



| Your molecule
Our mission

Biocatalysis R&D, Services & Technologies Bulk Enzyme
Supplier

Wiesbaden, Germany

Overview

Wiesbaden Site

20 years experience in industrial biocatalysis
Large libraries of proprietary enzymes (> 700 enzymes)
Acquired by Cambrex in 2010 (previously IEP
1999-2010)

Leadership

Drug Substance President

- Joe Nettelton, Business Unit President

Site Leadership

- Antje Gupta, PhD, General Manager

Services

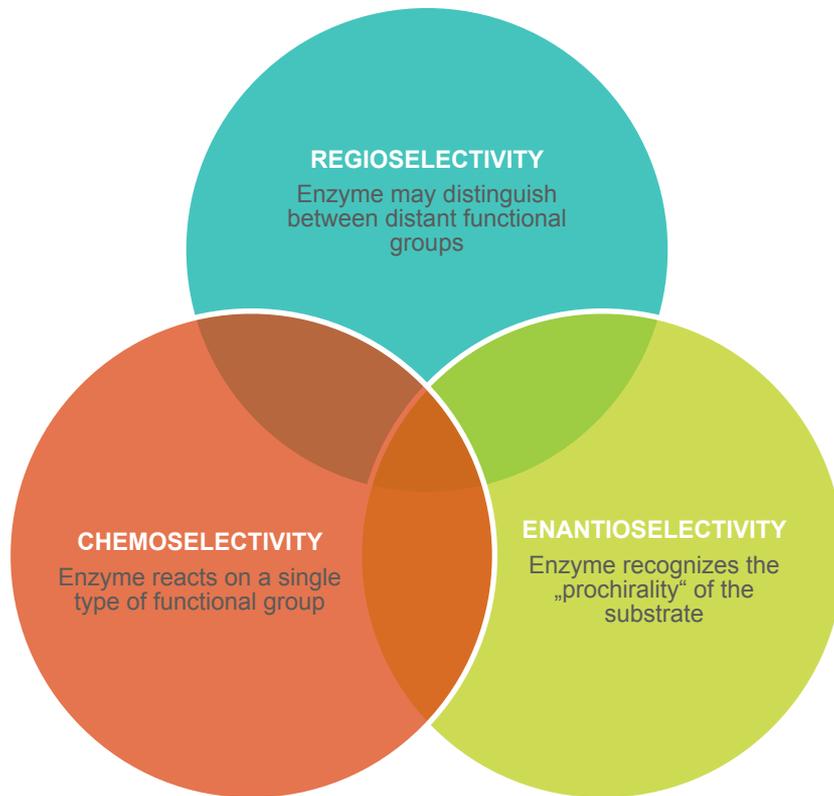
- Enzyme screening and R&D services
- Enzyme custom development and enzyme manufacturing
- Route scouting, enzyme discovery and improvement
- Bulk enzyme supplier



Core Technologies

- Ketoreductases (>250 enzymes)
- Transaminases (>100 enzymes)
- Esterases and Lipases (60 enzymes)
- Nitrilases (>20 enzymes), Amidases (10 enzymes)
- Oxidases
- ENE-Reductases (20 enzymes)
- Lactate dehydrogenase, Format dehydrogenase, Glucose dehydrogenase, Katalase, Nitro- and Azoreductases, Monoamine oxidase, Aldolases, Phosphorylase and many other >70 enzymes)

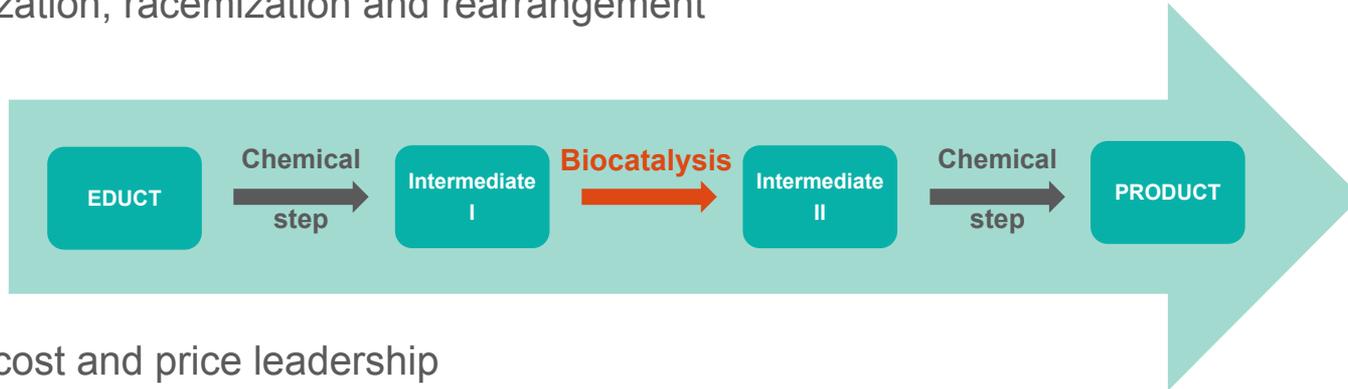
Advantages of Biocatalysis



Applying Biocatalysis

Value-adding introduction of a biocatalytic step into a chemical synthesis

- Biocatalysts are environmentally preferable, being completely degraded in the environment
- Biocatalysts allow to avoid typical side-reactions of chemical synthesis: decomposition, isomerization, racemization and rearrangement

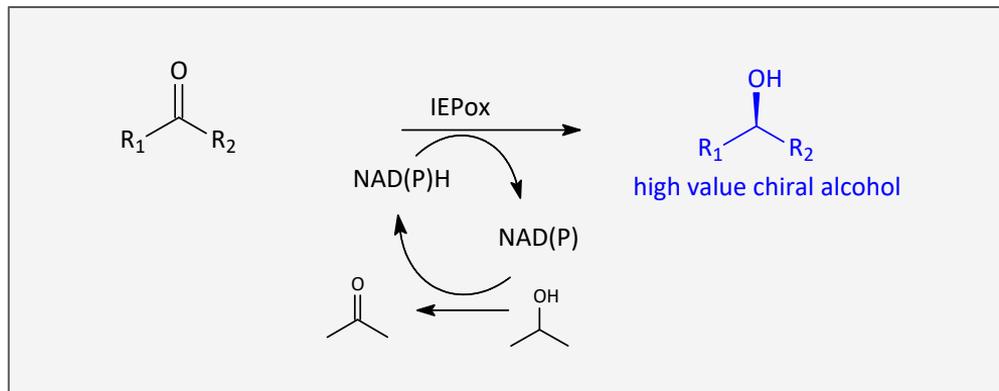


- Global cost and price leadership
- New synthesis routes with proprietary IP
- Useful for making APIs, agrochemicals, flavour and fragrances, and bulk chemicals

