# Perkin 1 Abstracts: Biocatalysis in Organic Synthesis

ABSTRACTS
PERKIN

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*Perkin 1 Abstracts: Biocatalysis in Organic Synthesis* aims to cover recent literature concerning the applications of enzymes and micro-organisms as catalysts in organic synthesis. The abstracts will emphasise the key synthetic step(s) that are mediated by the biocatalyst. Emerging technologies for biocatalyst design and optimisation will also be included.

penicillin G

#### An enzyme labile 'safety-catch' linker for solid phase synthesis

Penicillin G acylase

MeO NH<sub>2</sub> NH<sub>2</sub> HX-target

X-target

U. Grether and H. Waldmann, Angew. Chem., Int. Ed., 2000, 39, 1629.

Soluble polymer PEG POE 6000 was used to make substrate accessible to enzymes. Heck, Suzuki and Sonogashira transformations were successfully performed on bound aryl iodides with quantitative conversions. Mitsunobu and Diels-Alder reactions were also demonstrated. With amides coupled to the linker, heating to  $60\,^{\circ}\text{C}$  was required for lactam formation.

#### Chemoenzymatic synthesis of PSGL-1 glycopeptides

#### Glycosyltransferase

K. M. Koeller, M. E. B. Smith and C.-H. Wong, Bioorg. Med. Chem., 2000, 8, 1017.

Sulfation of tyrosine has profound effect on glycosyltransferase activity. The sulfated substrate reacts much slower in the  $\beta$ 1,4-GalT reaction (threefold difference in  $k_{cml'}$ / $K_m$ ) and does not react in the  $\alpha$ 2,3-SiaT reaction.

# Reduction of 2-hydroxy and 2-acetoxy ketones

ÓR

#### Geotrichum sp.

Z.-L. Wei, G.-Q. Lin and Z.-Y Li, Bioorg. Med. Chem., 2000 8, 1129.

Yields of acetoxy alcohols 15-59%, ees 36-92%. Two enzymatic routes to diols were observed, via O-acetate hydrolysis-reduction or reduction-O-acetate hydrolysis. 2-Acetoxy ketones are transformed to (S)-products.

#### Removal of p-nitrobenzyl ester protecting group

p-CH<sub>3</sub>SO<sub>2</sub>NH

## Catalytic antibody

O2N antibody 7B9 catalyses hydrolysis of esters O2N 
$$\begin{array}{c} \mathbf{1} \ \mathbf{R}^1 = \mathbf{R}^2 = \mathbf{H} \\ \mathbf{2} \ \mathbf{R}^1 = \mathbf{Me}, \ \mathbf{R}^2 = \mathbf{H} \\ \mathbf{3} \ \mathbf{R}^1 = \mathbf{H}, \ \mathbf{R}^2 = (R) \text{-Me} \\ \mathbf{4} \ \mathbf{R}^1 = \mathbf{H}, \ \mathbf{R}^2 = (S) \text{-Me} \end{array}$$
 
$$\begin{array}{c} \mathbf{5} \ \mathbf{R} = \mathbf{L} \text{-}(\mathbf{CH}_3)_2 \mathbf{CHCH}_2 \\ \mathbf{6} \ \mathbf{R} = \mathbf{D} \text{-}(\mathbf{CH}_3)_2 \mathbf{CHCH}_2 \\ \mathbf{8} \ \mathbf{R} = \mathbf{D} \text{-}\mathbf{CH}_3 (\mathbf{CH}_2)_3 \\ \mathbf{8} \ \mathbf{R} = \mathbf{D} \text{-}\mathbf{CH}_3 (\mathbf{CH}_2)_3 \\ \mathbf{10} \ \mathbf{R} = \mathbf{D} \text{-}\mathbf{PhCH}_2 \\ \mathbf{Enantiomers transformed at comparable rates.} \end{array}$$

3 and 4 transformed at comparable rates.

