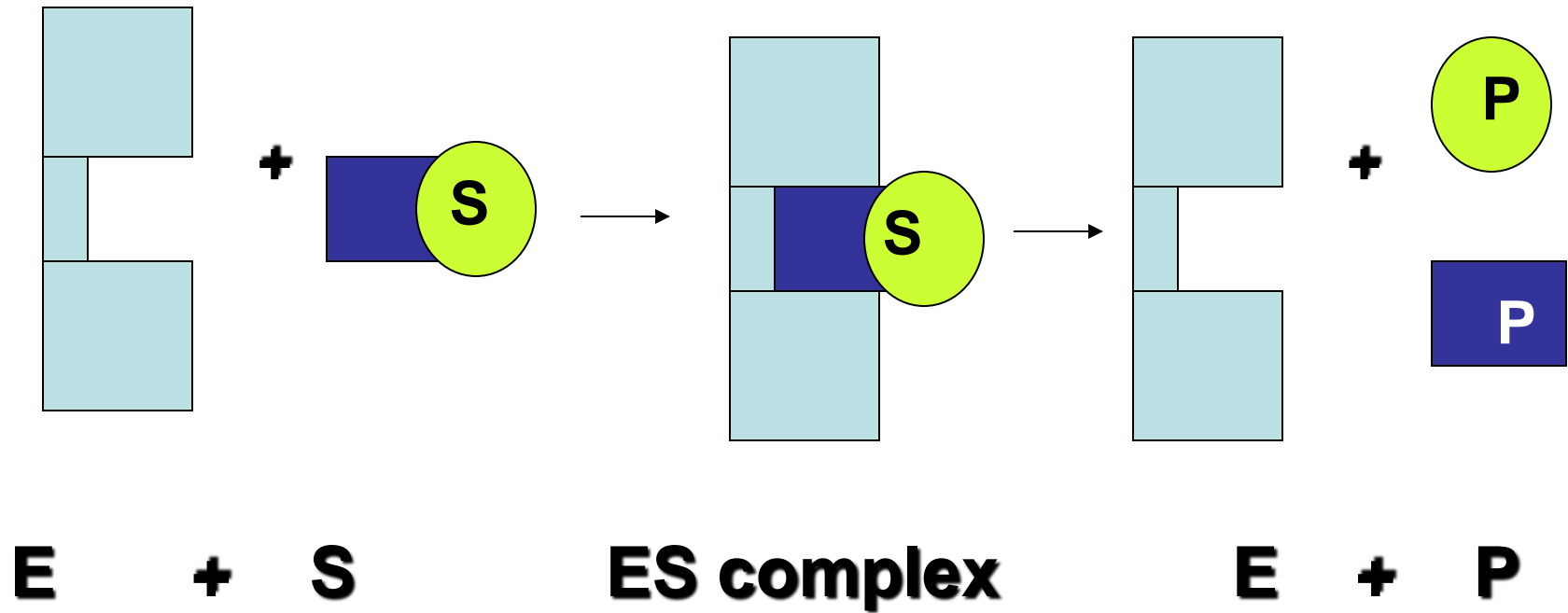
Animal Feed



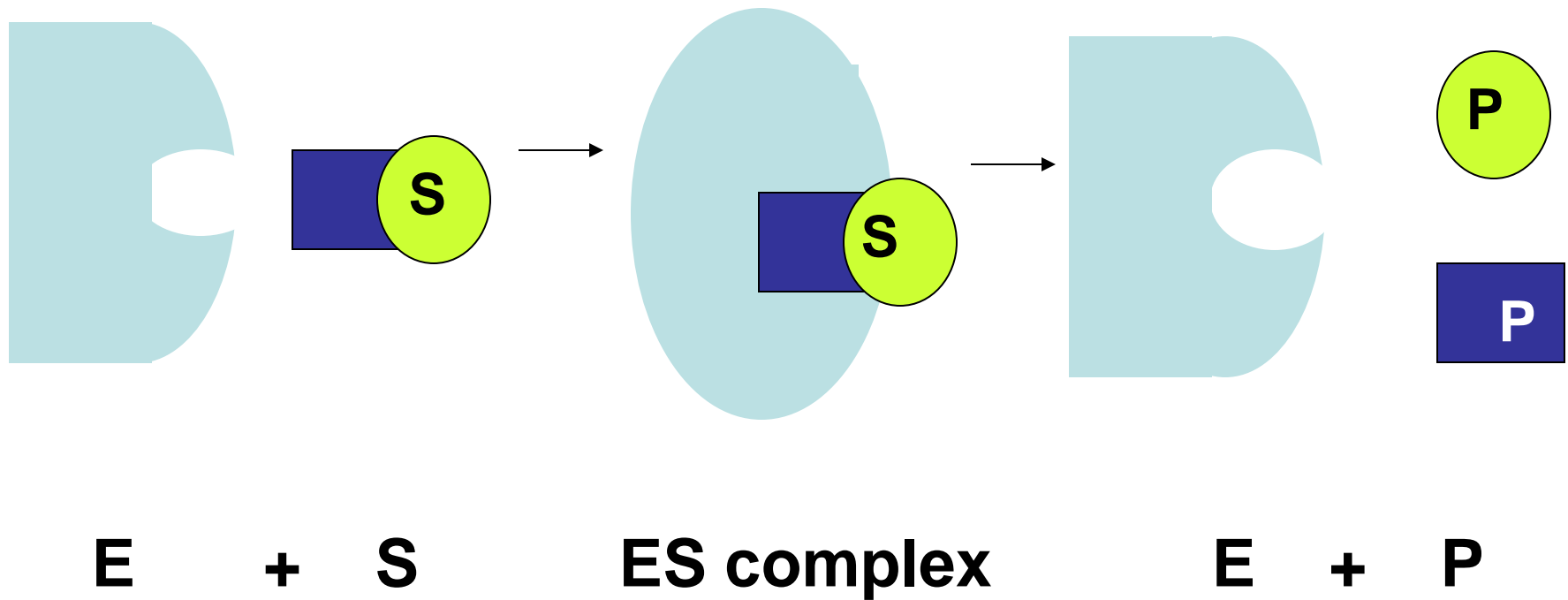
# Advantages of Enzymes over chemical reactions in APIs Industry

- Enzymes process are much safer and easy to control than chemical.
- Avoidance of hazardous reagents.
- Enzymes works in aqueous and non aqueous media
- Enzymes operate under milder conditions( Ambient temp, pH Etc)
