Perkin 1 Abstracts: Biocatalysis in Organic Synthesis

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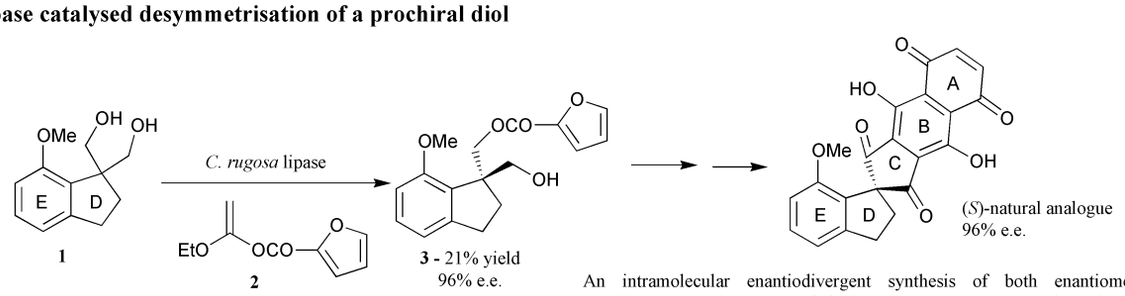
Perkin 1 Abstracts: Biocatalysis in Organic Synthesis aims to cover recent literature concerning the applications of enzymes and micro-organisms as catalysts in organic synthesis. The abstracts will emphasise the key synthetic step(s) that are mediated by the biocatalyst. Emerging technologies for biocatalyst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

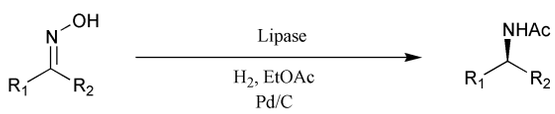
Lipase catalysed desymmetrisation of a prochiral diol ***Lipase***



S. Akai, T. Tsujino, N. Fukuda, K. Iio, Y. Takeda, K. Kawaguchi, T. Naka, K. Higuchi and Y. Kita, *Org. Lett.*, 2001, **3**, 4015.

An intramolecular enantiodivergent synthesis of both enantiomers of the ABCDE-ring analogue 22 of fredericamycin A is reported. A lipase-catalysed enantioselective desymmetrisation of prochiral diol **1** using 1-ethoxyvinyl 2-furoate **2** led to the pivotal intermediate (*R*)-**3**

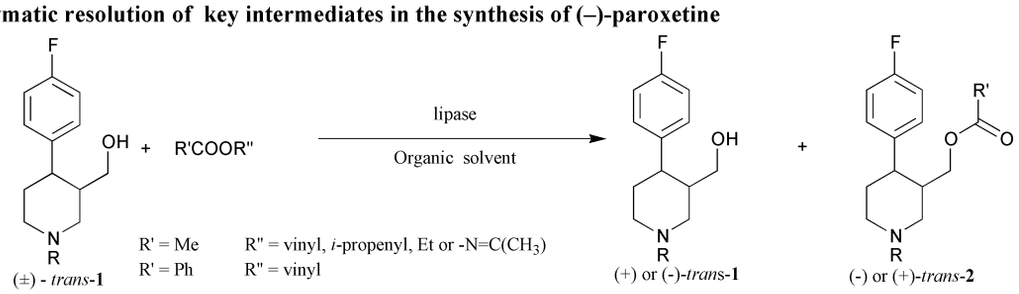
Lipase/palladium-catalysed asymmetric transformations of ketoximes to optically active amines ***Lipase***



Y. K. Choi, M. J. Kim, Y. Ahn and M.-J. Kim, *Org. Lett.*, 2001, **3**, 4099.

Prochiral ketoximes were asymmetrically transformed to optically active acetylated amines by coupled lipase/palladium catalysis in the presence of an acyl donor under 1 atm of hydrogen.

