ABSTRACTS

Perkin 1 Abstracts: Biocatalysis in Organic Synthesis

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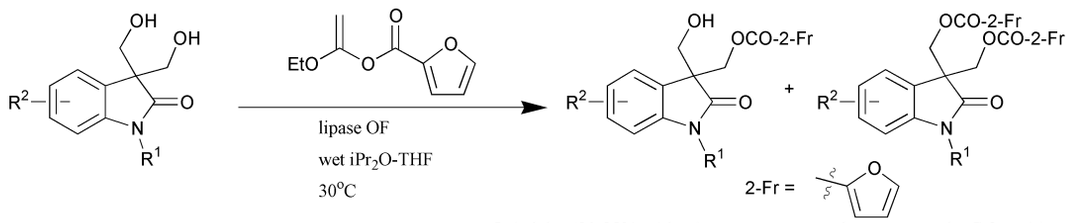
Perkin 1 Abstracts: Biocatalysis in Organic Synthesis aims to cover recent literature concerning the applications of enzymes and micro-organisms as catalysts in organic synthesis. The abstracts will emphasise the key synthetic step(s) that are mediated by the biocatalyst. Emerging technologies for biocatalyst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

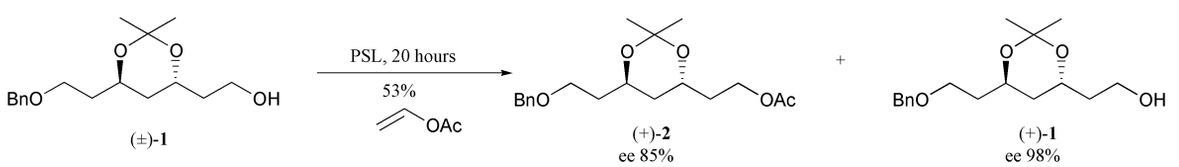
Desymmetrization of prochiral 3,3-bis(hydroxymethyl)oxindoles ***Lipase***



S. Akai, T. Tsujino, T. Naka, K. Tanimoto and Y. Kita, *Tetrahedron Lett.*, 2001, **42**, 7315.

Oxindoles (91-98% ee) having a quaternary carbon centre at the C-3 position were prepared from readily available oxindoles in 50-64% overall yields, in which an enantioselective desymmetrization of prochiral 1,3-diols using a *Candida rugosa* lipase (Meito OF) and 1-ethoxyvinyl 2-furoate was employed as the key step.

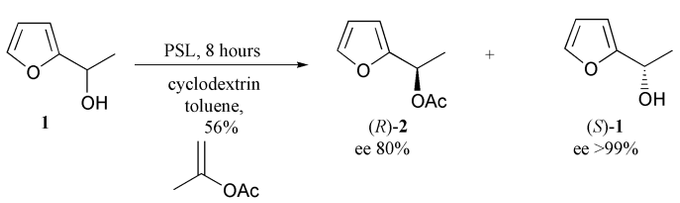
Preparation of 1,3- *anti*- and *syn*-tetrols *via* enantioselective biocatalytic resolution ***Lipase***



C. Bonini, L. Chiummiento and M. Funicello, *Tetrahedron: Asymmetry*, 2001, **12**, 2755.

The synthesis of optically active 1,3-tetrols with an *anti*-relative configuration is reported. The racemic compound (±)-**1** was enzymatically resolved under transesterification conditions to afford (+)-**2** and (+)-**1** in good yield. The *syn*- compounds were obtained by similar procedures.