- Enzymes offer high optical purity ,high chemo selectivity, high regio- and stereo-selectivity.
- Enzymes produce no harmful by-products.
- Enzymes are biodegradable and reusable.
- High yield due to excellent selectivity
- Reduce number of manufacturing steps

# Lock and Key Model



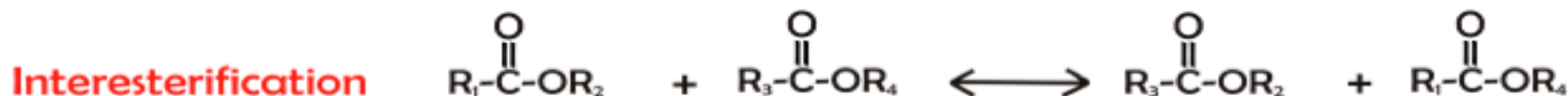
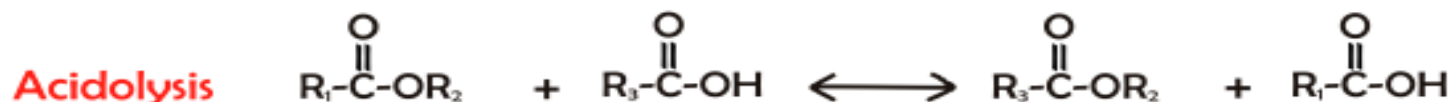
# Induced Fit Model



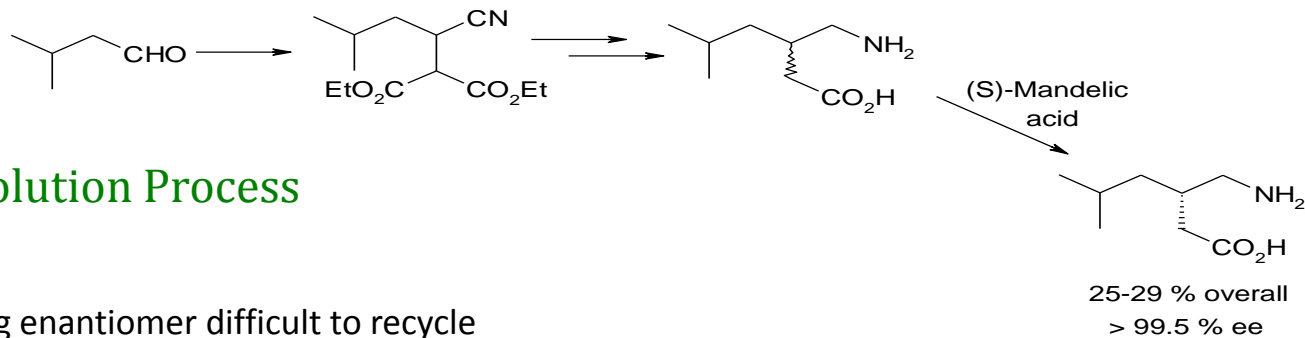
## Pharma applications of:

