Perkin 1 Abstracts: Biocatalysis in Organic Synthesis

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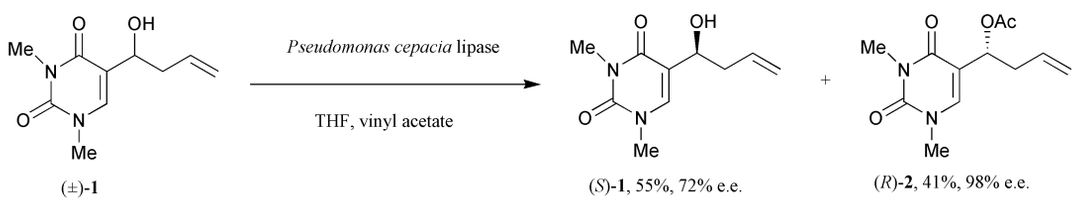
Perkin 1 Abstracts: Biocatalysis in Organic Synthesis aims to cover recent literature concerning the applications of enzymes and micro-organisms as catalysts in organic synthesis. The abstracts will emphasise the key synthetic step(s) that are mediated by the biocatalyst. Emerging technologies for biocatalyst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

Chemoenzymatic synthesis of optically active homoallylic alcohols ***Lipase***



(±)-**1**

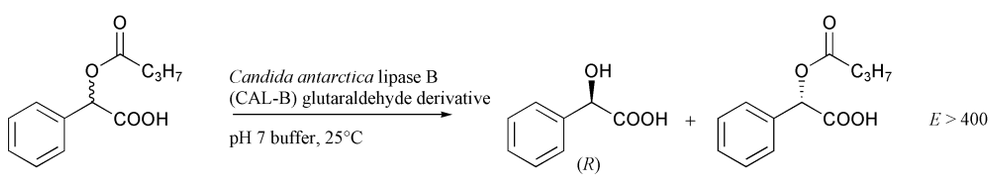
(*S*)-**1**, 55%, 72% e.e.

(*R*)-**2**, 41%, 98% e.e.

Lipase PS-C Amano II from *Pseudomonas cepacia* was employed to resolve uracil substituted homoallylic alcohol **1** with an *E* value of 216 for the transformation. Chroman substituted homoallylic alcohols were resolved in a similar fashion.

S. Singh, S. Kumar and S. S. Chimni, *Synlett*, 2002, 1277.

Modulation of enantioselectivity by conformational engineering ***Lipase***

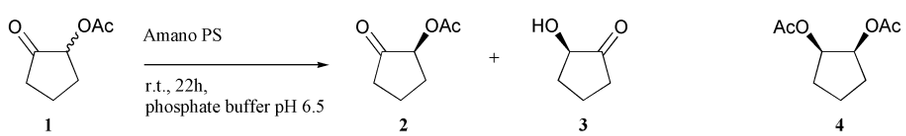


e.e. > 99.5%

6 Lipase derivatives were studied. For each of these derivatives, the effect on 3 different substrates was investigated, with changes in temperature, pH, salt concentration or dioxane concentration. The effect of immobilising the lipase was also studied. Such changes to the enzyme or reaction conditions could result in significant change in the *E* value.

J. M. Palomo, G.Fernández-Lorente, C. Mateo, M. Fuentes, R. Fernández-Lafuente and J. M. Guisan, *Tetrahedron: Asymmetry*, 2002, **13**, 1337.