Core Technologies & Products

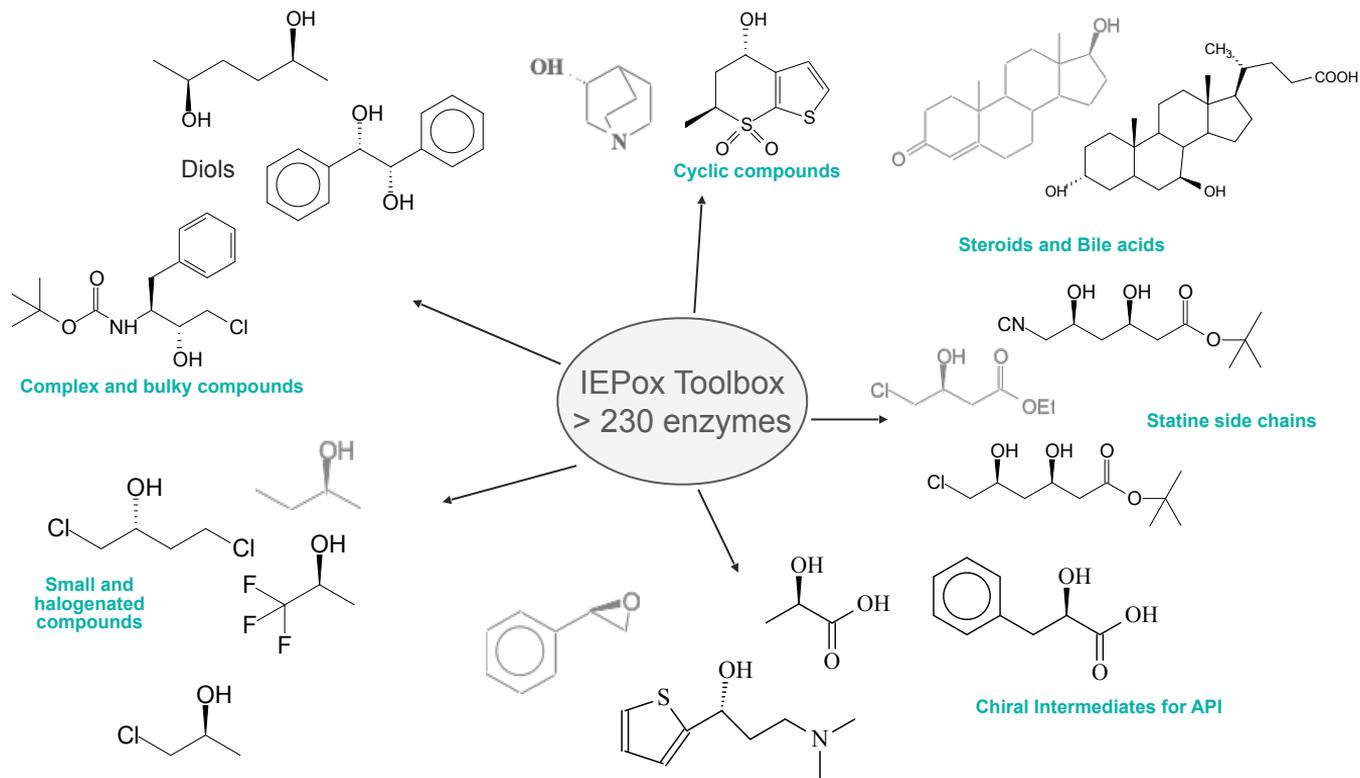


Core Technology: Ketoreductases

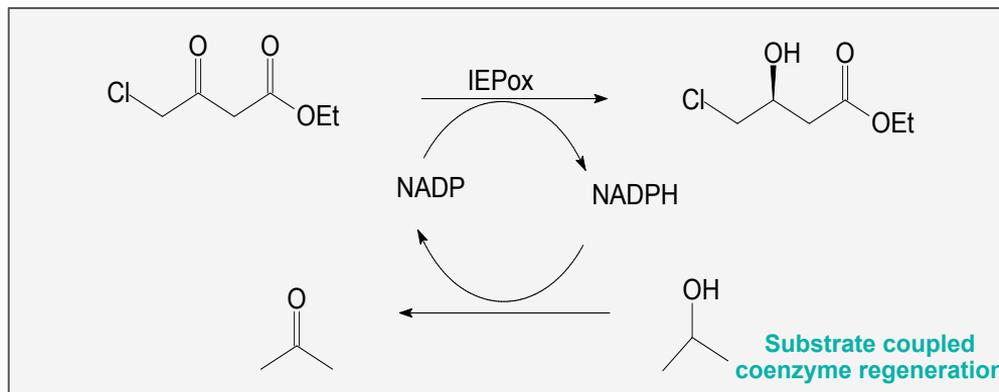


- Substrate load 100-400g/l
- Simple technology and equipment/standard batch reaction
- Inexpensive enzymes for R and S alcohols available in any scale
- Excellent enantio purity (>99.8%)
- Complete and quick conversion in 6-12 hours
- Cost contribution of coenzyme NAD(P) < 1 €/kg product
- No expensive ingredients or solvents
- Easy work up and removal of enzyme
- Environmental friendly