- Lipases
- Alcohol Dehydrogenase/Ketoreductase
- Transaminase
- Nitrilase

# Lipases are versatile Biocatalyst



# Pregabalin Chemical Process

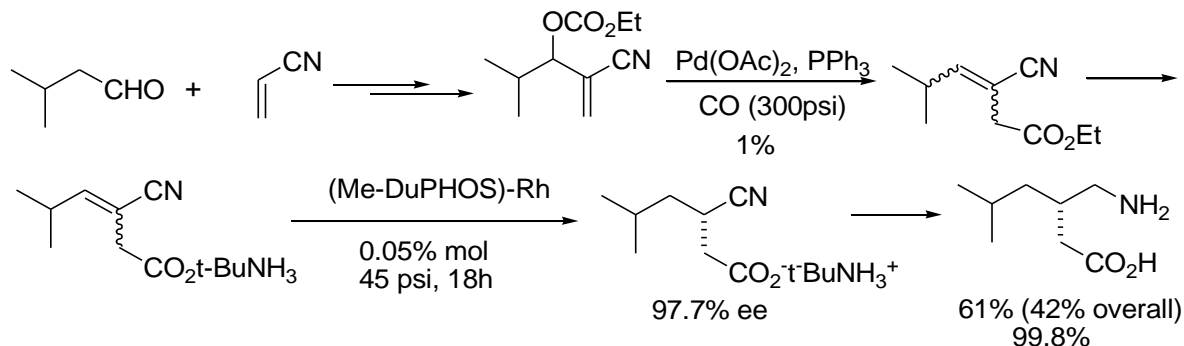


## Resolution Process

- Wrong enantiomer difficult to recycle
- Final Step Classical Resolution
- Efficient synthesis of racemic Pregabalin
- E-Factor 86

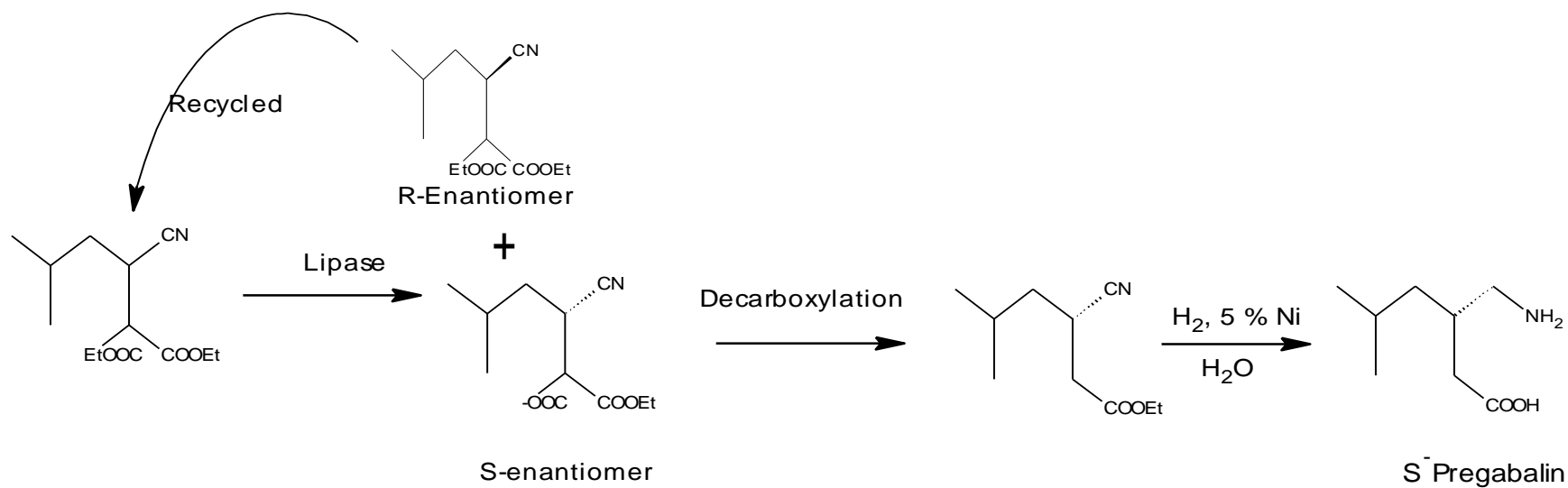
(Org. Process R and D, 1997, 1, 26)