Resolution of a keto acetate ***Lipase***



1 **2** **3** **4**

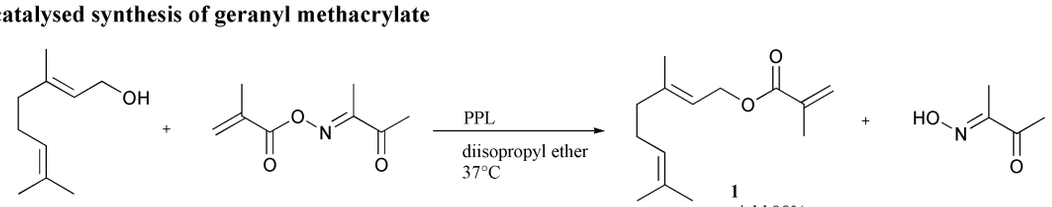
yield 45%
e.e. 96 - 98%

yield 28-32%
e.e. 96 - 98%

The 2-hydroxyketone **3** was found to racemise over time. The e.e. was determined by first treating the product mixture with (*R*)-Mosher's acid to form the MTPA derivative of **3**, prior to chromatographic separation. The *meso*-diacetate **4** gave an optically inactive mixture on treatment with Amano PS and it was concluded that this was due to racemisation by *in situ* intramolecular acyl migrations.

S. Easwar, S. B. Desai, N. P. Argade and K. N. Ganesh, *Tetrahedron: Asymmetry*, 2002, **13**, 1367.

Lipase catalysed synthesis of geranyl methacrylate ***Lipase***

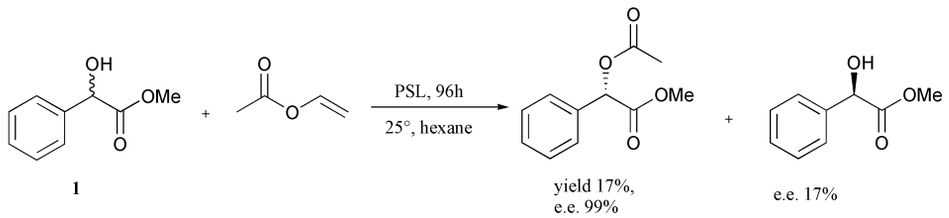


1
yield 98%

A study of the synthesis of geranyl methacrylate, **1**, using lipase catalysed reactions, is reported. The key enzymatic step involved transesterification of geraniol using PPL, giving the desired product in good yield under mild conditions.

V. Athawale, N. Manjrekar and M. Athawale, *Tetrahedron Lett.*, 2002, **43**, 4797.

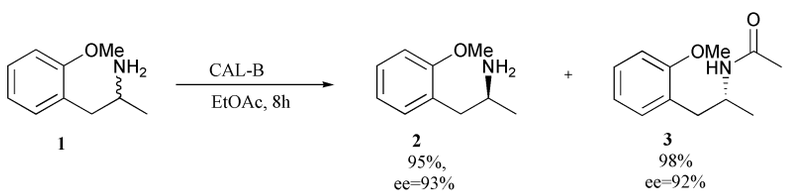
Immobilised lipase catalysed resolution of (*R,S*)-methyl mandelate ***Lipase***



N. Queiroz and M. da Graça Nascimento, *Tetrahedron Lett*., 2002, **43**, 5225.

The use of *Pseudomonas* sp. lipase (PSL) immobilised on poly(ethylene oxide) polymer for the acylation of *R,S*-methyl mandelate, **1**, is reported. Solid support was found to increase the activity of PSL as well as allowing it to be used more than once for this type of reaction.

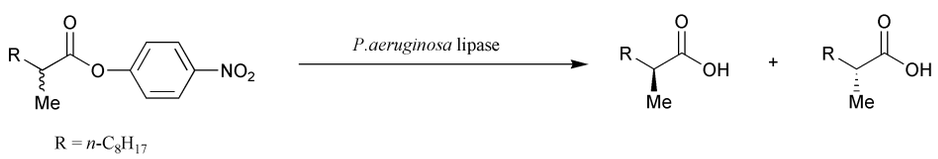
CAL-B-catalysed resolution of β-substituted isopropylamines ***Lipase***



J. González-Sabín, V. Gotor and F. Rebolledo, *Tetrahedron: Asymmetry*, 2002, **13**, 1315.

The use of *Candida antarctica* lipase (CAL-B) for the resolution of pharmacologically active amines is reported. CAL-B catalysed enantioselective acylation of racemic amine, **1**, produced the (*S*)-amine, **2**, and the (*R*)-acetamide, **3**, in good yield.