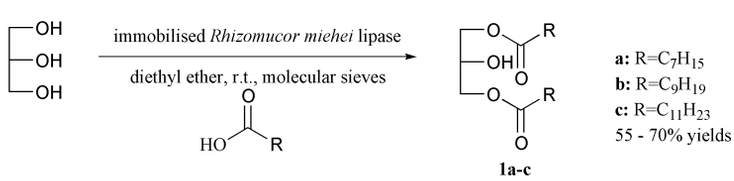
Peracetylated β-cyclodextrin as an additive in enzymatic reactions ***Lipase***



A. Ghanem and V. Schurig, *Tetrahedron: Asymmetry*, 2001, **12**, 2761.

Peracetylated β-cyclodextrin has been employed as an additive to enhance the reaction rate and enantiomeric ratio, *E*, in the *Pseudomonas cepacia* lipase catalysed enantioselective transesterification of (±)-1-(2-furyl)ethanol, **1**, with isopropenyl acetate.

Chemoenzymatic synthesis of structured triacylglycerols ***Lipase***



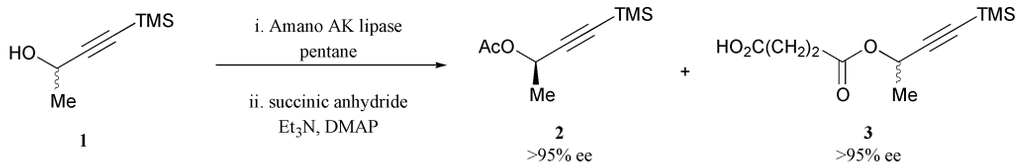
a: R=C_7H_{15}
b: R=C_9H_{19}
c: R=$C_{11}H_{23}$
55 - 70% yields

A. Halldorsson, C. D. Magnusson and G. G. Haraldsson, *Tetrahedron Lett.*, 2001, **42**, 7675.

Diacylglycerols **1a-c** were prepared using *Rhizomucor miehei* lipase. Thereafter, six regioisomerically pure structured triacylglycerols were prepared by coupling **1a-c** with icosapentaenoic acid or docosahexaenoic acid at the secondary position.

Lipase-mediated resolution of 4-trimethylsilylbut-3-yn-2-ol

Lipase

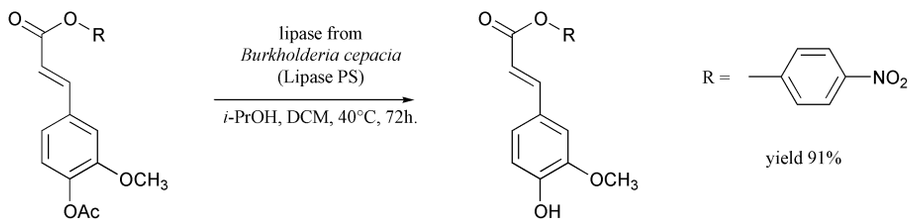


J. A. Marshall, H. R. Chobanian and M. M. Yanik, *Org. Lett.*, 2001, **21**, 3369.

Due to the volatility of 4-trimethylsilylbut-3-yn-2-ol **1**, an improved method has been developed for its resolution using a lipase. The reaction is carried out in pentane rather than hexane, using vinyl acetate as the acyl donor. The crude reaction mixture is then treated with succinic anhydride to give the non-volatile products **2** and **3** which can be separated. Removal of the ester is effected using DIBAL to give the enantiomeric alcohols.

Chemoselective ester hydrolysis

Lipase

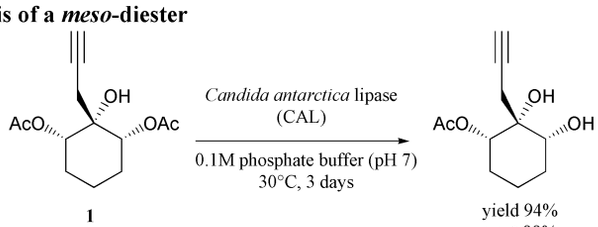


M. Mastihubová, V. Mastihuba, L. Kremnický, J. L. Willet and G. L. Côté, *Synlett*, 2001, 1559.

A total of 4 substrates with variation in R were tested. Yields ranged from 84-91%. The products are substrates for feruloyl esterases.

