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Dynamic Kinetic Resolution with Enzyme and Palladium Combinations

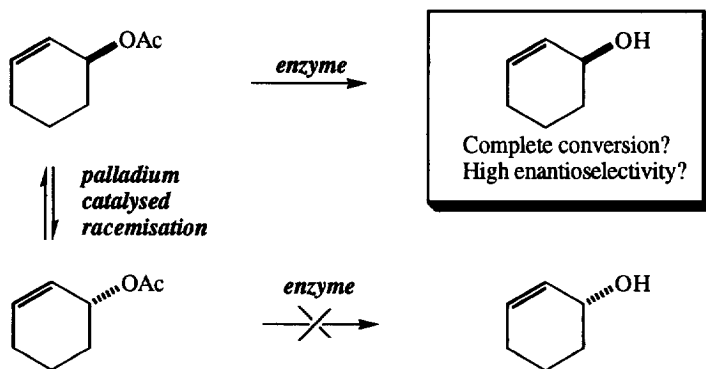
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Abstract: The dynamic kinetic resolution of certain allyl acetates has been achieved by enzymatic hydrolysis to the corresponding allyl alcohols. In the presence of a palladium catalyst, the allyl acetate is racemised, allowing a dynamic resolution to take place.

Both enzymes and transition metal catalysts have been used for the preparation of enantiomerically enriched products. Herein we report our preliminary results using a combination of enzyme and transition metal catalysed processes to effect a dynamic kinetic resolution process.¹

The basic idea of this work is depicted in Scheme 1. It was anticipated that an enzyme could be used to enantioselectively hydrolyse one enantiomer of an allyl acetate. At the same time, a palladium catalyst would be employed to racemise the starting material (but not the product!). Thus, the enantiomer of substrate favoured by the enzyme would be replenished, and so both enantiomers of allyl acetate would be converted into a single enantiomer of allyl alcohol.



Scheme 1. Postulated conversion of a racemic acetate into an enantiomerically enriched alcohol by a novel dynamic resolution process.

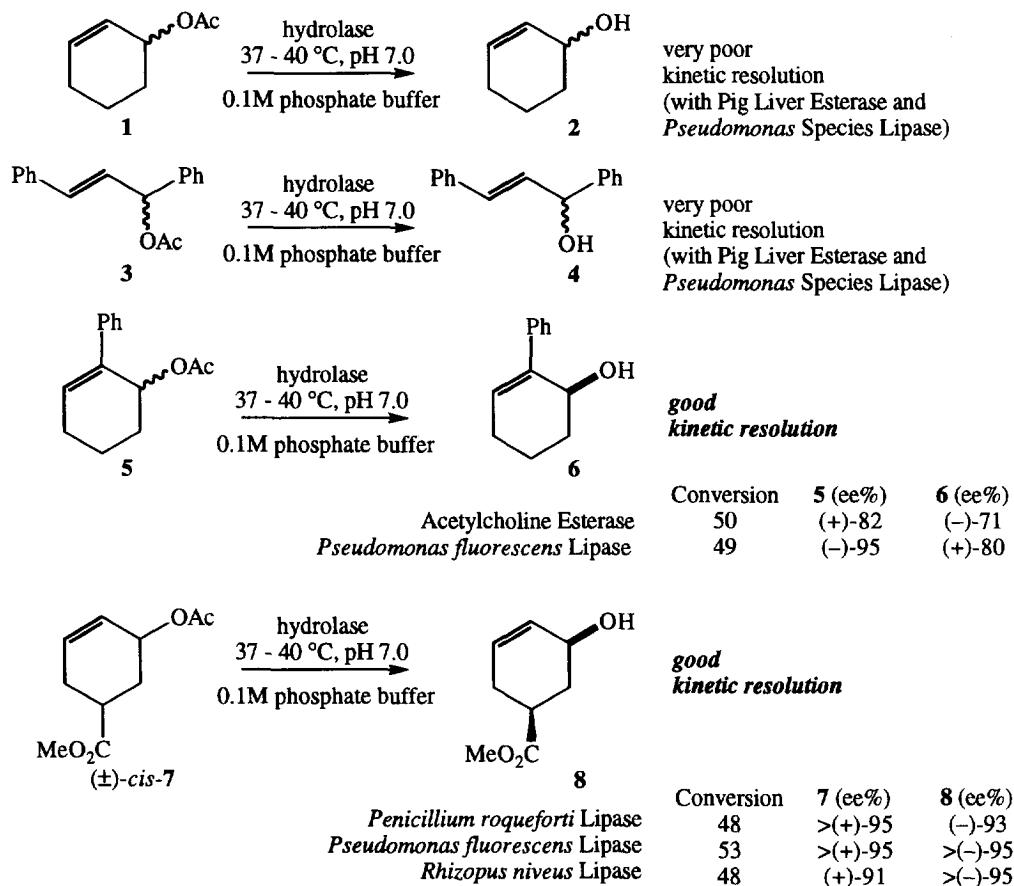
There are three considerations that need to be addressed in order for this approach to dynamic resolution to be successful. Firstly, an enzyme capable of effecting a simple kinetic resolution needs to be identified.