Directed evolution of selective enzymes and hybrid catalysts ***Lipase***

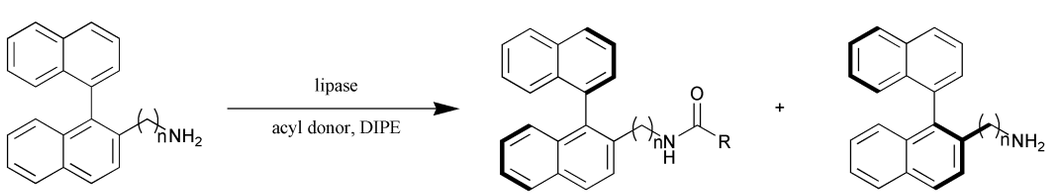


R = *n*-C_8H_{17}

M. T. Reetz, *Tetrahedron*, 2002, **58**, 6595.

The enantioselectivity of a lipase catalyst in the hydrolytic kinetic resolution of a chiral ester was dramatically improved from *E*=1.1 to *E*=51. This was achieved by a combination of random mutagenesis and a high throughput screening system.

Kinetic resolution of 1,1'-binaphthylamines *via* lipase-catalysed amidation ***Lipase***



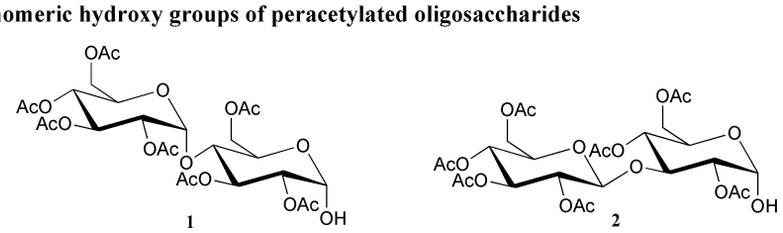
n = 0, 1 or 2

R = Me, Et, ^{n}Pr or CF_3

N. Aoyagi and T. Izumi, *Tetrahedron Lett.*, 2002, **43**, 5529.

Lipase-catalysed amidation of 2-(2-aminoethyl)-1,1'-binaphthyl gave optically active 2-[2-(acylamino)ethyl]-1,1'-binaphthyls with high enantiomeric excess.

Deprotection of anomeric hydroxy groups of peracetylated oligosaccharides ***Aspergillus niger***

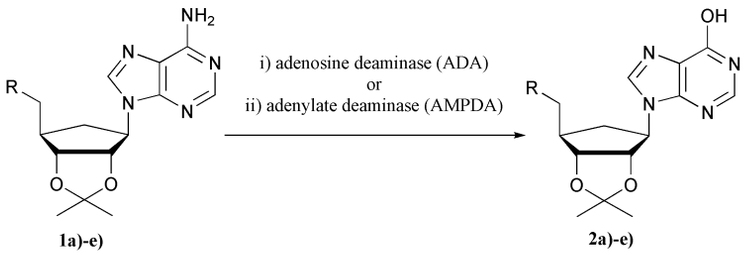


A. Giordano and A. Trincone, *Tetrahedron Lett.*, 2002, **43**,4939.

The use of *A. niger* lipase for the hydrolysis of 1-*O*-acetyl groups in a number of oligosaccharides is reported. Compounds such as **1** and **2** were obtained in good yield and under mild conditions.

Deamination of 5'-substituted-2',3'-isopropylidene adenosine derivatives

Deaminase



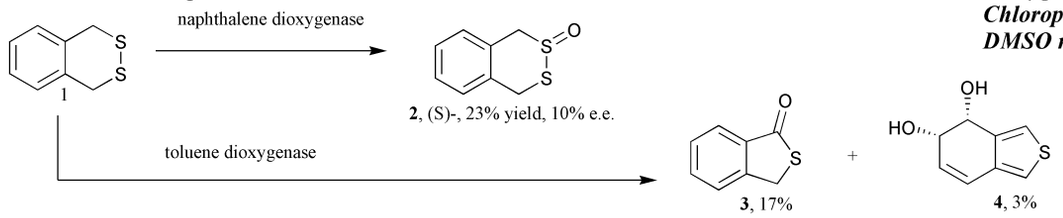
a) R = OH
b) R = OAc
c) R = N_3
d) R = NH_3
e) R = NHAc

P. Ciuffreda, A. Loseto and E. Santaniello, *Tetrahedron*, 2002, **58**, 5767.

ADA catalyses the deamination of **1a)** and **1d)** only, whereas AMPDA accepts all five compounds **1a)-e)**.