## Asymmetric Hydrogenation Route

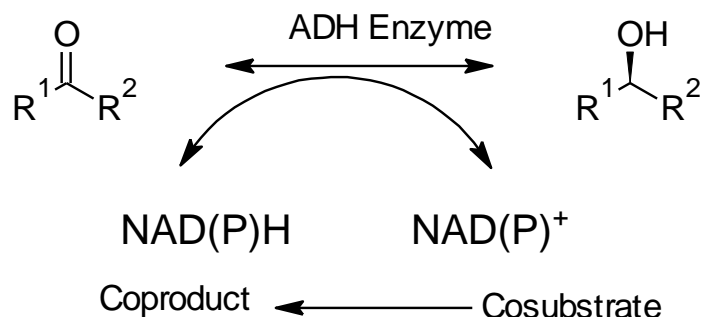


- 42% overall
- Original Catalyst (Me-DuPHOS-Rh, S/C ratio 2700)
- chiral ligand expensive
- Chemistry Published (2004JACS5966) (2003JOC5731)

# Pregabalin Biocatalytic Route



# Alcohol Dehydrogenases (ADHs)/KRED

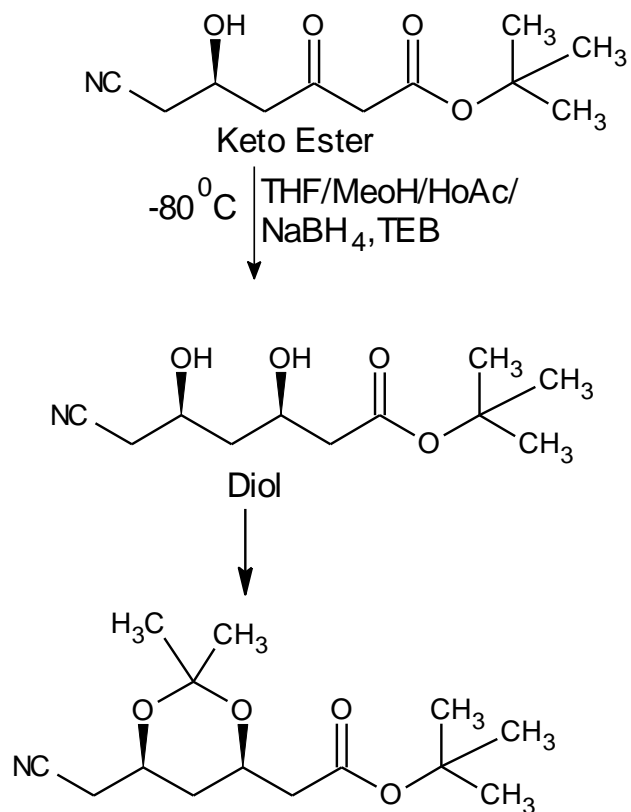


- Catalyze the reduction of ketones or aldehydes to alcohols
- Reaction is highly stereoselective
- Depend on a cofactor  $NAD^+$  /  $NAD(P)^+$  (Nicotinamide adenine dinucleotide (phosphate))
- Cofactor is recycled