Secondly, a catalyst capable of effecting *in situ* racemisation needs to be identified. *Thirdly, and most significantly, a system needs to be found where the performance of the enzyme and the palladium catalyst are not adversely affected by the presence of each other.*

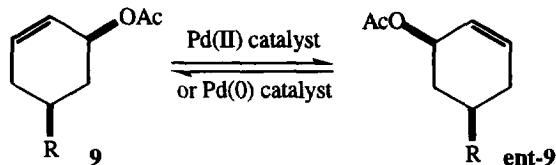
Herein we report such a system, although not with cyclohexenyl acetate itself as the substrate.

We have examined the enzyme catalysed hydrolysis of several racemic allyl acetates. Like other researchers,² we were unable to identify an enzyme that was able to provide a satisfactory kinetic resolution of cyclohexenyl acetate **1**. Similarly, a suitable enzyme has not yet been identified for the allyl acetate **3**.

However, the enantioselective conversion of the phenyl-substituted cyclohexenyl acetate **5**³ into the alcohol **6** was achieved much more easily.⁴ Additionally, the substituted cyclohexenyl acetate **7**⁵ was employed as a substrate, and converted into the enantiomerically enriched alcohol **8**.⁴



In the absence of palladium, the enantioselectivity of the process for the substituted cyclohexenyl acetates is encouraging. However, to obtain high enantioselectivities and high conversions, an *in situ* racemisation of the allyl acetate needs to be achieved. In principle, either palladium(0)⁶ or palladium(II)⁷ catalysed processes could be employed.



We chose to use palladium(II) catalysis for the racemisation reaction, since in this mechanism, the acetate never leaves the substrate. However, for a palladium(0) catalysed racemisation, an intermediate allylpalladium complex can be attacked by nucleophiles other than acetate.

The substrates **5** and **7** (which gave good results in the simple kinetic resolution) were subjected to enzymatic hydrolysis reactions in the presence of a palladium(II) catalyst. The results are presented in Tables 1 and 2.

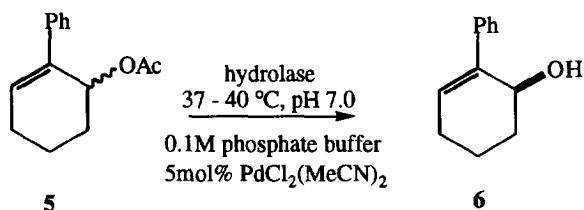


Table 1. Enzyme/Palladium catalysed hydrolysis of acetate 5

Enzyme	Reaction Time (days)	Conversion (%) ^a	Alcohol 6 E.e. (%) ^b	Yield (%)
ACE	23	68	(-)-85	47
PFL	19	96	(+)-96	81

^a Determined by either ¹H NMR analysis or GC analysis.

^b Determined by chiral HPLC analysis

PFL = *Pseudomonas fluorescens* Lipase, ACE = Acetylcholine Esterase

The reaction proceeded to approximately 50% conversion within 2 days, but the rate of conversion slowed down after this. We therefore assume that the racemisation is the rate-limiting step. It is known that a substituent in the 2-position of an allyl acetate dramatically reduces the rate at which the 1,3-acetate shift takes place.⁸

Nevertheless, using PFL as the enzyme in the presence of a palladium catalyst has achieved the desired goal - the dynamic resolution of the acetate.

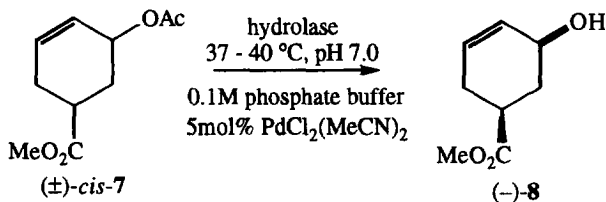


Table 2. Enzyme/Palladium catalysed hydrolysis of acetate 7

Enzyme (Lipase used)	Reaction Time (days)	Conversion (%) ^a	E.e. (%) Alcohol 8 ^b	E.e. (%) Acetate 7 ^c
<i>P. roqueforti</i>	12	31	78	4
<i>P. fluorescens</i>	11	>98 (87) ^d	50	-
<i>R. niveus</i>	14	28	85	47
<i>C. viscosum</i>	9	47	30	44

^a Determined by GC analysis

^b Determined by chiral HPLC analysis

^c Determined by chiral shift ¹H NMR, with Eu(hfc)₃

^d Isolated yield

Although with *P. roqueforti* lipase, the conversion is low, it is encouraging that the enantiomeric excess of the acetate starting material remains low, suggesting that the palladium catalyst is functioning, but that it is also reducing the activity of the enzyme. Using *P. fluorescens* lipase, the desired dynamic resolution has been achieved, although the ee of the product is lower than in the enzyme only system. *R. niveus* lipase and *C. viscosum* lipase both appear to have rendered the palladium catalyst inactive - immobilisation strategies are being considered to overcome this problem.

In conclusion, we have demonstrated that several enzymes are able to catalyse the enantioselective hydrolysis of acetates in the presence of a palladium catalyst. With the combination of PFL and a palladium catalyst, a dynamic resolution of substrates 5 and 7 has been demonstrated.

We envision many possibilities for dynamic resolution based upon transition metal and enzyme combinations, and we are currently working on extensions of this methodology to other systems.

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References and Notes:

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