Asymmetric hydrolysis of a *meso*-diester

Lipase



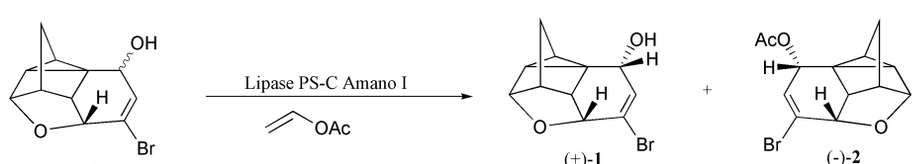
yield 94%
e.e. >99%

T. Matsumoto, T. Konegawa, H. Yamaguchi, T. Nakamura, T. Sugai and K. Suzuki, *Synlett*, 2001, 1650.

The desymmetrisation of **1** using CAL has been achieved in high yield and ee. Other lipases (PPL and PLE) were also effective. The reaction proceeded with similar yields and ee for substrates with a propenyl or methyl group in place of a propynyl moiety. The diol shown was an intermediate in the proposed synthesis of aquayamycin.

Kinetic resolution of a polycyclic alcohol

Lipase

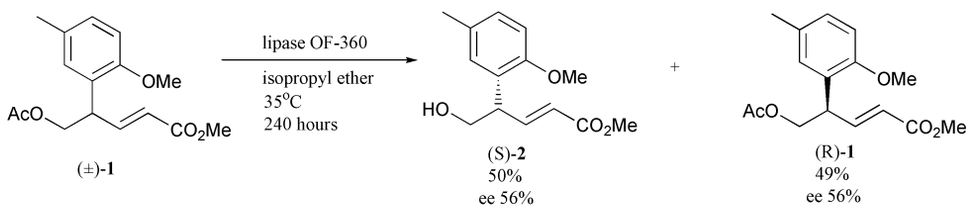


F. D. P. Morisso and V. E. U. Costa, *Tetrahedron*: *Asymmetry*, 2001, **12**, 2641.

Transesterification of alcohol (±)-**1** was conducted with a number of lipase preparations. The best kinetic resolution was obtained with *Pseudomonas cepacia* lipase immobilised on chemically modified ceramic particles.

Lipase catalysed resolution of intermediates of the synthesis of (+)- and (–)-elvirol

Lipase

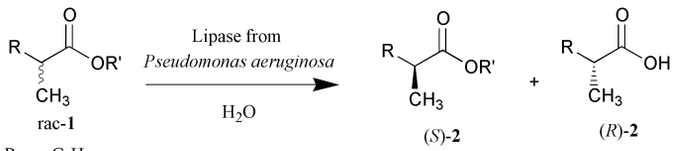


M. Ono, K. Suzuki, S. Tanikawa and H. Akita, *Tetrahedron*: *Asymmetry*, 2001, **12**, 2597.

The synthesis of (+)- and (–)-elvirol based on enzymatic resolution using *Candida rugosa* lipase is reported. When (±)-**1** was subjected to enantioselective hydrolysis, alcohol (*S*)-**2** and unreacted (*R*)-**1** were obtained. Both intermediates were then used in the preparation of elvirol.

