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Selective Racemisation of Esters: Relevance to Enzymatic Hydrolysis Reactions

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Abstract: The selective racemisation of an ester in the presence of the corresponding acid has been demonstrated. Phenyl esters are significantly more prone to racemisation than methyl esters. Preliminary results indicate the utility of these results in enzyme-catalysed hydrolysis reactions.

The importance of the racemisation of organic compounds is now well recognised, and has recently been reviewed.[1] Dynamic resolution reactions couple the *in situ* racemisation of a starting material with a kinetic resolution, thereby providing a route for the conversion of both enantiomers of starting material into one enantiomer of product.[2] However, there is an important caveat: The reaction product must be essentially inert to racemisation.

For these reasons, we have been interested in the racemisation of 2-phenylpropionic acid **1** and ester derivatives. Non-nucleophilic bases have proved to be the most convenient, since they avoid any hydrolysis or attack on the carbonyl group. We were pleased to find that in competition reactions, the methyl ester **2** was almost fully racemised (10% ee) by DBU (1,8-diaza[5.4.0]undec-7-ene) in 7 hours, whereas the acid **1** retained most of its enantiomeric excess (92% ee).[3] We rationalise that the acid is slower to racemise since as a carboxylate salt (formed in the presence of the base) the enolate is harder to form.

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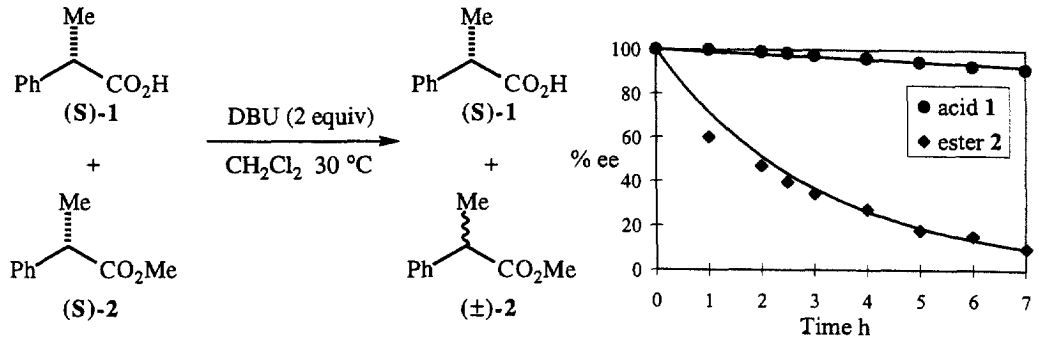
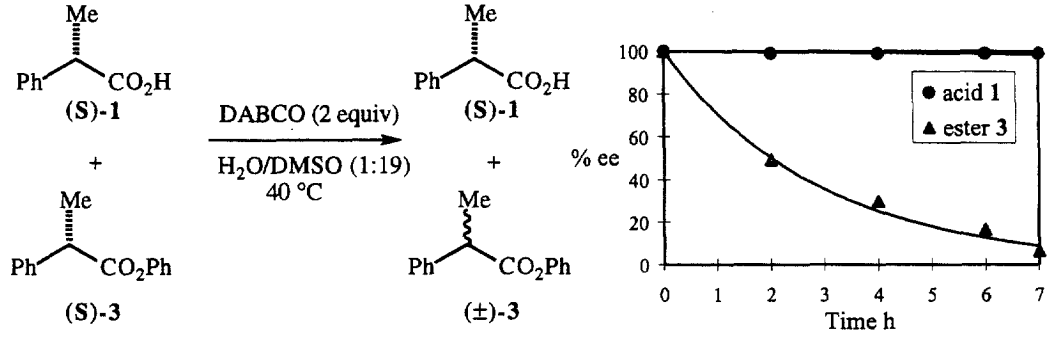
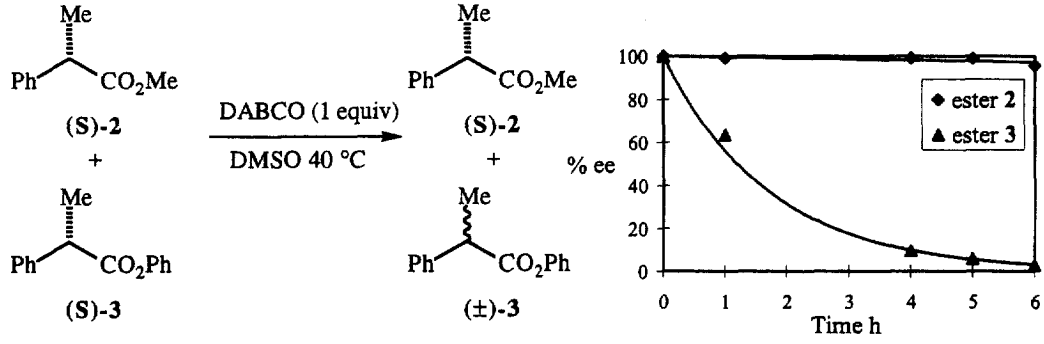


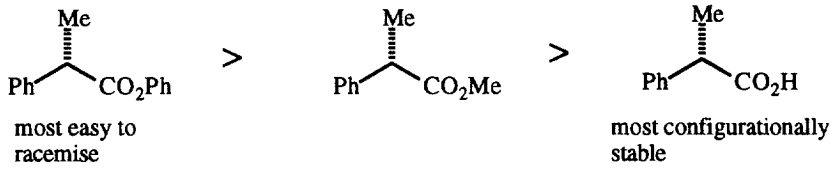
In the search for milder bases to racemise methyl ester **2**, we found that although the weaker base DABCO (1,4-diazabicyclo[2.2.2]octane) was not able to racemise the methyl ester, the phenyl ester **3** was racemised fairly easily.[4] In a competition experiment between phenyl ester **3** and carboxylic acid **1**, the ester was racemised much more quickly than the acid. The choice of solvent was important, since the phenyl ester racemised more slowly in dichloromethane (still 89% ee after 24hr).[5]



These observations demonstrate that the phenyl ester is more prone to racemisation than the methyl ester, and this was shown by conducting a competition experiment between the two esters. The difference in racemisation rate is quite dramatic, and may be rationalised by simple resonance effects. The oxygen lone pair in the methyl ester loses conjugation upon enolate formation, whereas the lone pair in the phenyl ester still has aromatic conjugation.