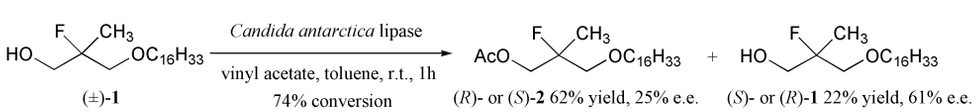
Enzymatic resolution of key intermediates in the synthesis of (–)-paroxetine ***Lipase***



G. de Gonzalo, R. Brieva, V. M. Sánchez, M. Bayod and V. Gotor, *J. Org. Chem.*, 2001, **66**, 8947.

Two *Candida antarctica* lipases catalyse the enantioselective acylation of *N*-substituted *trans*-4-(4'-fluorophenyl)-3-hydroxymethylpiperidine in organic solvents. The (*3S, 4R)* isomer, is an intermediate for the synthesis of (–)-paroxetine.

Synthesis of a fluorinated ether lipid ***Lipase***

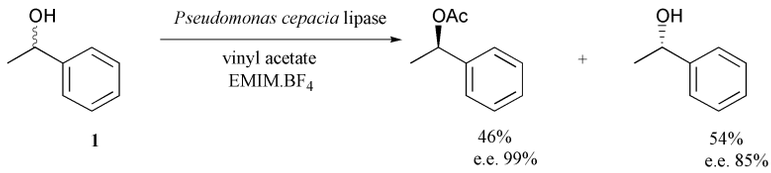


G. Haufe and A. Burchardt, *Eur. J. Org. Chem.*, 2001, 4501.

The synthesis of racemic 2-fluoro-3-hexadecyloxy-2-methyl-1-propyl 2'-(trimethylammonio)ethyl phosphate from (±)-**1** is described. Attempts to produce an enantioselective synthesis *via* enzyme catalysed resolution of (±)-**1** gave products possessing low e.e.'s.

Ionic liquid media for enzyme catalysed reactions

Lipase

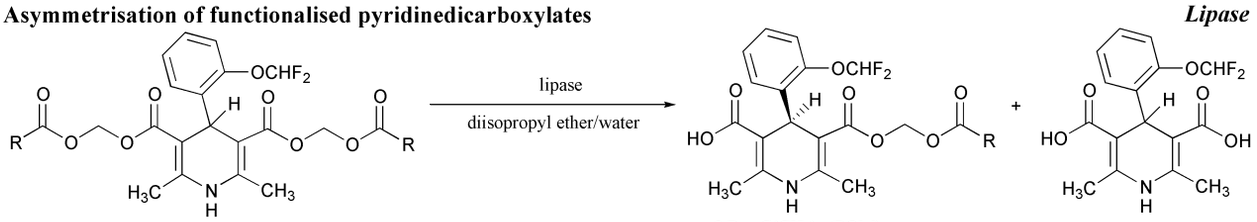


An improved preparation of ionic liquids involving washing with aqueous sodium carbonate is reported. The ionic liquids prepared in this way are suitable for a wide range of lipase catalysed reactions. The lipase catalysed enantioselective acylation of **1** in a number of different ionic liquids was investigated and found to proceed most efficiently in 3-ethyl-1-methylimidazolium tetrafluoroborate.

S. Park and R. J. Kazlauskas, *J. Org. Chem.*, 2001, **66,** 8395.

Asymmetrisation of functionalised pyridinedicarboxylates

Lipase



1 R = $C(CH_3)_3$ (POM)
2 R = $CH(CH_3)_2$ (*i*-BOM)

3 R = $C(CH_3)_3$ (POM)
4 R = $CH(CH_3)_2$ (*i*-BOM)

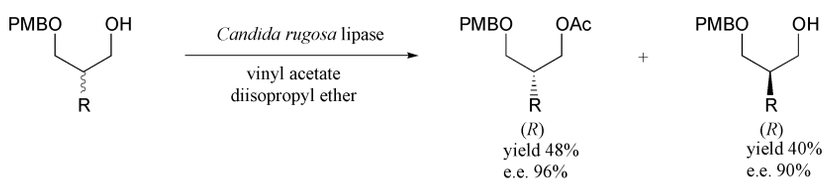
5

A. Sobolev, M. C. R. Franssen, B. Vigante, B. Cekavicus, N. Makarova, G. Duburs and A. de Groot, *Tetrahedron: Asymmetry*, 2001, **12**, 3251.