Directed evolution of *Pseudomonas aeruginosa* lipase

Lipase



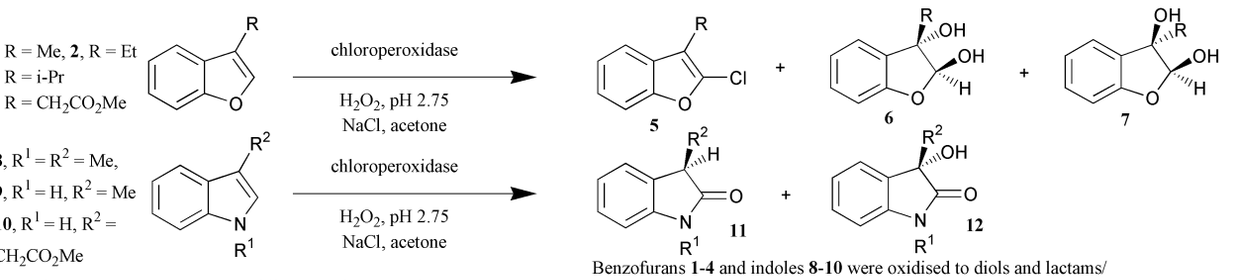
R = *n*-C_8H_{17}
R' = *p*-$NO_2C_6H_4$

M. T. Reetz, S. Wilensek, D. Zha and K.-E. Jaeger, *Angew. Chem., Int. Ed.*, 2001, **40**, 3589.

Combinatorial Multiple Cassette Mutagenesis (CMCM) has been used to improve the enantioselectivity of the lipase from *Pseudomonas aeruginosa* at the resolution shown (E = 1.1 for the wild-type enzyme). Using saturation mutagenesis at pre-identified 'hot-spots' (amino acid positions 160-163), several improved mutants were identified, including variant 'G' exhibiting an E value of 30. Saturation mutagenesis using CMCM at positions 155 and 162 yielded variants L and I with E values of 34 and 30 respectively. Further recombination experiments led to an improved variant J exhibiting an E value of >51.

Oxidation of benzofurans

Chloroperoxidase

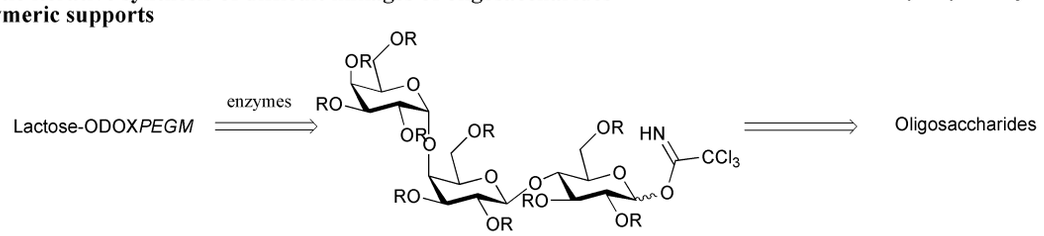


R. G. Alvarez, I. S. Hunter, C. J. Suckling, M. Thomas and U. Vitinius, *Tetrahedron*, 2001, **57**, 8581.

Benzofurans **1-4** and indoles **8-10** were oxidised to diols and lactams/ hydroxylactams respectively by chloroperoxidase (CPO) from *Caldariomyces fumago*, using conditions which suppressed the catalase activity of CPO.

Chemoenzymatic iterative synthesis of difficult linkages of oligosaccharides on soluble polymeric supports

Glycosyltransferases

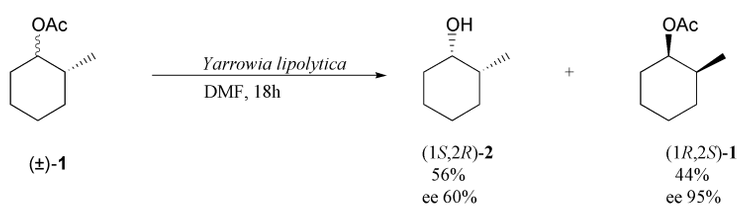


F. Yan, M. Gilbert, W. W. Wakarchuk, J.-R. Brisson and D. M. Whitfield, *Org. Lett.*, 2001, **3**, 3265.

A trisaccharide donor containing a *cis*-Gal*p*α(1-4)Gal*p* linkage was prepared using a synthetic strategy based on chemoenzymatic oligosaccharide synthesis on a soluble polymeric support. MPEG-attached trisaccharide was shown to bind to Verotoxin-1 by transfer NOE studies through the Gal*p*α(1-4) Gal*p* portion of the molecule.

Enantioselective hydrolyses with *Yarrowia lipolytica*

Hydrolase

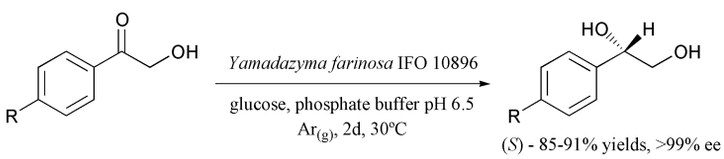


G. Fantin, M. Fogagnolo, A. Guerrini, A. Medici, P. Pedrini and S. Fontana, *Tetrahedron*: *Asymmetry*, 2001, **12**, 2709.