Core Technology: Ketoreductases for Multiple Applications

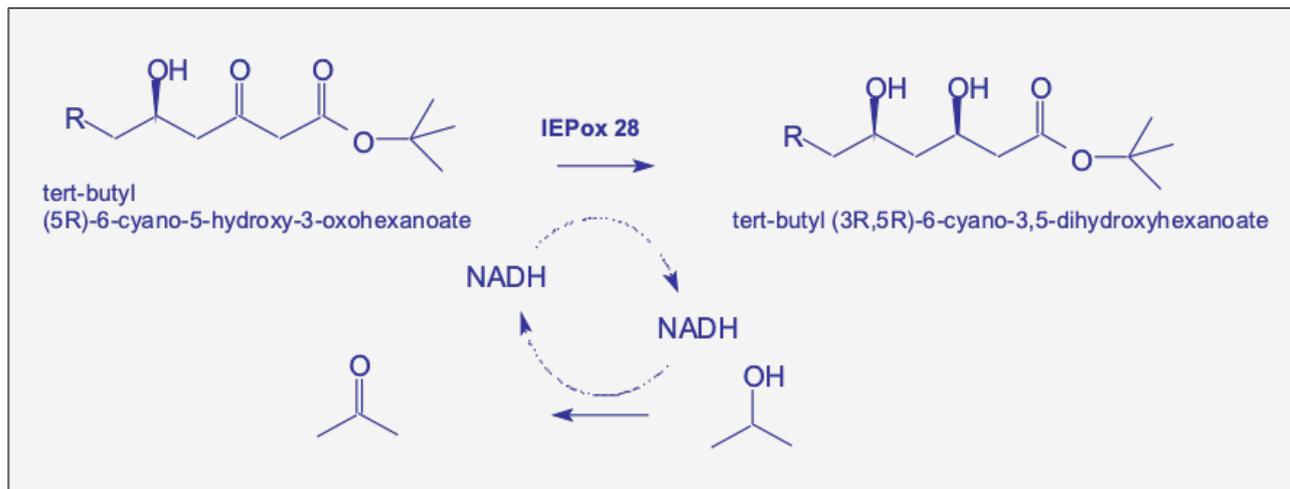


Large Scale Biocatalytic Manufacturing Process



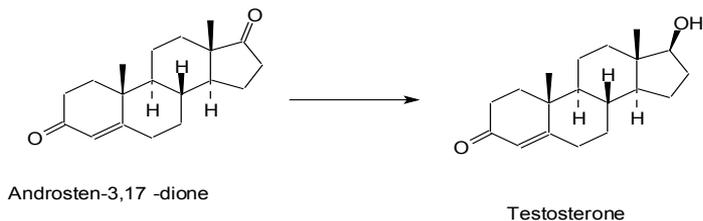
- Substrate concentration $\geq 30\%$
- Total turn-over number for cofactor $\geq 100,000$
- Inexpensive enzyme
- 100 % conversion in 24 h (no separation of product/educt)
- Stirred vessel
- 100 % ee

Process for Statine Intermediate Second Step

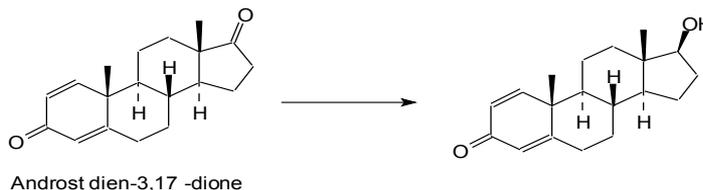


- Substrate concentration ≥ 20 %
- High total turn-over number for cofactor
- Inexpensive enzyme
- Stirred vessel
- 100 % ee

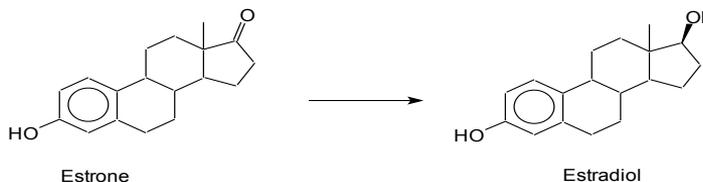
Examples of Steroid Biotransformations



Process available
(20-30 % substrate
concentration,
95%-99.5% conversion)

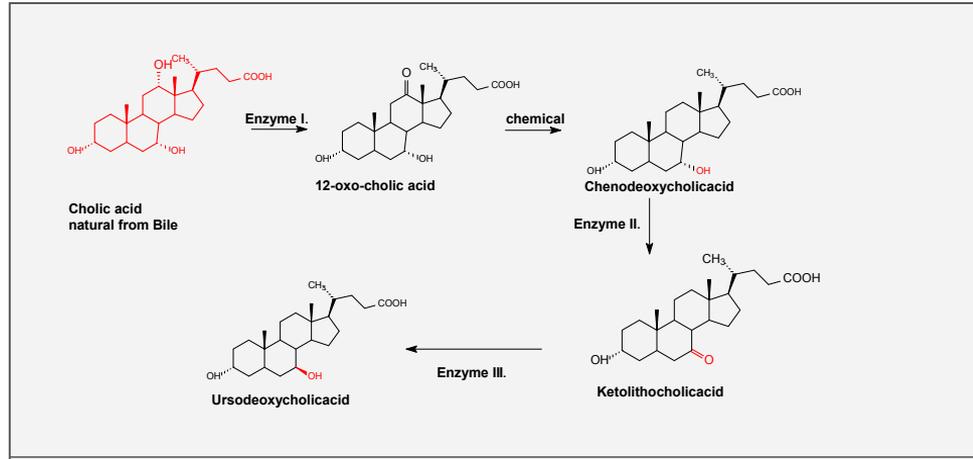


Process available
(20-30 % substrate
concentration,
95%-99.5% conversion)



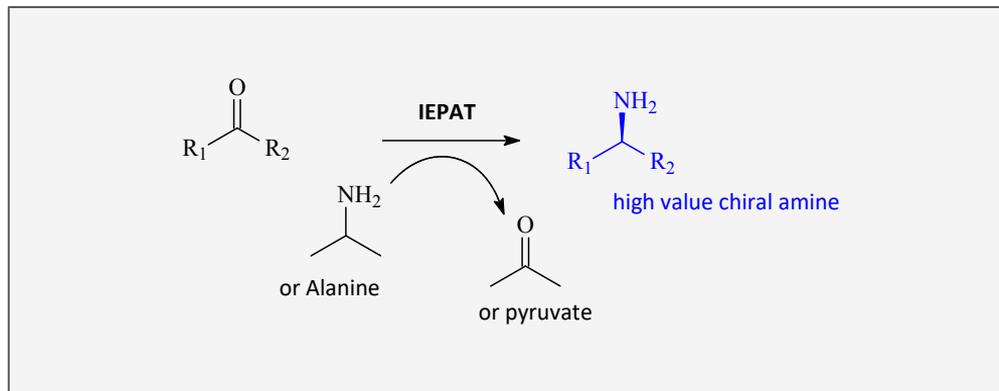
Process available
(10-20 % substrate
concentration,
95%-99.5% conversion)