The bis POM ester **1** was hydrolysed by *Candida rugosa* lipase, in water saturated diisopropyl ether, to yield 34% of monoacid **3** with 84% e.e. 9% diacid **5** was also obtained. Hydrolysis of the bis *i*-BOM ester analogue **2** gave a 1:1:3 ratio of **2**:**5**:**4**, monoacid **4** having an e.e. of >95%.

Resolution of monoprotected 3-substituted propane-1,3-diols

Lipase

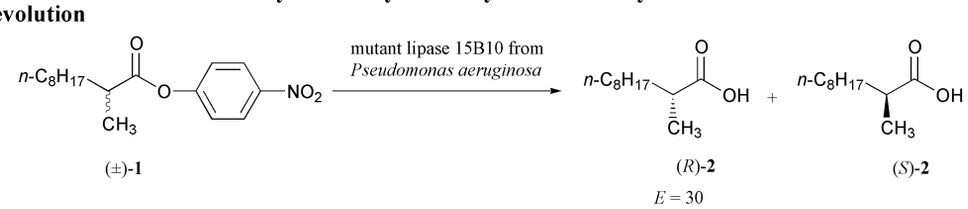


The (*S*)-alcohols were obtained by chemical hydrolysis of the (*R*)-acetate. 9 different compounds with variation in R were treated in this way. Other solvents tested were less effective. The products were intermediates in the synthesis of substrates for soybean lipoxygenase.

J. S. Yadav and S. Nanda, *Tetrahedron*: *Asymmetry*, 2001, **12**, 3223.

Reversal of enantioselectivity of an enzyme-catalysed reaction by directed evolution

Lipase



(±)-**1**

(*R*)-**2**

E = 30

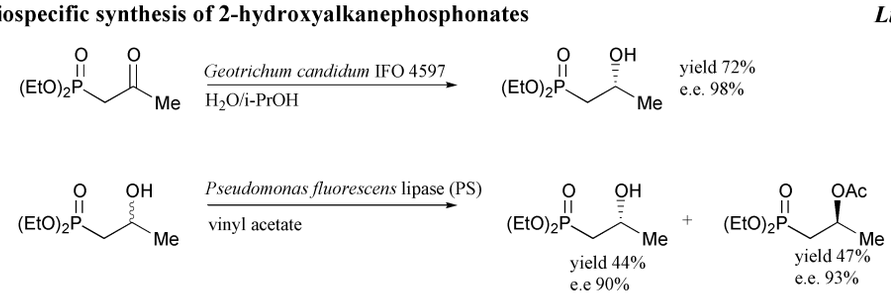
(*S*)-**2**

The wild-type lipase from *Pseudomonas aeruginosa* catalyses the resolution of the ester **1** with a slight preference for the *S*-acid **2**. A combination of error prone PCR at high mutation rate, and DNA shuffling, was used to invert the direction of enantioselectivity of the lipase catalysed resolution of **1** (*E*=30).

D. Zha, S. Wilensek, M. Hermes, K.-E. Jaeger and M. T. Reetz, *Chem. Commun.*, 2001, 2664.

Enantiospecific synthesis of 2-hydroxyalkanephosphonates

Lipase/Geotrichum candidum

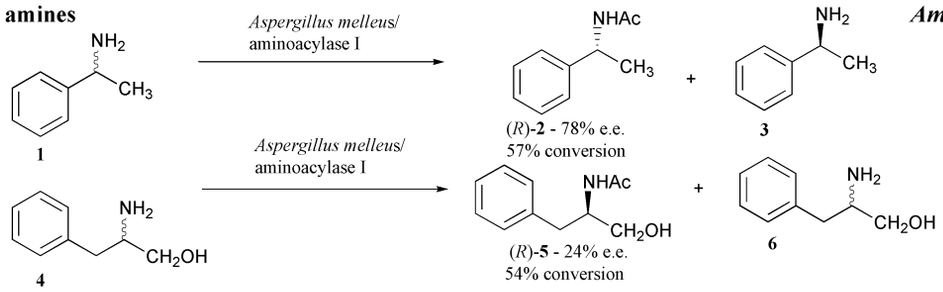


R. Zurawinski, K. Nakamura, J. Drabowicz, P. Kielbasinski and M. Mikolajczyk, *Tetrahedron*: *Asymmetry*, 2001, **12**, 3139.