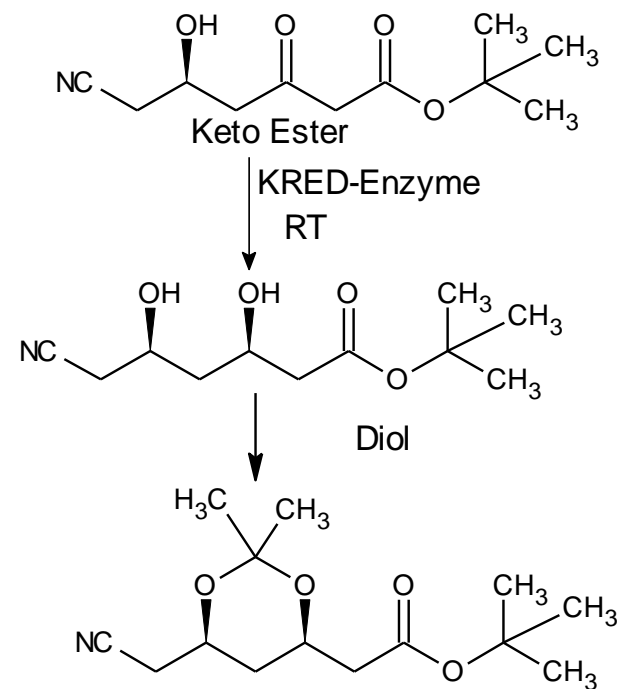


# Chemoenzymatic Synthesis of Atorvastatin Side Chain

## Chemical Route



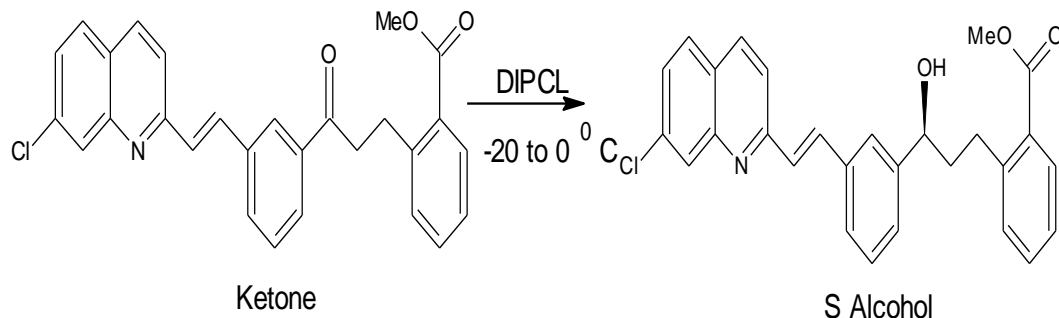
## Enzyme Route



Cryogenic conditions  $-80^{\circ}\text{C}$   
Pyrophoric Reagent, Triethyl borane (TEB)  
Six distillations

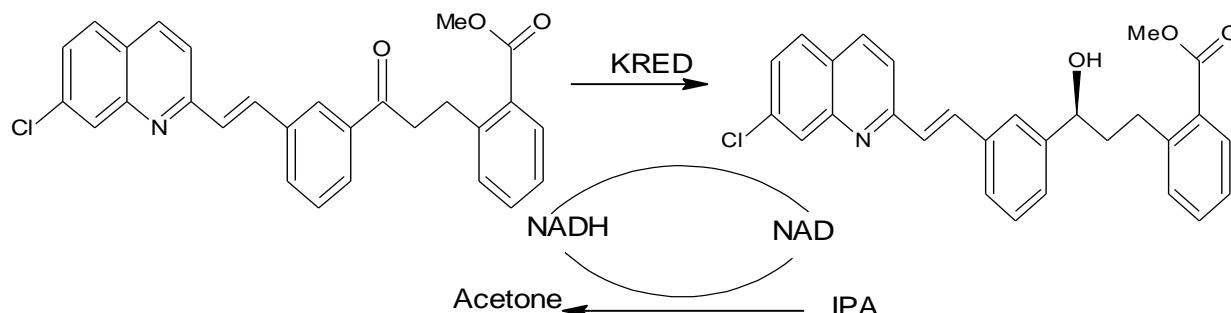
# Montelukast Intermediate

## Chemical Step



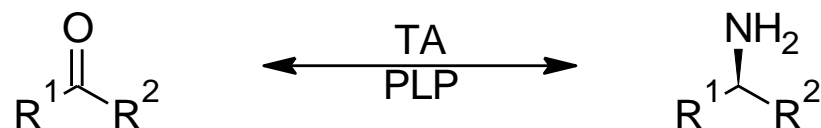
- Toxic & Corrosive
- Moisture Sensitive
- 85% yield lead high cost contribution
- Low purity need crystallization