The use of *Yarrowia lipolytica* YL2 in kinetically resolving racemic secondary esters, γ-lactones, enol esters and styrene oxide *via* hydrolysis is reported.

Asymmetric reduction of α-hydroxyketones in the anti-Prelog selectivity

Microbe

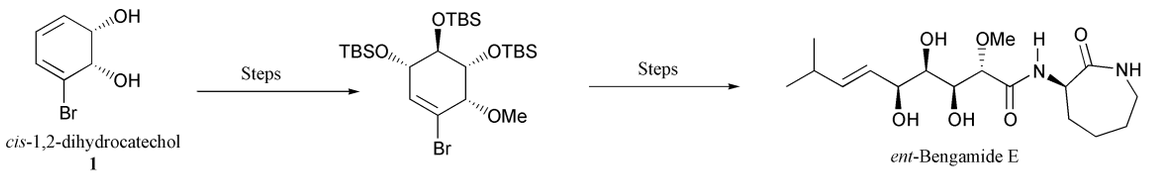


T. Tsujigami, T. Sugai and H. Ohta, *Tetrahedron: Asymmetry,* 2001, **12**, 2543.

Y. farinosa IFO 10896 was found to reduce α-hydroxyketones bearing a phenyl ring with anti-Prelog selectivity (*i.e. S*) which is enantiocomplementary to the corresponding baker's yeast reduction (*i.e. R*).

A chemoenzymatic total synthesis of *ent*-bengamide E

Microbial oxidation



cis-1,2-dihydrocatechol
1

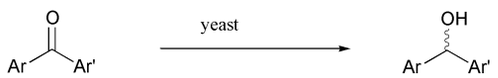
ent-Bengamide E

M. G. Banwell and K. J. McRae, *J. Org. Chem.*, 2001, **66**, 6768.

The *cis*-1,2-dihydrocatechol **1** is obtained in enantiomerically pure form by microbial dihydroxylation of bromobenzene. This has been converted into *ent*-bengamide E, a cyclolysine-based marine natural product.

Use of chiral HPLC-MS for rapid evaluation of the yeast-mediated enantioselective bioreduction of a diaryl ketone

Microbial reduction

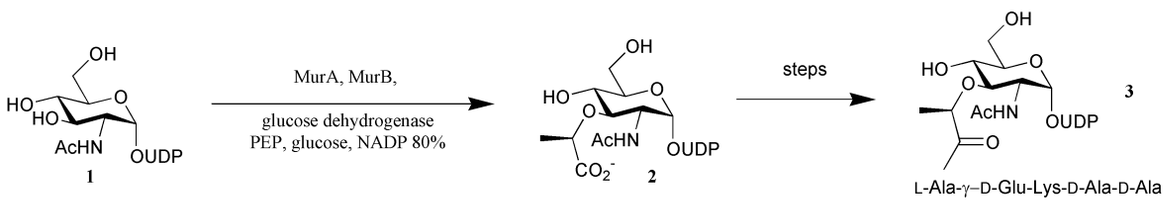


C. J. Welch, B. Grau, J. Moore and D. J. Mathre, *J. Org. Chem.*, 2001, **66,** 6836.

The HPLC-UV analysis of yeast-mediated enantioselective bioreduction of diaryl ketones is often complicated by the fact that the residual starting ketone overlaps with the product. Chiral HPLC-MS is used to allow the overlapping ketone and alcohols to be conveniently resolved and detected by MS allowing the rapid enantiopurity analysis required for high throughput reaction screening.