S. Kurihara, T. Tsumuraya, K. Suzuki, M. Kuroda, L. Liu, Y. Takaoka and I. Fujii, Chem. Eur. J., 2000, 6, 1656.

Modelling studies show  $\alpha$ ,  $\beta$  and  $\gamma$ -substituents to be outside combining site, explaining broad antibody specificity. Comparative results with other antibodies suggest that linker design in hapten formulation may be important for ultimate antibody selectivity.

#### Resolution of alcohols via lipase catalysed transformation and sulfation

Lipase

K. Tomimatsu and Y. Mizuno, Chem. Lett., 2000, 448.

A method for the large scale isolation of enantiopure alcohols or esters is presented, using sulfur trioxide pyridine for alcohol complexation and solvation T. Yamano, F. Kikumoto, S. Yamamoto, K. Miwa, M. Kawada, T. Ito, T. Ikemoto, in the aqueous phase. Six lipases were used successfully. Six structural examples are given. 1-(R)-Phenylethanol was isolated in 42% yield with 99% ee.

#### Lipase catalysed transformation of linear and cyclic poly(3-hydroxybutanoate)s

Linear and cyclic P(3HB) polymer species were subjected to hydrolysis, transesterification and intramolecular esterification by lipase. Two series of polymers of linear and cyclic structures were observed, having variable molecular weights of higher and lower mass than that of the substrate.

Y. Osanai, K. Toshima and S. Matsumura, Chem. Lett., 2000, 576.

#### Deglycosylation of 2'-mercaptocytidine

Hammerhead Ribozyme

M. L. Hamm, J. P. Schwans and J. A. Piccirilli, J. Am. Chem. Soc., 2000, 122,

When X = O the HH16 ribozyme catalyses a phosphotransesterification reaction.

# Chemoenzymatic synthesis of a PSGL-1 N-terminal glycopeptide

#### Glycosyltransferase

2000, 122, 4241.

Glycoconjugate 1 was constructed using Finoc-based SPPS and transformed using  $\beta$ -1,4-galactosyltransferase,  $\alpha$ -2,3-sialyltransferase and  $\alpha$ -1,3-lucosyltransferase-V. The K. M. Koeller, M. E. B. Smith, R.-F. Huang and C.-H. Wong, J. Am. Chem. Soc., yields of each glycosyltransferase step were improved by the addition of a protease inhibitor cocktail

## Reconstructed aldolase antibodies

Aldolase antibody

F. Tanaka, R. A. Lerner and C. F. Barbas III, J. Am. Chem. Soc., 2000, 122, 4835.

Gene shulfling was used to reconstruct aldolase antibodies while retaining the catalytic residues, mechanism and enantioselectivity of the parental antibodies.

#### Kinetic resolution of racemic hydroperoxides

Bacillus subtilis

$$R^1 = Me$$
, Et, Pr, *i*-Pr, Bu  
 $R^2 = Me$ , H

X = CI, H

$$R^1 = Me$$
,  $R^2 = H$   
(S)-30% ee, 64% conversion

$$R^1 = Me, R^2 = H$$
  
(R)-88% ce

OH

Resolutions using Bacillus subtilis gave (R)-hydroperoxides with ees of 16-99% depending on extent of conversion. Reactions were less enantioselective when R1 was larger or X = Cl. A. niger gave (S)-hydroperoxides with poorer enantioselectivities in general.

# W. Adam, Z. Lukacs, C. R. Saha-Möller and P. Schreier, J. Am. Chem. Soc., 2000,

# Di- and tri-hydroxylation of monosubstituted benzenes

# Dioxygenase Transformations carried out using mutant

CN SMe OCOMe

D. R. Boyd, N. D. Sharma, N. I. Bowers, J. Duffy, J. S. Harrison and H. Dalton, J. Chem. Soc., Perkin Trans. 1, 2000, 1345.