## Enzyme Step



98% Yield cost reduction  
99.9% Purity no need for crystallization

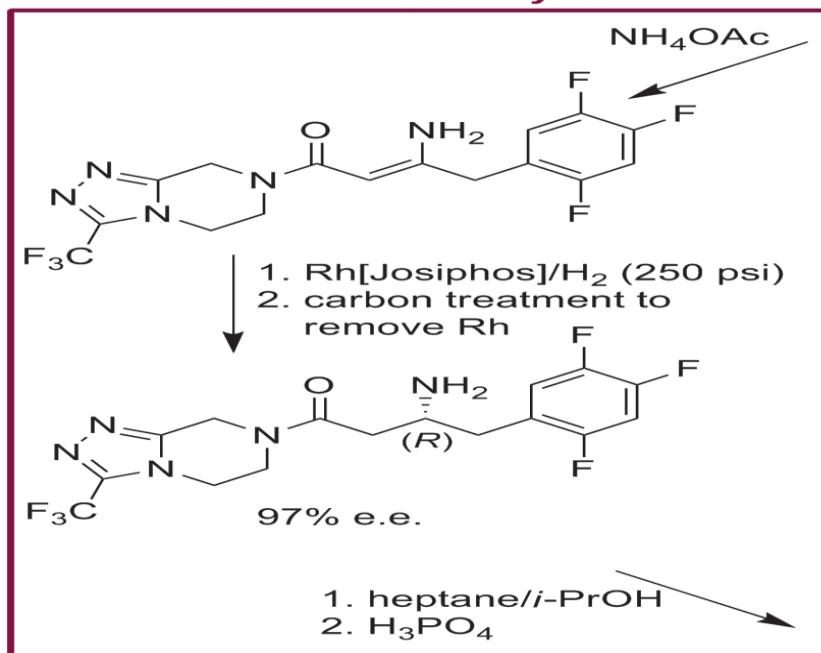
# Transaminases (TAs)



- catalyze the reductive transfer of ammonium to ketons or aldehydes
- Reaction is reversible, so enzymes can be used for **racemic resolution** of amines
- Depend on a cofactor pyridoxal-5-phosphate (PLP)
- often highly stereoselective

# Sitagliptin

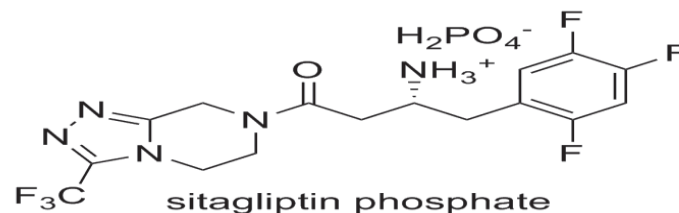
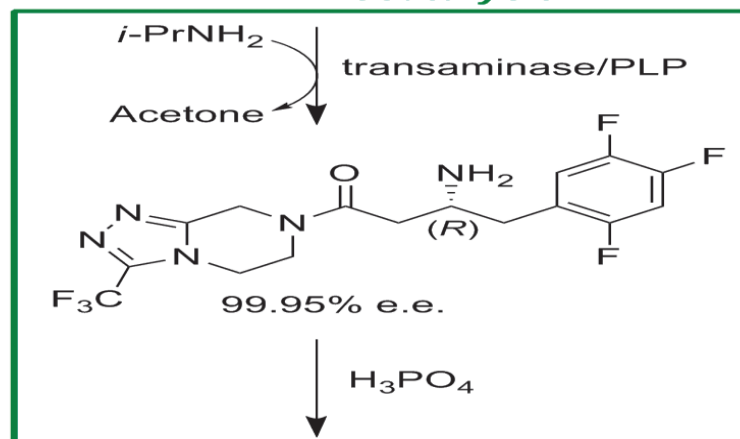
## A Chemocatalytic



*i*-Pr = isopropyl

10-13% increase in overall yield,  
53% increase in productivity,  
19% reduction in total waste,  
elimination of all heavy metals,  
reduction in total manufacturing cost,  
no need for specialized, high-pressure hydrog.  
equipment.