For each transformation, a range of substrates with different substituents were tested, but e.e.'s were generally lower. Similarly other lipases tested were found to be less effective.

Acylation of chiral amines

Aminoacylase

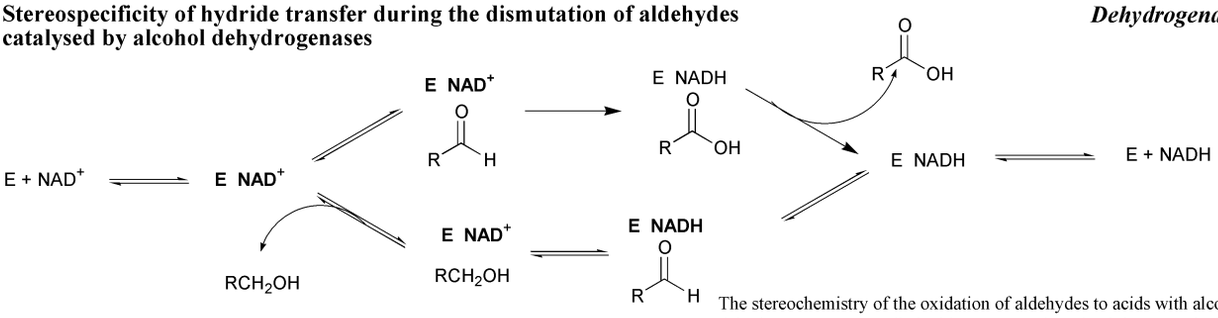


M. I. Youshko, F. van Rantwijk and R. A. Sheldon, *Tetrahedron:Asymmetry*, 2001, **12**, 3267.

Arylalkylamines of type **1** were acylated with moderate enantioselectivity by aminoacylase I using methylmethoxyacetate as acyl donor in *tert*-butyl methyl ether. Amino alcohols of type **4** were exclusively acylated at the amine position with poor to moderate enantioselectivity.

Stereospecificity of hydride transfer during the dismutation of aldehydes catalysed by alcohol dehydrogenases

Dehydrogenase

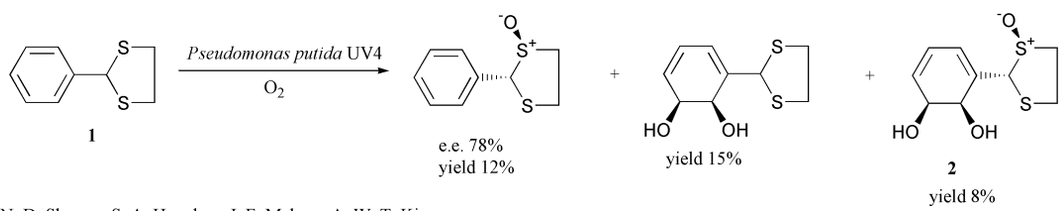


K. Velonia and I. Smonou, *Tetrahedron: Asymmetry*, 2001, **12**, 3119.

The stereochemistry of the oxidation of aldehydes to acids with alcohol dehydrogenase was studied with respect to the selectivity towards the cofactor.