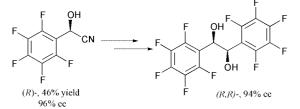
strain (UV4) of Pseudomonas putida. The (1S,2R) cis-dihydrodiols were formed in yields ranging from 9-60% and typical ees of >98% were obtained. Dioxygenase catalysed oxidation of benzene rings can result in either benzylic mono hydroxylation or cis-dihydroxylation depending on the size and nature of the benzylic substituent. In some cases the formation of benzylic alcohol metabolites, followed by spontaneous decomposition to benzaldehyde and oxidation to the cis-dihydrodiol of benzyl alcohol has been observed.

#### Synthesis of perfluoro-1,2-diols

# Lipase

Bacillus subtilis/ Aspergillus niger

T. Sakai, Y. Miki, M. Tsuboi, H. Takeuchi, T. Ema, K. Uueyama and M. Utaka, J. Org. Chem., 2000, 65, 2740



The (S)-acetate was chemically hydrolysed and then used to synthesise the (S.S)-antipode in 91% ce. Crystallisation improved the ee of both compounds to

# Enzymatic synthesis of Gal-β-1-3GlcNAc derivatives

#### Phosphorylase

Lipase/Adenosine deaminase

E. Farkas, J. Thiem, F. Krzewinski and S. Bouquelet, Synlett, 2000, 728.

Only \alpha-glycosides were used as acceptors. Yields of 14-30\% could be improved if 1.2 molar equivalents acceptor used instead of 1. No reaction was observed with substrate 4.

#### Deamination of adenosine and deoxyadenosine acetates

# adenosine deaminase (ADA) Pseudomonas sp. lipase (PSL) НО vinyl acetate, THF, molecular sieves, 60 °C OH

90% yield

P. Ciuffreda, S. Casati and E. Santaniello, Tetrahedron, 2000, 56, 3239

# 94% vield HO

The acetates of adenosine and 3'-deoxyadenosine were also prepared using either PSL or Candida antarctica lipase. The ADA-catalysed deamination of each acetate was Only acetates with free 5'-hydroxy groups react to afford the corresponding inosine acetates confirming that the 5'-hydroxy group plays a crucial role at the ADA active site

ÓAc

#### Zeolite immobilised enzymes in peptide synthesis

Protease

ZTyrOEt <sup>1</sup> GlyGlyOEt linmobilised α-chymotrypsin ZTyrGlyGlyOEt

The effectiveness of  $\alpha$ -chymotrypsin and thermolysin immobilised on a range of zeolites has been investigated. The reusability, effect of changing reaction time and percentage of water in the solvent were studied.

G.-W. Xing, X.-W. Li, G.-L. Tian and Y.-H. Ye, Tetrahedron, 2000, 56, 3517.

#### Dynamic kinetic resolution: synthesis of optically active $\alpha$ -amino acid derivatives

Lipase

S. A. Brown, M.-C. Parker and N. J. Tumer, *Tetrahedron: Asymmetry*, 2000, 11, 1687.

CAL-B has been shown to be effective in catalysing the synthesis of optically active  $\alpha$ -amino acid derivatives. Yields and ees vary according to solvent, R, R' and presence of organic base.

#### Preparation of optically active cyclobutane derivatives

Lipase

50% conversion

I. Petschen, M. P. Bosch and A. Guerrero, *Tetrahedron: Asymmetry*, 2000, 11, 1691.

A chiral intermediate for the synthesis of grandisol and oleander scale pheromone has been prepared by transesterification in the presence of Lipase PS or *Pseudomonas fluorescens* lipase.

#### Highly enantioselective synthesis of pantolactone acrylate

Lipase

47% conversion

 Haughton, J. M. J. Williams and J. A. Zimmermann, Tetrahedron: Asymmetry, 2000, 11, 1697. Lipase catalysed resolution of pantolactone has been investigated. Conversion and ees depend on solvent, reaction time and concentration of acyl donor and enzyme (CLEC-CCL).

# Resolution of intermediates for pheromone synthesis O O CH<sub>2</sub>CH<sub>2</sub>CHOHCH<sub>3</sub> Chirazyme L-2 vinyl acetate dichloromethane Chirazyme L-2 vinyl acetate dichloromethane I. Izquierdo, M. T. Plaza, M. Rodríguez and J. Tamayo, Tetrahedron: Asymmetry, 2000, 11, 1749.