Enzymatic Process to Convert Cholic Acid to Ursodeoxycholic Acid



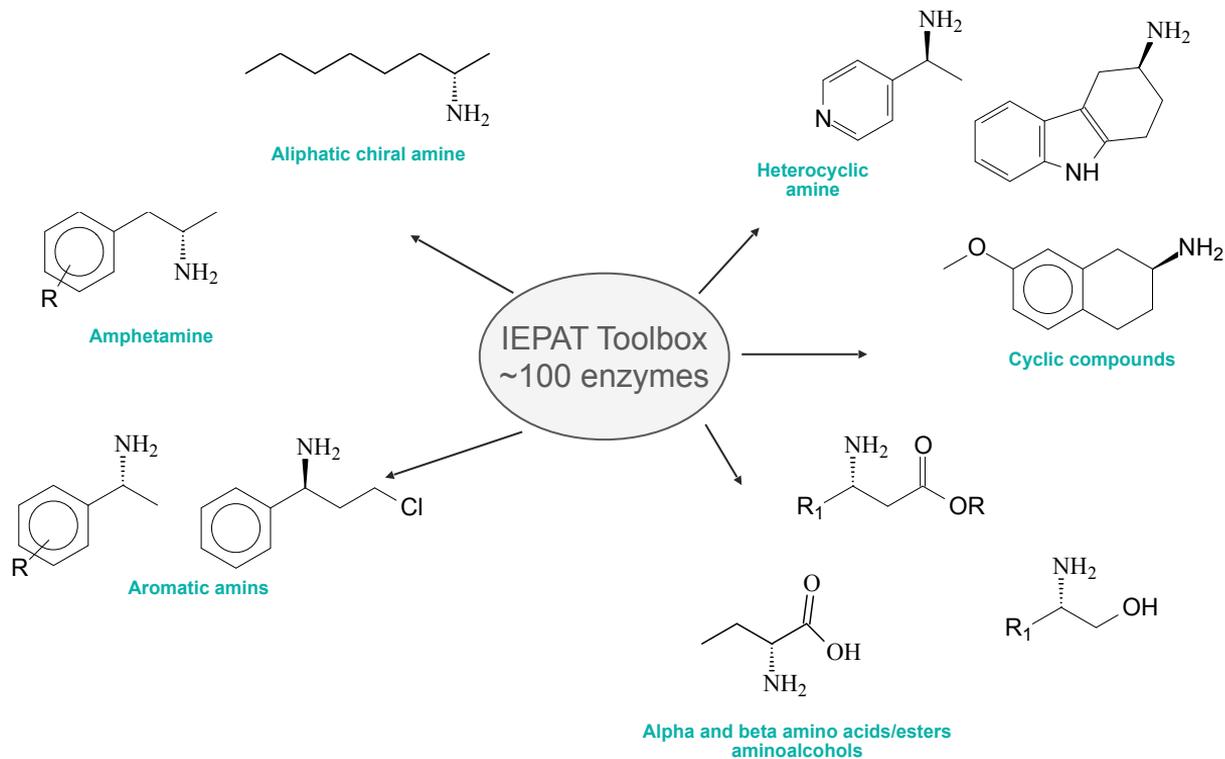
- Fully developed process inclusive methods to remove protein from final product and analytical methods to proof final product protein free
- All enzymes commercially available in spray dried form
- Total yield > 90%
- Inexpensive enzyme

Core Technology: Transaminases



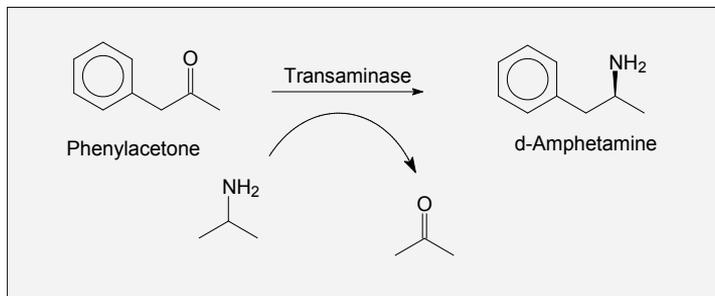
- Substrate load 50-150g/l
- Simple technology and equipment/standard batch reaction
- Inexpensive enzyme for R and S amines available in any scale
- Excellent enantio purity (>99.8%)
- > 90 % conversion in 6-12 hours
- No expensive ingredients or solvents
- Easy work up and removal of enzyme
- Environmental friendly

Core Technology: Transaminases for Multiple Applications

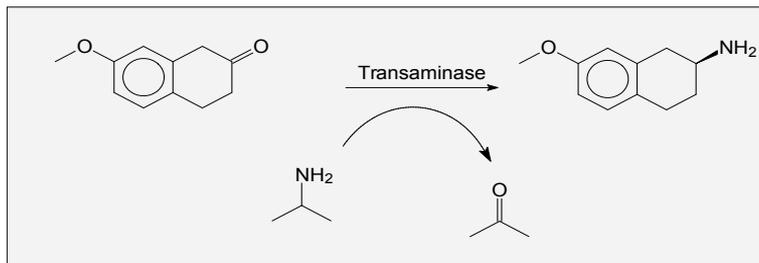


Large Scale Transaminase Process Example

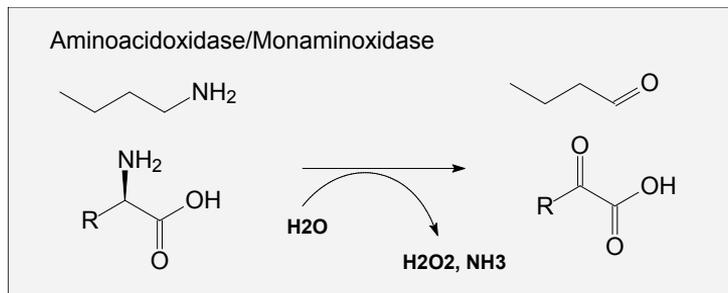
Manufacture of D-amphetamine (In-house manufacture on multi-ton scale)



Manufacture of tetraline (In-house manufacture on multi-ton scale)