Chemoenzymatic synthesis of enantiopure *cis*-diol sulfoxides

Dioxygenase

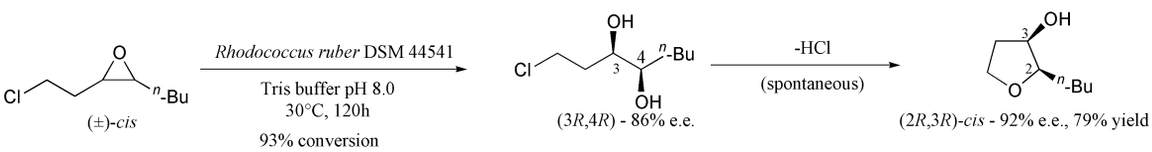


D. R. Boyd, N. D. Sharma, S. A. Haughey, J. F. Malone, A. W. T. King, B. T. McMurray, A. Alves-Areias, C. C. R. Allen, R. Holt and H. Dalton, *J. Chem. Soc., Perkin Trans. 1,* 2001, 3288.

A study on the synthesis of enantiopure diol-sulfoxides is reported. The reaction proceeds *via* tandem *cis*-dihydroxylation-sulfoxidation of thioacetate and dialkyl sulfides.

Enzyme-triggered enantioconvergent transformation of haloalkyl epoxides

Epoxide hydrolase

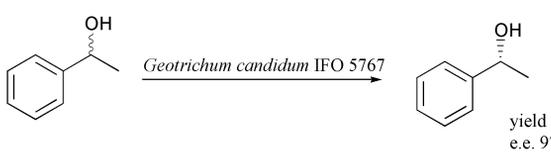


S. F. Mayer, A. Steinreiber, R. V. A. Orru and K. Faber, *Eur. J. Org. Chem.*, 2001, 4537.

Various haloalkyl oxiranes were chosen as substrates in order to study the influence of relative *cis* and *trans* configuration of the oxirane moiety, length of haloalkyl spacer, choice of halogen and length of the alkyl chain.

Stereoinversion of arylethanols

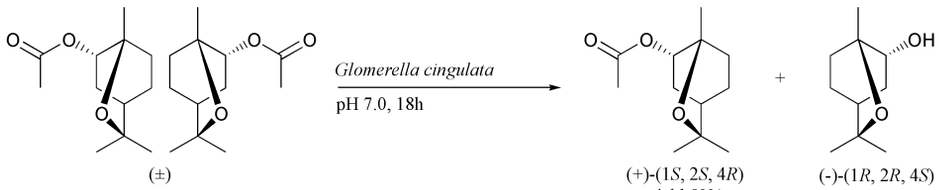
Geotrichum candidum



K. Nakamura, M. Fujii and Y. Ida, *Tetrahedron*: *Asymmetry*, 2001, **12**, 3147.

Of 18 microbes tested, *G. candidum* IFO 5767 was found to be most suitable. Mechanistic studies suggest that at least 2 enzymes are present, one that oxidises the (*S*) enantiomer, and one which reduces the ketone to the (*R*) enantiomer. Slight enhancement was observed under aerobic conditions. Use of additives failed to improve the efficiency. Other secondary alcohols were subjected to this stereoinversion. Isolated yields ranged from 25 - 99% and e.e.'s from 78 - 100%.

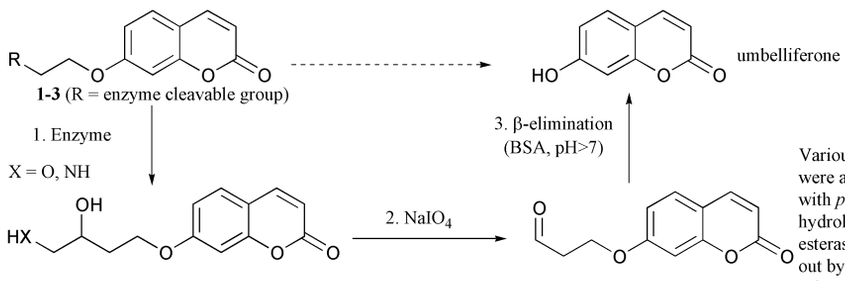
Resolution of 2-*endo*-acetoxy-1,8-cineole ***Glomerella cingulata***



M. Miyazawa and Y. Hashimoto, *Tetrahedron*: *Asymmetry*, 2001, **12**, 3139.

The corresponding alcohol and acetate of each enantiomer was prepared by hydrolysis or acetylation. The odor differences between the enantiomers are described.