#### Reduction of oxyaminoketones

#### Saccharomyces cerevisiae

E. Buchalska, I. Madura, K. Okrasa, J. Plenkiewicz and J. Zachara, *Tetrahedron: Asymmetry*, 2000, **11**, 1781.

First report of the preparation of optically active oxyamino alcohols. The stereochemistry of the product was confirmed by X-ray crystallography.

#### Resolution of phenylglycine in organic solvents

#### Acylase

$$\begin{array}{c} \text{H}_2\text{N} & \text{CO}_2\text{CH}_3 \\ \text{H}_2\text{N} & \text{CO}_2\text{CH}_3 \\$$

A. Basso, P. Braiuca, L. De Martin, C. Ebert, L. Gardossi and P. Linda, *Tetrahedron: Asymmetry*, 2000, 11, 1789.

Enantioselectivity of PGA in organic solvents is demonstrated. The stereochemistry of the products was confirmed by electrospray mass spectrometry and kinetic studies. L-enantiomer of the methyl ester of phenylglycine reacts 18 times faster than the D-enantiomer.

#### Resolution of secondary alcohols

#### Aminoacylase

M. Bakker, A. S. Sprnijt, F. van Rantwijk and R. A. Sheldon, *Tetrahedron: Asymmetry*, 2000, **11**, 1801.

The transesterification of secondary alcohols by an aminoacylase was studied and shown to proceed with higher productivity than the corresponding lipase reaction. A variety of secondary alcohols were investigated and the reaction rates and stereochemical results rationalised in terms of the active site. Yields ranged from 22-47%.

#### Hydrolysis of cyclic carbonates

#### Pseudomonas diminuta

K. Matsumoto, Y. Sato, M. Shimojo and M. Hatanaka, *Tetrahedron: Asymmetry*, 2000, 11, 1965.

When n=0, THF is added to inhibit side-reactions caused by oxido-reductases present in the organism.

# Selective acetylation of sucrose

P. Potier, A. Bouchu, G. Descotes and Y. Queneau, *Tetrahedron Lett.*, 2000, 41, 3597.

Faster reactions were obtained with up to 7% (vol.) of water in DMF. A shurry of the enzyme with a minimum volume of aqueous dimethyl sulfoxide could also be used offering an alternative solvent.

# Synthesis of cis-5,6-dihydro-5,6-dihydroxy-1-methyl-2-pyridone

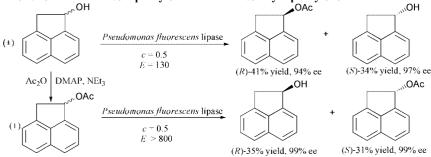
Dioxygenase

L. Modyanova and R. Azerad, Tetrahedron Lett., 2000, 41, 3865.

First example of NDO catalysed  $\emph{cis}$ -dihydroxylation of a monoheterocyclic nitrogen compound.

# Kinetic resolution of acenaphthylen-1-ol and 1-acetoxynaphthylene

Lipase



L. Aribi-Zouioueche and J.-C. Fiaud, Tetrahedron Lett., 2000, 41, 4085.

Flexible analogues 1-(1-naphthyl)ethyl acctate and 1-(1-naphthyl)ethanol were inactive under the same reaction conditions. Rabbit gastric lipase gave poor enantioselectivities for all substrates.

ΟH

# Asymmetric reduction of acetophenone

#### Geotrichum candidum

T. Matsuda, T. Harada, N. Nakajima and K. Nakamura, *Tetrahedron Lett.*, 2000. 41, 4135

The mechanism of improved asymmetric reduction with APG4 was elucidated by using the cell-free extract of APG4 in the presence and absence of cyclopentanol with either NADP $^+$  or NADPH as cofactor. Only the (S)-enzyme but not the (R)-enzyme can use cyclopentanol for recycling of NADPH which explains the high stereoselectivity of the APD4 system.