## B Biocatalytic

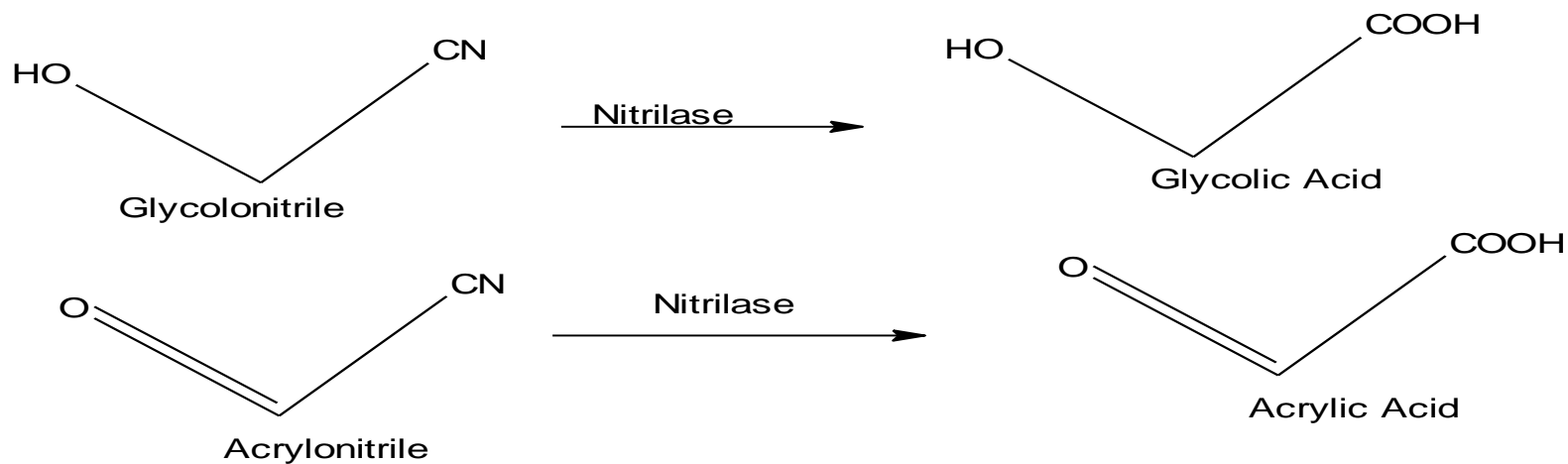
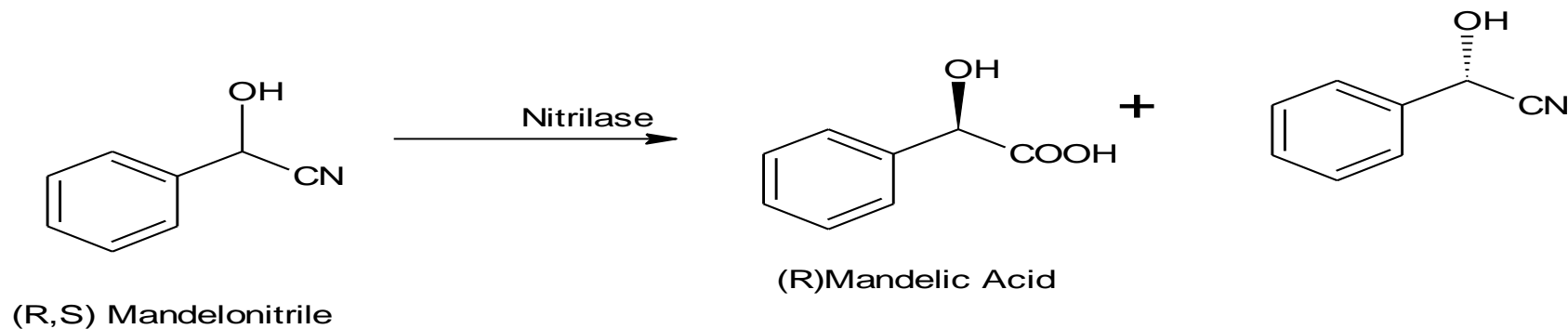


**Winner 2010**  
EPA Presidential Green  
Chemistry Challenge Award



# Nitrilases

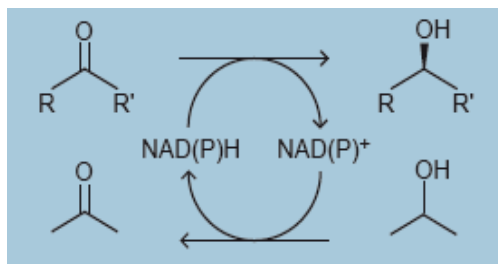
**Nitrilases** : Enzymes catalyse the hydrolysis of nitriles to carboxylic acids and ammonia,