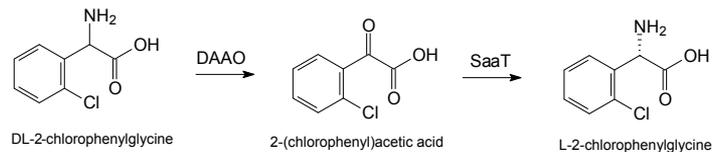


Monoamine - or Amino Acid Oxidases



- For conversion of racemic amins to chiral L- amins or access to 2-keto acid

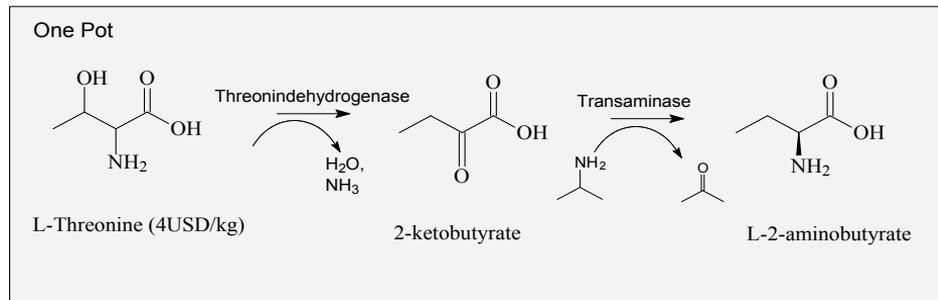
- Example



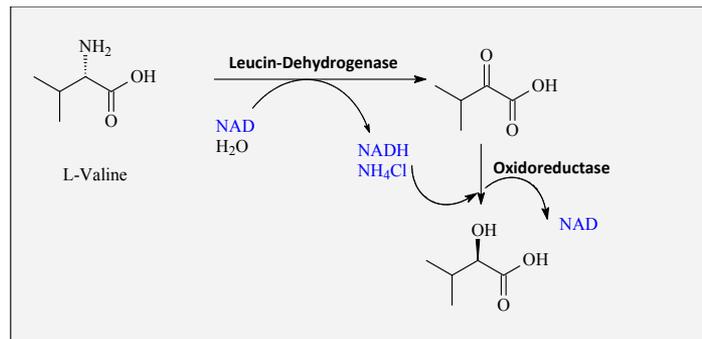
- L-2-chlorophenylglycine (Clopidogrel, Generik)
- L-Dopa
- L-Homophenylalanine

Concepts to Unnatural Amino Acids (Using Cheap Naturally Amino Acids)

SABAM

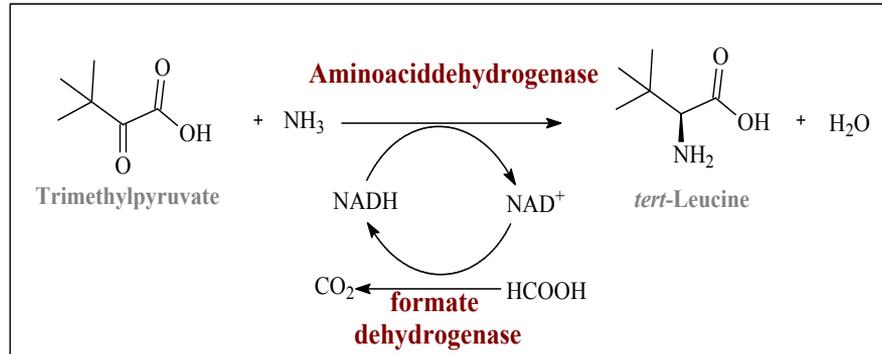


D- α -Hydroxyisovaleric acid from L-Valine

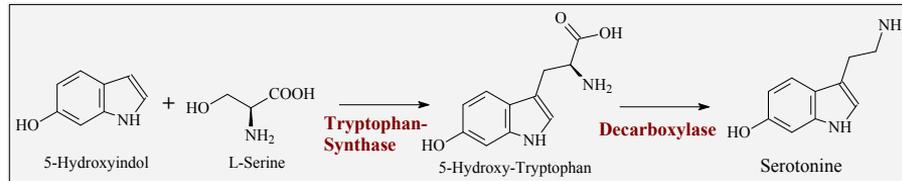
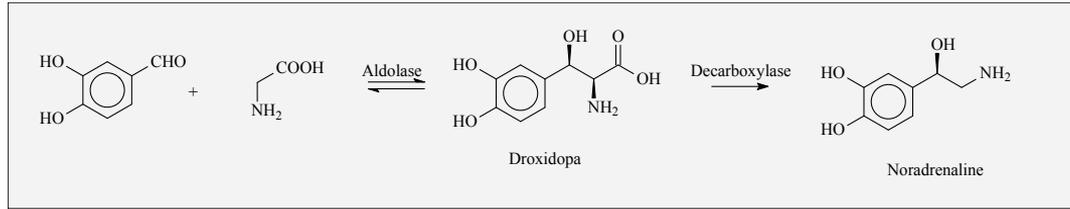


Concepts to Unnatural Amino Acids (Using Cheap Naturally Amino Acids)

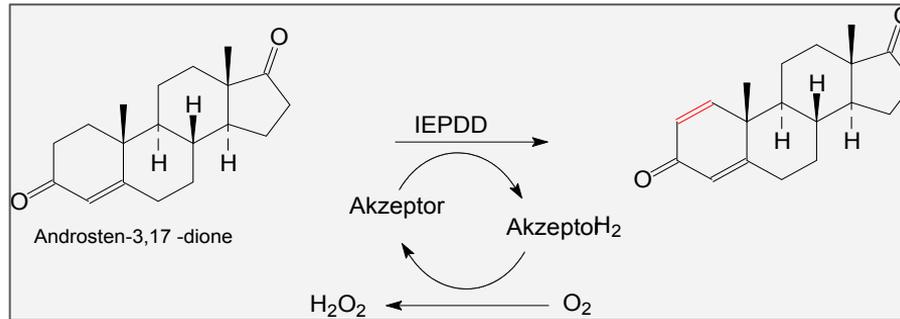
L-tert-Leucine



Example

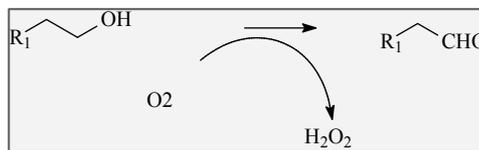
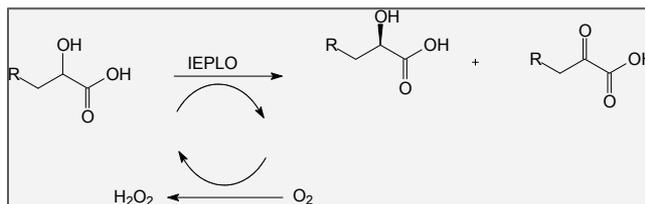