Biotransformations leading to chiral thiosulfinates

Dioxygenase/ Chloroperoxidase DMSO reductase

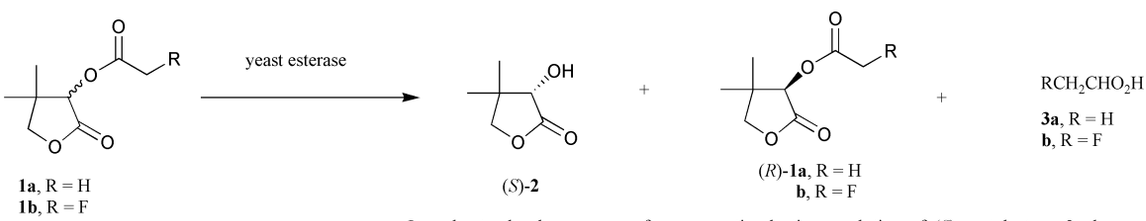


D. R. Boyd, N. D. Sharma, M. A. Kennedy, S. D. Shepherd, J. F. Malone, A. Alves-Areias, R. Holt, S. G. Allenmark, M. A. Lemurell, H. Dalton and H. Luckarift, *Chem. Commun.*, 2002, 1452.

A variety of biocatalysts were employed in an effort to generate chiral thiosulfinates. Naphthalene dioxygenase yielded a small amount of chiral product **2** from substrate **1**. Toluene dioxygenase produced **3** and **4** from **2**. Chloroperoxidase yielded **2** from **1** in 60% yield with 47% e.e. Dimethyl sulfoxide reductase from *Citrobacter braakii* resolved racemic **2** to yield (*S*)-**2** with 77% e.e.

A screen for enantioselective esterases based on differential cell growth

Esterase

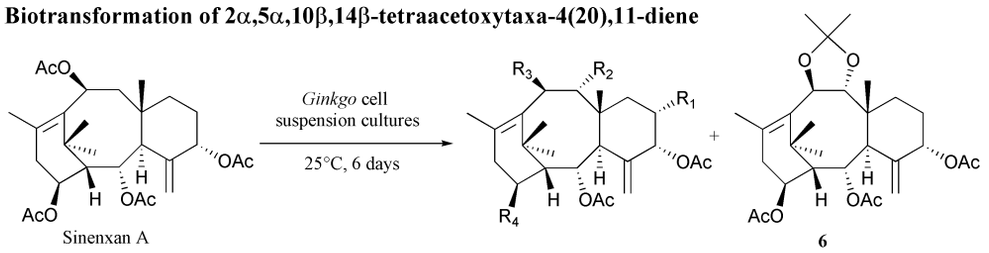


M. T. Reetz and C. J. Rüggeberg, *Chem. Commun*., 2002, 1428.

In order to develop a screen for an enantioselective resolution of (*S*)-pantolactone **2**, the enantiomers of fluoroacetate esters of pantolactone (*R*)- and (*S*)- **1b** were synthesised and submitted to hydrolysis by a strain of yeast expressing an (*S*)-selective esterase. Acetic acid **3b** acts as a carbon source for growth, but fluoroacetic acid **3b** is toxic to yeast cells. Thus, yeast grown on (*R*)-**1b** grew better than yeast grown on (*S*)-**1b**, which was hydrolysed, leading to toxic **3b** and thus inhibition of yeast growth.