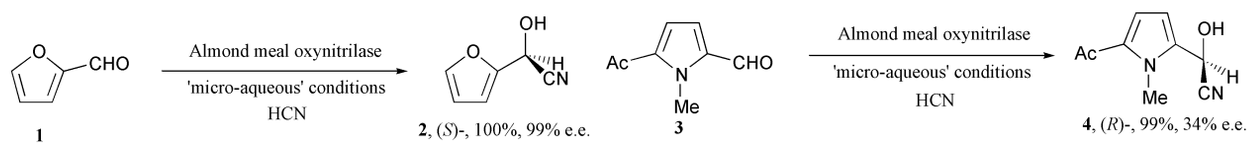
Enzyme fingerprints by fluorogenic and chromogenic substrate arrays ***Hydrolase***



D. Wahler, F. Badalassi, P. Crotti and J.-L. Reymond, *Angew. Chem., Int. Ed.*, 2001, **40**, 4457.

Various amides, epoxides, esters and carbonates related to **1-3** were assembled in arrays. A chromogenic array was prepared with *p*-nitrophenol as the leaving group. A series of hydrolytic enzymes were screened. Enzyme classes, such as esterases and lipases, amidases, and epoxide hydrolases, stand out by their preferential reactivity with the corresponding substrates. The arrays provide fingerprints that differentiate between closely related hydrolytic enzymes.

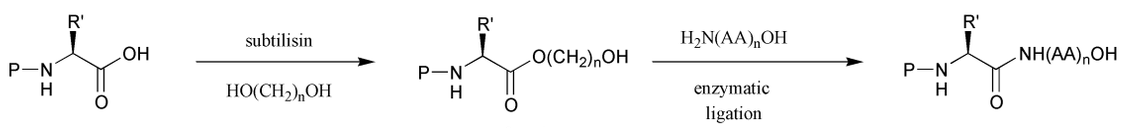
Hydrocyanation of heteroaryl carboxaldehydes ***Oxynitrilase***



P. Chen, S, Han, G. Lin, H. Huang and Z. Li, *Tetrahedron:Asymmetry*, 2001 **12**, 3273.

Furan-2-yl carboxaldehydes such as **1** and 2-thienyl analogues were transformed to optically active cyanohydrins using almond meal oxynitrilase under 'micro aqueous' conditions (9% aqueous suspension in isopropyl ether). Pyrrolyl substrates such as **3** were transformed with, in most cases, poor to moderate yields and e.e.'s.

Subtilisin-catalysed synthesis of amino acid and peptide esters ***Protease***



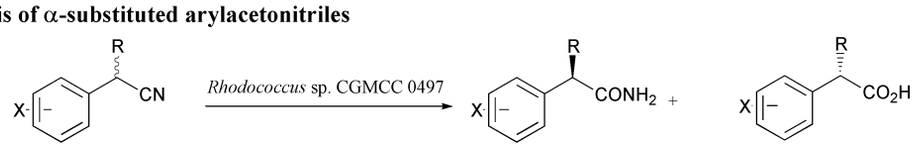
P = Boc or peptide chain

n = 3 or 4

C.-F. Liu and J. Tam, *Org. Lett.*, 2001, **3**, 4157.

The serine protease subtilisin Carlsberg (EC 3.4.21.62) was found to efficiently catalyse the specific formation of C^{α}-carboxy 3-hydroxypropyl or 4-hydroxybutyl esters of certain Boc-amino acids and peptides in high content propane-1,3-diol or butane-1,4-diol solution, with substrate specificity parallel to that of the normal hydrolytic reaction.

Hydrolysis of α-substituted arylacetonitriles ***Rhodococcus* sp.**



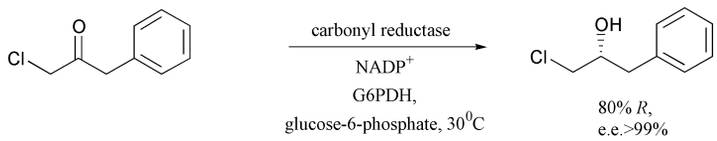
R = *e.g.* Me, Et, *n*-Pr
X = *e.g.* H, NO_2, OMe, Cl, Br

Z.-L. Wu and Z.-Y. Li, *Tetrahedron: Asymmetry*, 2001, **12**, 3305.