Delta1/Delta 4 Dehydrogenation



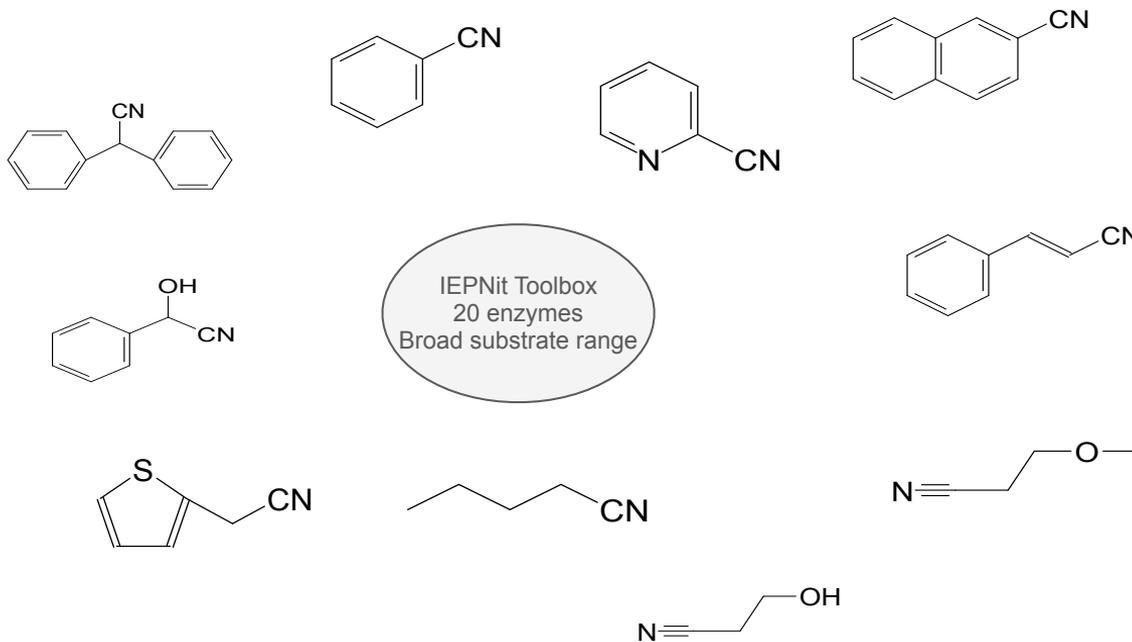
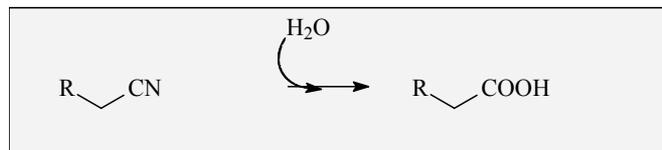
- Substrate concentration 50 up to 120 g/l
- Simple technology and equipment
- Inexpensive enzyme, recombinant over-expressed (< 10 €/kg product)
- > 95% conversion in 24 hours
- Cost contribution of co-enzyme < 5 €/kg product
- No expensive ingredients or solvents
- Easy work up and removal of enzyme
- Environmental friendly

Oxidases

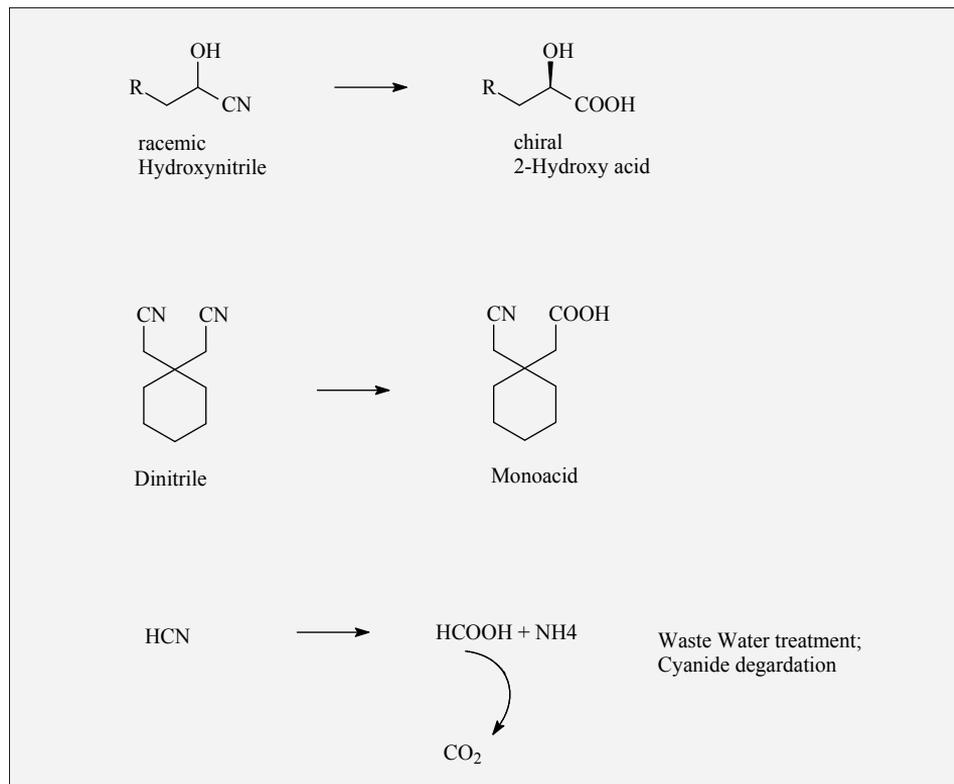


- Substrate concentration 100 g/l
- Simple technology and equipment
- Inexpensive enzymes, recombinant over-expressed
- More than 95% conversion in 24 hours
- No additional acceptor required
- No expensive ingredients or solvents
- Easy work up and removal of enzyme
- Environmental friendly

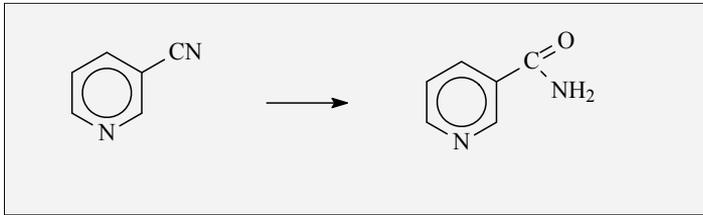
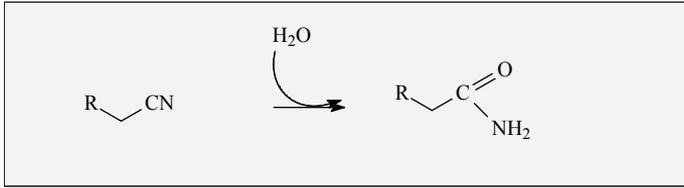
Nitrilases