Biotransformation of 2α,5α,10β,14β-tetraacetoxytaxa-4(20),11-diene

Ginkgo biloba



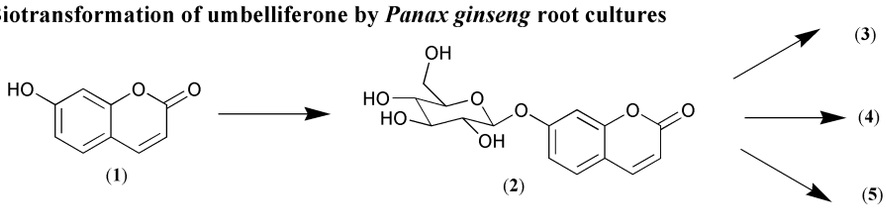
1: R_1=H, R_2=OH, R_3=R_4=OAc
2: R_1=H, R_2=R_3=OH, R_4=OAc
3: R_1=H, R_2=R_4=OH, R_3=OAc
4: R_1=R_3=OH, R_2=H, R_4=OAc
5: R_1=R_2=R_3=OH, R_4=OAc
7: R_1=H, R_2=OCHO, R_3=R_4=OAc
8: R_1=H, R_2=R_4=OAc, R_3=OCHO

J. Dai, M. Ye, H. Guo, W. Zhu, D. Zhang, Q. Hu, J. Zheng and D. Guo, *Tetrahedron*, 2002, **58**, 5659.

The optimal concentration of sinenxan A added was 60mg/L and the substrate was mainly converted into **1** and **2** in the first 48h after addition and then into the minor products.

Biotransformation of umbelliferone by *Panax ginseng* root cultures

Glycosyl Transferase

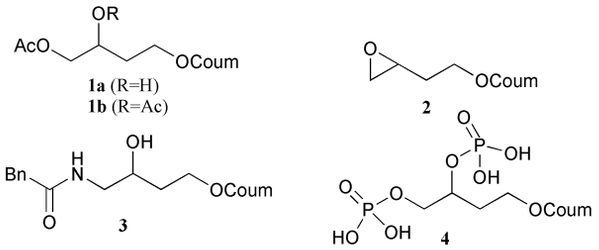


W. Li, K. Koike, Y. Asada, T. Yoshikawa and T. Nikaido, *Tetrahedron Lett.*, 2002, **43**, 5633.

Panax ginseng root cultures biotransformed umbelliferone (**1**) to 7-*O*-β-D-glucopyranose (**2**) 7-*O*-β-D-glucoyranosyl (1-6) β-D-glucopyranoside (**3**), 7-*O*-β-D-xylopyranosyl (1-6) β-D-glucopyranoside (**4**) and 7-*O*-α-L-rhamnopyranosyl (1-2) β-D-glucopyranoside (**5**). The roots showed high glycosylation activity towards 7-hydroxycoumarin. The glycosylation was catalysed by a glycosyltransferase rather than glycosidase, was demonstrated by adminstration of inhibitors.

Enzyme fingerprints of activity, stereo- and enantioselectivity from fluorogenic and chromogenic substrate arrays

Hydrolase

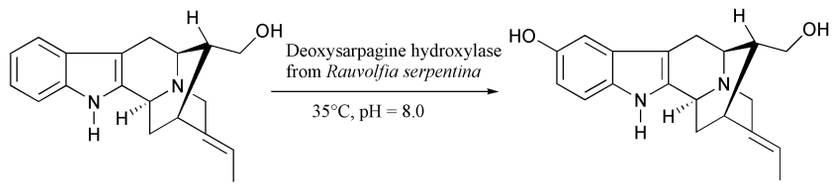


Substrates **1-4** were synthesized and used to characterise enzyme activity profiles of esterases, lipases, proteases, peptidases, phosphatases and epoxide hydrolases. Fingerprints of activity, enantio- and stereoselectivity are displayed as arrays of colour-scale squares that are analysed visually.

D. Wahler, F. Badalassi, P. Crotti and J.-L. Reymond, *Chem. Eur. J.*, 2002, **8**, 3211.

Hydroxylation of deoxysarpagine

Hydroxylase

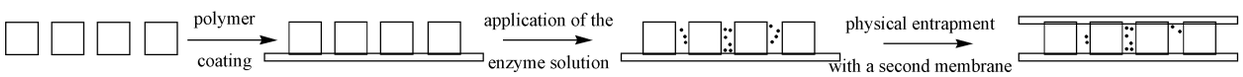


The data reported indicates that deoxysarpagine hydroxylase is a cytochrome P450-dependent monooxygenase.