Seventeen arylacetonitriles of type **1** were subjected to biotransformation by suspensions of *Rhodococcus* sp. CGMCC 0497. Each was resolved to the (*R*)- amide and (*S*)- acid as shown. Yields and enantiomeric excesses were high in most cases, except where X = NO_2 or R = *n*-Pr. β–Naphthyl analogues were also hydrolysed with good selectivities, though poor to moderate yields were observed.

Carbonyl reductase as a versatile biocatalyst

Saccharomyces cerevisiae

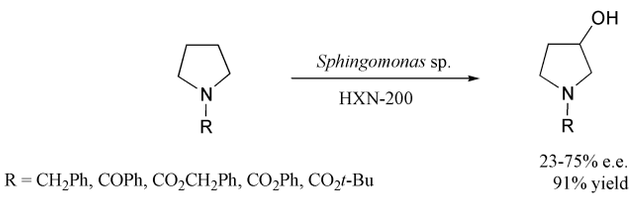


T. Ema, H. Moriya, T. Kofukuda, T. Ishida, K. Maehara, M. Utaka and T. Sakai, *J. Org. Chem.*, 2001, **66,** 8682.

A study on the use of a carbonyl reductase purified from *S.cerevisiae* is reported. This enzyme, which showed high enantioselectivity and broad substrate specificity, was found to be a versatile biocatalyst for the asymmetric reduction of carbonyl compounds.

Preparation of (*R*)- and (*S*)-*N*-protected 3-hydroxypyrrolidines

Sphingomonas sp.

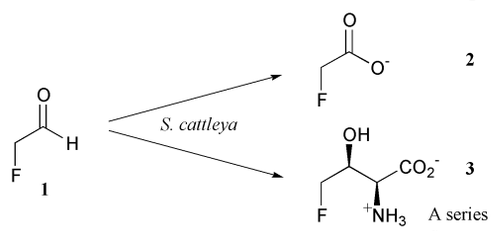


Z. Li, H.-J. Feiten, D. Chang, W. A. Duetz, J. B. van Beilen and B. Witholt, *J. Org. Chem.*, 2001, **66,** 8424.

A variety of *N*-substituted pyrrolidines were converted to the corresponding 3-hydroxypyrrolidines with *Sphingomonas* sp. The reaction proceeded with high activity, high conversion and excellent regioselectivity by use of either frozen/thawed or growing cells.

Biosynthesis of fluoroacetate and 4-fluorothreonine in *Streptomyces cattleya*

Streptomyces cattleya

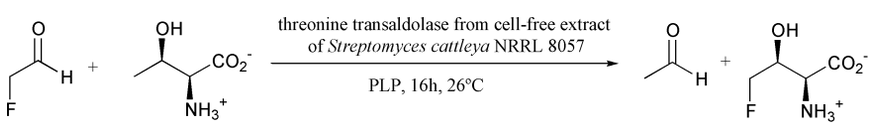


C. Schaffrath, C. D. Murphy, J. T. G. Hamilton and D. O'Hagan, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3100.

A series of isotope labelling experiments were conducted to investigate the biosynthesis of fluoroacetate, **2**, and 4-fluorothreonine, **3**, in resting cells of *Streptomyces cattleya.* Fluoroacetaldehyde, **1**, is a known precursor to these two metabolites and it is reported that the former is in turn derived from a C_3 glycolytic intermediate rather than a C_2 amino acid metabolite.

Identification of a PLP-dependent threonine transaldolase

Transaldolase



C. D. Murphy, D. O'Hagan and C. Schaffrath, *Angew. Chem., Int. Ed.*, 2001, **40**, 4479.

A threonine aldolase has been identified that does not use glycine as a substrate unlike more classical threonine aldolases.