Applications



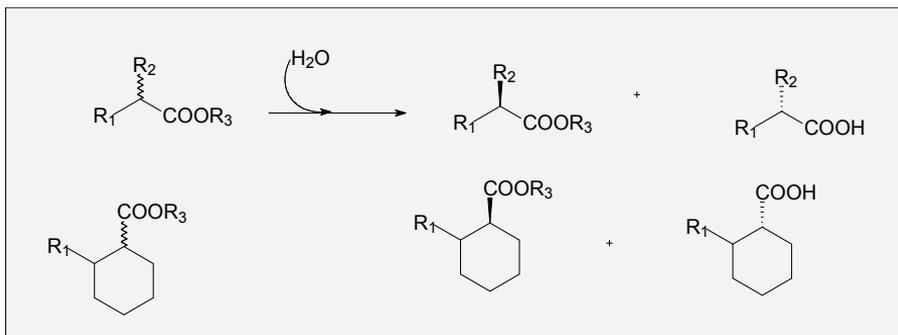
Nitrile-Hydratase



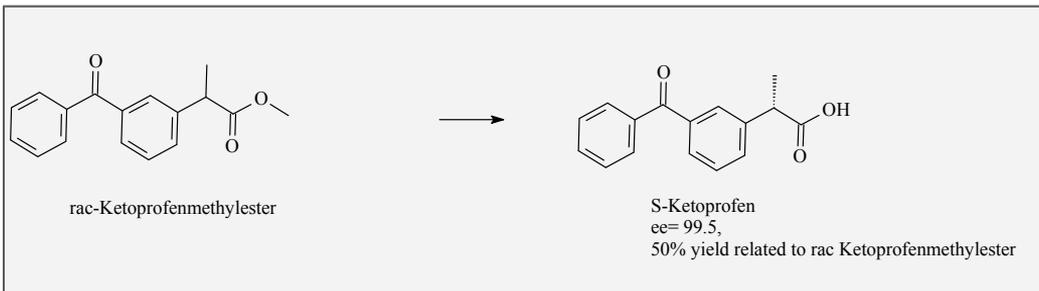
Production of Nicotinamid

Esterases/Lipases/Hydrolases

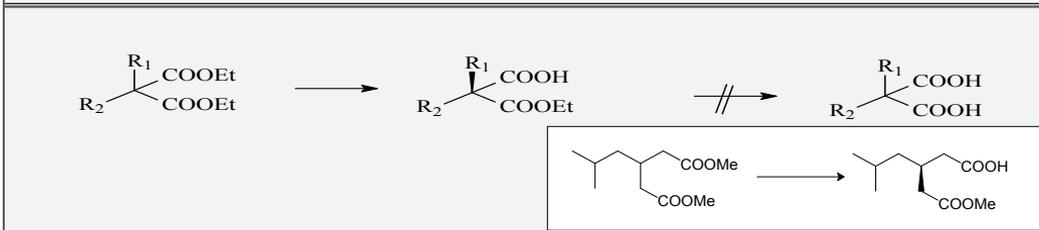
40 enzymes



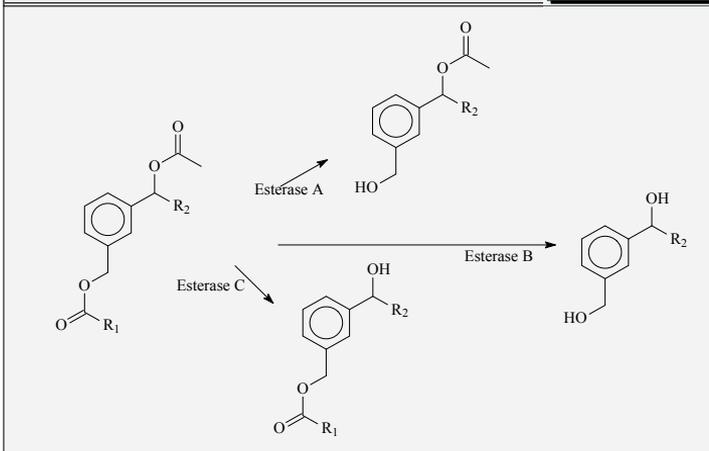
- High substrate concentrations
- Simple technology and equipment (Batch reaction)
- Recombinant enzymes available at any scale
- High conversions
- Expensive coenzymes are not required
- Enantioselectivity often very dependent on R₁, R₂, R₃ and reaction conditions
- Selective protection group chemistry



Resolution



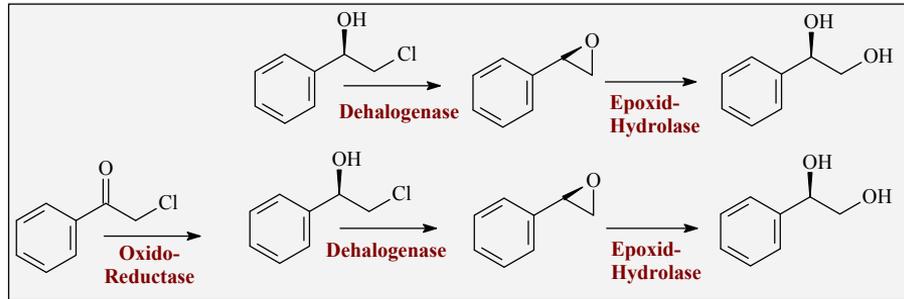
Introduction of Chirality



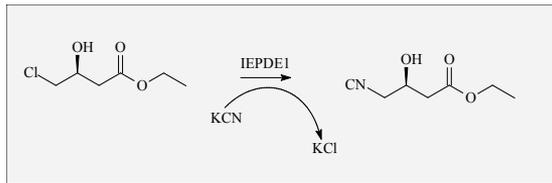
Regioselective
Protectiongroup- cleaving