Synthesis of UDP-*N*-acetylmuramyl peptides

MurA/MurB



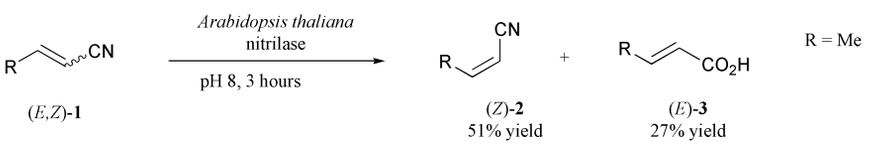
1 **2**

H. Liu, R. Sadamoto, P. S. Sears and C.-H. Wong, *J. Am. Chem. Soc.*, 2001, **123**, 9916.

The synthesis of UDP-*N*-acetylmuramic acid **2** from UDP-GluNAc **1** was accomplished in one pot by MurA and MurB with *in situ* regeneration of NADPH. **2** served as a synthon for MurNAc pentapeptides of type **3**, which were prepared in up to 56% yield in only a three step synthesis from **1**. Fluorescent analogues of **3** were also prepared in this manner.

(*E*)-Selective hydrolysis of (*E,Z*)-α,β-unsaturated nitriles

Nitrilase



(*E,Z*)-**1**

(*Z*)-**2**
51% yield

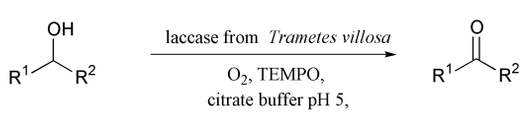
(*E*)-**3**
27% yield

F. Effenberger and S. Oβwald, *Tetrahedron*: *Asymmetry*, 2001, **12**, 2581.

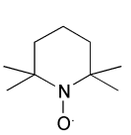
A study on the synthetic application of recombinant nitrilase AtNIT1 from *Arabidopsis thaliana* is reported. The (*E*)-isomer of α,β-unsaturated nitrile **1** was exclusively hydrolysed to the corresponding (*E*)-acid, **3**, enabling isolation of the isomerically pure (*Z*)-nitrile, **2**.

Oxidation of alcohols

Oxidase



R^1	R^2	Yield(%)
C_6H_5	H	92
4-MeO-C_6H_4	H	99
3,4-dimethoxy-C_6H_4	H	99
4-MeO-C_6H_4	Me	85
4-MeO-C_6H_4	Et	95



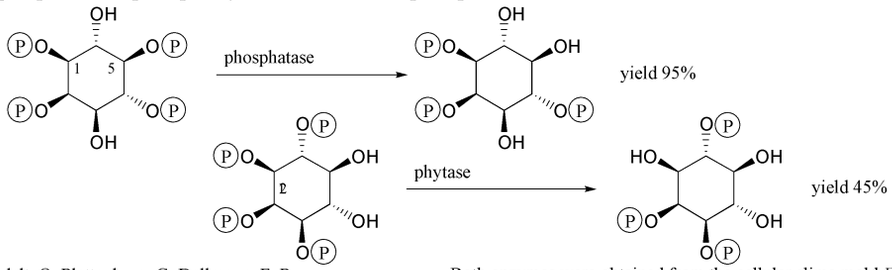
TEMPO

M. Fabbrini, C. Galli, P. Gentili and D. Macchitella, *Tetrahedron Lett.*, 2001, **42**, 7551.

The oxidation of primary and secondary aryl alcohols to carbonyl compounds is reported; it requires the laccase/TEMPO mediator system as the catalyst. Primary and secondary alkyl alcohols were oxidised in lower yields (15-96%).