B. Yu, M. Ruppert and J. Stöckigt, *Bioorg. Med. Chem.*, 2002, **10**, 2479.

Use of enzymes deactivated by site-directed mutagenesis for the preparation of enantioselective membranes

Lyase

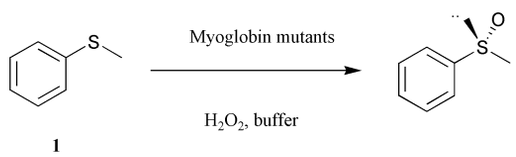


Enantioselective membranes can facilitate the transport of one enantiomer of a racemate, therefore providing a simple and fast resolution method. Histidine ammonia lyase (HAL) and phenylalanine ammonia lyase (PAL) were mutated to remove the essential methylidene imidazole (MIO) residue, whilst maintaining their binding affinity.

A. Skolaut and J. Rétey, *Angew. Chem., Int. Ed.*, 2002, **41**, 2960.

Asymmetric sulfoxidation catalysed by myoglobin

Myoglobin



1

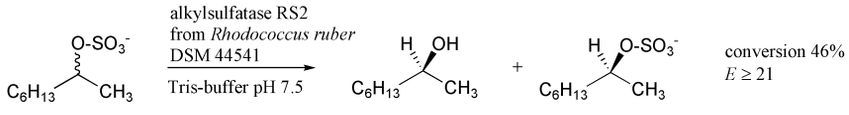
H64D/V68A 84% e.e. (*R*)-
H64D/V68S 88% e.e. (*R*)-
H64D 6% e.e. (*R*)-

Mutations in the active site of myoglobin were found to have a profound effect on the enantioselectivity of this catalyst with respect to the sulfoxidation of thioanisole **1**. Mutation of valine 68 was found to increase the enantiomeric excess of product (*R*)- **2** from 6% (H64D) to 88% (H64D/V68S).

S. Kato, H. J. Yang, T. Ueno, S. i. Ozaki, G. N. Phillips Jr., S. Fukuzumi and Y. Watanabe, *J. Am. Chem. Soc.*, 2002, 124, 8506.

Enantioselective stereoinversion of *sec*-alkyl sulfates

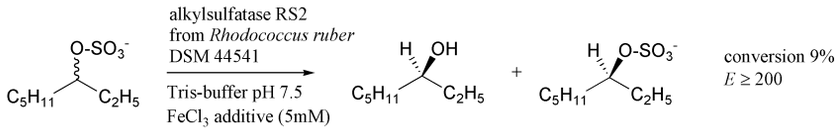
Sulfatase



20 Strains were screened for alkylsulfatase activity, and of these, *R. ruber* DSM 44541 showed most promise with respect to activity and selectivity. The hydrolysis occurs with absolute stereoselectivity with respect to inversion of configuration and with enantioselectivity for the (*R*)-enantiomer. 18 Sulfate esters were tested for suitability as substrates. *sec*-Alkyl sulfates were readily accepted and best results obtained for those in which the R groups differed greatly in size. *prim*-Sulfate esters, branched substrates and derivatives bearing cyclic structural elements or lipophilic functional groups were not converted.

M. Pogorevc and K. Faber, *Tetrahedron: Asymmetry*, 2002, **13**, 1435.

Enantioselective hydrolysis of *sec*-alkyl sulfates ***Sulfatase***



M. Pogorevc, U.T. Strauss, T. Riermeier and K. Faber, *Tetrahedron*: *Asymmetry*, 2002, **13**, 1443.

Enantioselectivity was highest for substrates in which the relative size of alkyl substituents differed significantly. Detailed studies using *rac*-3-octyl sulfate showed that the use of carbohydrates, PEG and detergent additives, and enzyme immobilisation could enhance enantioselectivity. Enantioselectivity could also be enhanced by the addition of metal ions, though at the expense of reaction rate.