Special Biotransformations

Haloalcohol dehalogenases/Epoxidhydrolasen

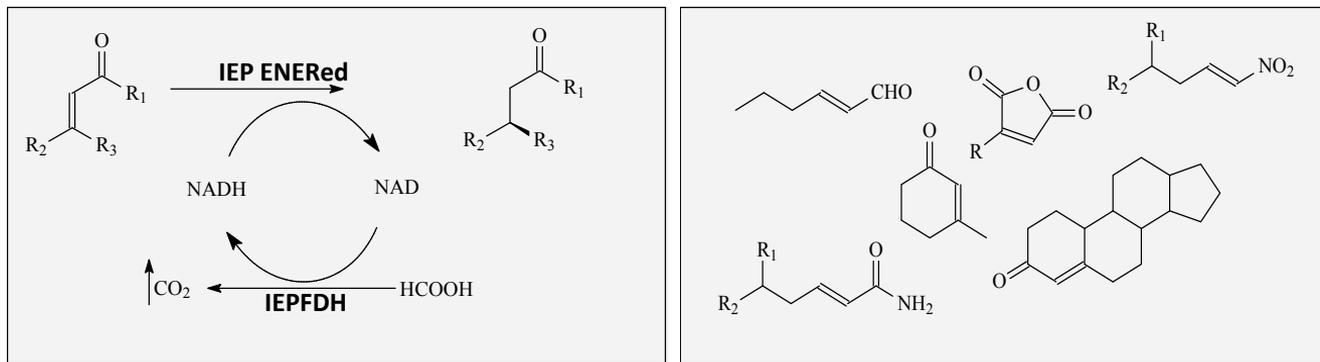


Commercial example



Special Biotransformations

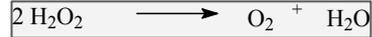
ENE- Reductases



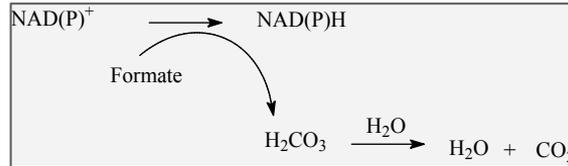
- Substrate load >100 g/l
- Simple technology and equipment/standard batch reaction
- Inexpensive enzymes in any scale
- Complete and quick conversion in 6-24 hours
- Cost contribution of coenzyme NAD(P) < 1 €/kg product
- No expensive ingredients or solvents
- Easy work up and removal of enzyme
- Environmental friendly
- Broad substrate range

And Many Others

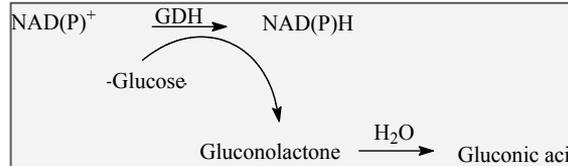
- Peroxidase/Katalases



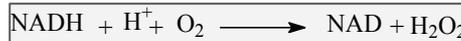
- NAD and NADP dependent Format dehydrogenases (Cofactoregeneration NADH and NADPH)



- NADP and NAD dependent Glucose dehydrogenase (Cofactoregeneration NADH and NADPH)



- NADH oxidase
- Lactatoxidase
- Glycolatoxidase
- Azoreductases

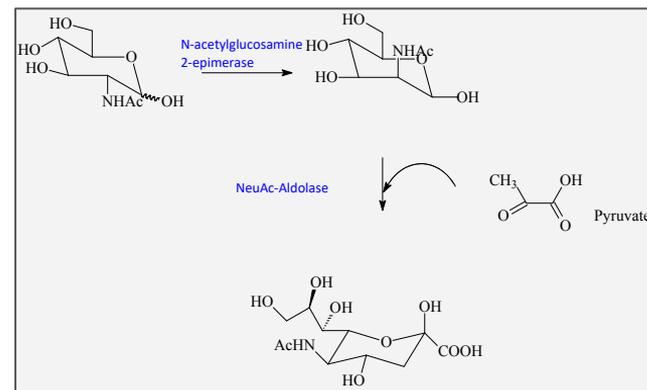


Extent Cambrex Wiesbaden Offer to Low Volume Highly Purified Enzymes for Special Transformations

- Application in Sugar and Nucleotid chemistry (Phosphorylasen, Glycosyltransferasen, etc.), Amino acid and Peptide chemistry
- Extension of lab space to one lab dedicated for protein purification (fermentation, centrifugation, UF, protein chromatography, assay development, protein purity determination via SDS and HPLC)

Examples

- Purine-Nucleoside-Phosphorylase
- N-acetylglucosamine-2-epimerase
- Uridine-Phosphorylase
- Nukleosid-deoxyribosyltransferase
- Fucosyltransferase
- Tryptophansynthase
- C. Perfringens NeuAc Aldolase
- D-beta-glucosidase
- Typically about 100g scale of purified enzymes



Expertise & Services



Expertise

Enzymes Screening & Discovery

- Strain collection of 1000 strains (yeast, bacteria, fungi, algae)
- Equipment for cultivation and screening
- Exclusive cooperation with strain collections

Enzyme Development

- Cloning and gene discovery
- Characterization and description of genes for different enzymes and functions
- Using different expression systems

Process Development & Enzyme Manufacture

- Working with different organisms and enzymes
- Process know how for Industrial Enzyme Production
- Bulk Enzyme supply



Established CMO to Support Enzyme Supply

Commercial Suppliers Established (Italy, Bulgaria, Germany and India) and one academic partner

- Capacities from 3m³, 10m³, 15m³, 25m³, 50m³, 120m³ fermenter suitable for E.coli fermentation
- Spray dryers from 0,3mt/hour, 1mt/hour; 3.8 mt/hour and 5mt/hour
- High pressure homogenisation
- Centrifugation, separation
- Ultrafiltration
- Experience with different strain fermentation
- Experience with enzymes and products in area of API, food and feed application, flavours
- Kosher, BSA/TSA , Halal certification possible
- Logistic experience, transport and packaging for air and sea freight
- Large warehouse for 4°C and -20°C available in Frankfurt (Shipment at request)

Services

Bulk Enzyme Supply

- TSE/BSE certificate, GMO free certificate, Kosher certificate
 - Ready to use enzyme preparations
 - Easy implementation at any conventional chemical plant
 - Storable for more than 1 year 4-8°C
 - Enzyme suspension or powder
 - Low cost bulk enzymes
-
- Cooperation deals to screen for new enzymes and develop enzymatic processes
-
- Cooperation deals for cost improvement of existing enzymatic processes
-
- Synthetic route development / consulting in the area of biocatalysis
 - Contract Manufacturing Biocatalysis
 - Analytical method development



We are the experts you'll enjoy working with



| Your molecule
Our mission

Thank you

Your questions are welcome

Dr. Antje Gupta
Tel. +49 (0) 611 962 46 36
Cambrex Wiesbaden
Rheingaustrasse 190-196
Wiesbaden Germany 65203
antje.gupta@cambrex.com

www.cambrex.com