Regiospecific dephosphorylation of inositol phosphates

Phosphohydrolases

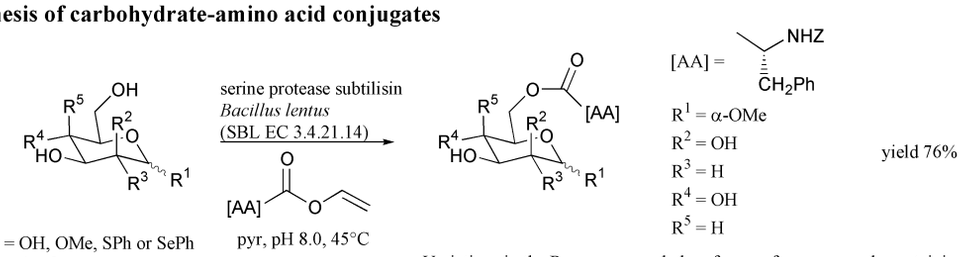


S. Adelt, O. Plettenburg, G. Dallmann, F. P. Ritter, S. B. Shears, H.-J. Altenbach and G. Vogel, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2705.

Both enzymes were obtained from the cellular slime mold *Dictyostelium discoideum*. The phosphatase reaction occurs highly specifically at the 5-position, whereas the phytase reacton has a tendency towards further hydrolysis. The effect on kinase activity of these inositol trisphosphates was studied.

Synthesis of carbohydrate-amino acid conjugates

Protease



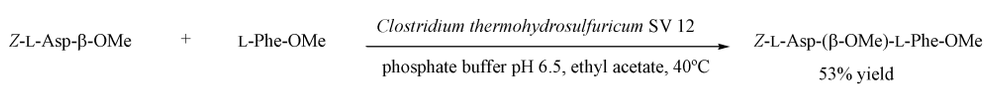
R^1 = OH, OMe, SPh or SePh
R^2, R^4, R^5 = OH or H
R^3 = H, OH or NHAc

V. Boyer, M. Stanchev A. J. Fairbanks and B. G. Davis, *Chem. Commun*., 2001, 1908.

Variations in the R groups revealed preference for compounds containing R^2 = OH. Yield improved for R^1 = OMe, although the anomeric stereochemistry had little effect on yield. Other amino acid acyl donors (based on Asp and Glu) were used but were ineffective. Variations in the *N*-protection (Ac and Boc) were tolerated. Yields decreased using the CLEC-thermolysin as the protease.

Dipeptide synthesis using novel thermophilic enzyme

Protease

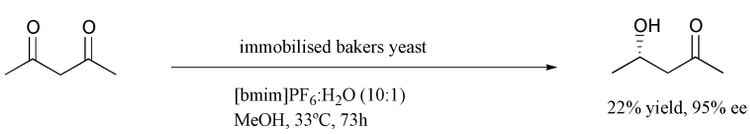


J. S. Yadav, H. M. Meshram, A. R. Prasad, Y. S. S. Ganesh, A. B. Rao, G. Seenayya, M. V. Swamy and M. G. Reddy, *Tetrahedron*: *Asymmetry*, 2001, **21**, 2505.

Compared with thermolysin, *Clostridium thermohydrosulfuricum* was found to be stable at higher temperatures with broad substrate specificity and high stereospecificity towards L-amino acids.

Reduction of ketones in an ionic liquid

Saccharomyces cerevisae

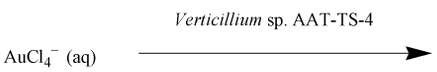


J. Howarth, P. James and J. Dai, *Tetrahedron Lett.,* 2001, **42**, 7517.

Several ketones were subjected to yeast mediated reductions. These represent the first examples of whole cell biotransformation in a moisture stable ionic liquid.

Bioreduction of $AuCl_4^-$

***Verticillium* sp.**



P. Mukherjee, A. Ahmad, D. Mandal, S. Senapati, S. R. Sainkar, M. I. Khan, R. Ramani, R. Perischa, P. V. Ajayakumar, M. Alam, M. Sastry and R. Kumar, *Angew. Chem., Int. Ed.*, 2001, **40**, 3585.

The fungus *Verticillium* sp. AAT-TS-4, was reported to reduce $AuCl_4^-$ ions to yield gold nanoparticles of 20 nm diameter, which accumulate both on the cell surface and on the cytoplasmic membrane The enzymatic mechanism of the reduction is still unclear, but was shown to be specific to the organism studied amongst a group of other fungi.