The relative rates of racemisation can be summarised as follows;

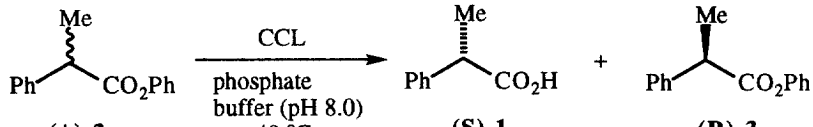


most easy to racemise

most configurationally stable

This hierarchy for the racemisation of (S)-2-phenylpropionic acid and its ester derivatives is of relevance to enzymatic kinetic resolution procedures, which could then be converted into dynamic resolution reactions. Indeed dynamic resolutions have been performed in the hydrolysis of particular ester substrates including imino esters,[6] thioesters[7] and esters of the anti-inflammatory agent Ketorolac.[8] Presumably the difference in the rate of racemisation in these cases may also be due to electronic effects (as well as to phase partioning).

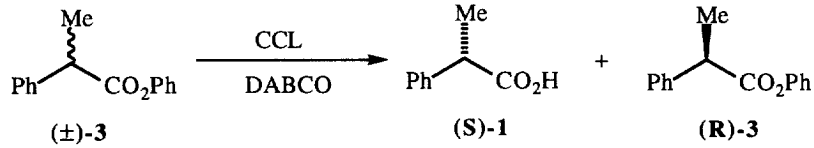
We found that racemic **1** underwent a convenient kinetic resolution using various enzymes, including Candida Cylindracea Lipase (CCL).[9]



(±)-3 | (S)-1 | (R)-3

48% conversion | 94% ee | 90% ee

In the presence of the DABCO, the enzyme catalysed hydrolysis is still selective, and the starting material is still undergoing racemisation, both good hallmarks for an efficient dynamic kinetic resolution, although to date we have been unsuccessful in effecting both very high enantioselectivity with very high conversion in a single operation.[10] The CLEC (cross-linked enzyme crystal) enzyme for CCL was also found to be effective.[11]



(±)-3 | (S)-1 | (R)-3

	37% conversion	99% ee	39% ee
Using CLEC-17	43% conversion	80% ee	3% ee

We are undertaking further study to try to identify suitable conditions where the enhanced racemisation tendancies of phenyl esters can be incorporated into dynamic resolution reactions using hydrolytic enzymes. Since the rate of racemisation of the phenyl ester is greater than the rate of racemisation of the methyl ester, transesterification reactions under dynamic resolution conditions may also be considered.

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References and Notes:

1 Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, P. M.; Bruggnink, A; Zwanenburg, B., *Tetrahedron* **1997**, *53*, 9417-9476; Koh, J. H.; Jeong, H. M.; Park, J., *Tetrahedron Lett.* **1998**, *39*, 5545-5548.

2 For a review on dynamic resolution, see: Caddick, S.; Jenkins, K., *Chem. Soc. Rev.*, **1996**, 447-456.

3 Enantiomeric exces was determined by chiral HPLC. Acid **1**, using Chiralcel OD column (98:1.98:0.02 hexane, iPrOH:HCO_2H), 1ml/min, 11.2 min (R) and 12.6 min (S), ester **2** using Chiralcel OJ column (90:10 hexane:iPrOH), 1ml/min, 9.6 min (R) and 7.8 min (S) and ester **3** using Chiralpak AD column (95:5 hexane:iPrOH) 1ml/min, 6.4 min (S) and 5.8 min (R).

4 DABCO also racemises the corresponding vinyl ester (the ee falls to 12.5% ee after 24h in acetonitrile at 40 °C). Both the phenyl ester **3** and the corresponding nitrophenyl ester undergo slow racemisation with triethylamine or trioctylamine (60-70% ee after 24h)

5 Phenyl ester **3** could be racemised by itself in the presence of sub-stoichiometric quantities of DABCO (0.2 equivalents in DMSO at 40 °C for 24 h reduced the ee to 28%)

6 Parmar, V. S.; Singh, A.; Bisht, K. S.; Kumar, N.; Belokon, Y. N.; Kochetkov, K. A.; Ikonnikov, N. S.; Orlava, S. A.; Tararov, V. I.; Saveleva, T. F., *J. Org. Chem.* **1996**, *61*, 1223-1227.

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9 Gu, Q-M.; Chen, C-S.; Sih, C. J., *Tetrahedron Lett.*, **1986**, *27*, 1763-1766. HLE (Hog Liver Esterase) also gave good kinetic resolution results

10 This research group has previously reported successful enzyme-catalysed dynamic resolution reactions for other substrates. Dinh, P.M.; Howarth, J. A.; Hudnott, A. R.; Harris, W.; Williams, J. M. J., *Tetrahedron Lett.*, **1996**, *37*, 7623-7626. Allen, J. V.; Williams, J. M. J. *Tetrahedron Lett.*, **1996**, *37*, 1859-1862

11 CLEC enzymes were purchased from Altus Biologics Inc. 40 Allston St. Cambridge, MA 02139-4211, USA..