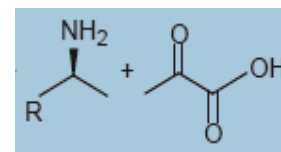
# Our enzyme platform

Ready-to-use enzymes for fine chemicals manufacture

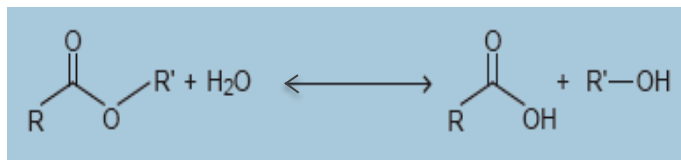
## ADH/KRED



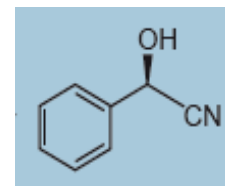
## Transaminases



## Lipases/Esterases



## Nitrilases/Nitrilehydratases



# Screening Platform for Novel Enzymes and Processes



- Alcohol Dehydrogenases (kit),
- Transaminases (kit),
- Hydroxynitrile lyases, Lipases & Esterases
- Oxidases, Nitrilases, Nitrile hydratases
- Sulfotransferases, Laccases
- Xylanases, sucrases, epimerases etc.



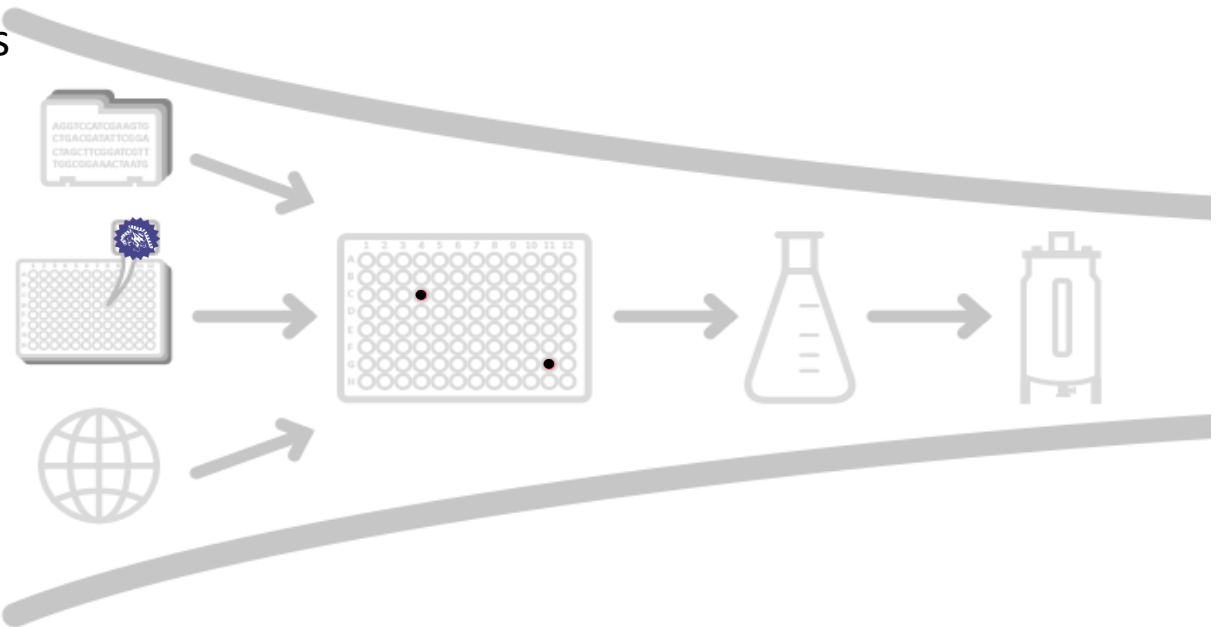
> 550 enzymes available & still growing...

# Customized products

Enzyme development: From R&D to commercial production

**Tailor-made enzymes** that fit customer needs....

- Proprietary enzyme-sequences
- Metagenomic libraries
- Directed enzyme-evolution
- Expression-toolbox
- Production strains



**Sources** ➡ **Enzymes** ➡ **Strains** ➡ **Process**



# Technological assessment

- We at Advanced Enzymes are manufacturing and exporting the enzymes to the various applications for last 50 years.
- Our technical and application lab is well equipped to develop and resolve the technical queries.
- Supported by the Enzymes experts for the Industrial applications.
- Talk to us for the new development and support.

## Contact us



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