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Enzyme Catalysed Kinetic Resolution of Racemic 2,2-Dimethyl-3-(2,2-Disubstituted Vinyl) Cyclopropane Carboxylic Acids Anchored on Polymer supports

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Abstract : **Kinetic resolution of *trans*-substituted cyclopropane carboxylic acids anchored on a solid support by lipase is described.** © 1999 Elsevier Science Ltd. All rights reserved.

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High-throughput organic synthesis based on polymeric supports has become a paradigm for the production of small molecule libraries for the screening approach to drug discovery.[1] There are many advantages that accrue from conducting reactions on solid supports.[2,3] In recent years the application of biocatalysts (especially enzymes), which provide unique advantages of efficiency, stereoselectivity and eco-friendliness has been explored in organic synthesis for specific chemical transformations which are difficult to carry out by purely chemical methods.[4,5] Furthermore in the light of intense interest in combinatorial chemistry, the successful implementation of enzymatic transformations on solid supports is of general interest. Though countless examples now exist of synthetic strategies based on polymeric supports, relatively few examples of polymer supported organic transformations catalysed by enzymes have been published.[6,7,8]

Here, we wish to report a novel enzymatic kinetic resolution of racemic substituted cyclopropane carboxylic acids anchored on polystyrene based resins (Scheme-1).

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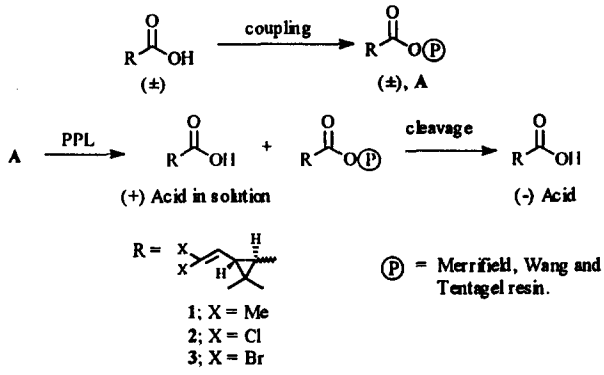
Scheme-1



The coupling of the acids with the resins was carried out by standard protocols.[9-11] The degrees of loading of the acids to the resins were found to be more than 90% in almost all cases. The coupled products were characterised by FTIR (1735 cm^{-1} for carbonyl stretching) and by Gel ^{13}C FTNMR (66 ppm for the methylene carbon).

In a typical resolution experiment the resin coupled acids (250 mg) and lipase (type-VI-S, from porcine pancreas, 1 g) were taken in 25 ml *t*-BuOH/THF (5:1, v/v) solution, 0.1 (M) phosphate buffer (pH = 7.8) was added and the solution incubated at 30°C in an orbital incubator shaker for the required time (Table-1).

Table-1 : Resolutions of substituted cyclopropane carboxylates (compounds 1-3) with lipase.[c]

Entry	Substrate[d]	t [h]	(+)-*R*-acid in solution		(-)-*S*-acid after cleavage	
			Yield[a] [%]	ee[b][%]	Yield [%]	ee[%]
1.	1a	8	40	90	25	85
2.	2a	7	48	94	35	82
3.	3a	6	60	90	30	90
4.	1b	16	20	80	15	80
5.	2b	14	25	82	18	85
6.	3b	13	32	88	20	89
7.	1c	15	15	85	15	75
8.	2c	14	25	88	18	80
9.	3c	12	28	90	25	83

[a] 50% conversion of one enantiomer constitutes the maximum yield (theoretical yield of 100%). [b] Configuration of the carbon [C-3] in the cyclopropane ring. [c] The enzyme lipase is used for several reaction cycles after lyophilisation. The enzymatic activity of the lipase decreased after two cycles. The relative enantiomeric excess is not influenced by reduced activity. [d] a,b,c indicates acids coupled with Tentagel, Merrifield and Wang resin respectively.

The initial enzymatic saponification was indicated by a decrease in pH and the pH was then maintained constant by a pH stat method. The reaction was followed by monitoring the product ratio using HPLC. After the incubation period the solution containing the hydrolysed acid was centrifuged and the supernatent solution was decanted. This was extracted with chloroform, dried ($MgSO_4$) and concentrated to give the (+)-*R*-acid. Further it was recrystallised from MeOH to give enantiomerically pure (+)-*R*-acid. The remaining solid mass was washed repeatedly with water to remove the enzyme and the resin was cleaved to give the (-)-*S*-acid.

The results in Table-1 show the higher rates of conversion and enantioselectivity when compared to our earlier studies.[12,13] The advantage of this methodology is that after being hydrolysed , one enantiomer comes into the solution and the other remains with the solid support and can be later cleaved from the resin; thus both the enantiomers are obtained with high optical purity. Among the three insoluble supports Tentagel resin outperformed Merrifield and Wang; it may be that the last two supports show an overall inability due to poor swelling properties in *t*-BuOH/THF as solvent. From Table-1, it was also observed that compounds **2** and **3** (bearing two halogen atoms) provide higher rates of hydrolysis compared to compound **1** (containing a geminal dimethyl group). This was confirmed by kinetic parameters,[15] and may be due to an increase in the affinity of the substrate to the enzyme catalytic active site.

In conclusion, we have developed a general and highly efficient method for the enzymatic resolution of resin bound racemic substituted cyclopropane acids. This finding might open new and advantageous routes in the development of novel enzymatic transformations on solid supports and its further application in automation to obtain optically pure compounds.

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Kinetic parameters

Substrate	km (mole min^{-1})	Vmax (mol. $min^{-1}.mg^{-1}$)
Compound 1	22	58
Compound 2	25	62
Compound 3	32	68