Dynamic kinetic resolution in the hydrolysis of an α-bromo ester

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Bromide can be employed to racemise an α-bromo ester more rapidly than the corresponding acid (carboxylate), and this rate difference has been employed as the basis of a dynamic kinetic resolution reaction.

Dynamic kinetic resolution strategies have been enjoying increasing attention in the last few years.[1] For an ideal dynamic kinetic resolution, the two enantiomers of starting material must react at very different rates. Furthermore, whilst the starting material enantiomers must be in equilibrium, the product must be essentially inert to racemisation. Recent work from this group has described racemisation procedures which strongly favour the starting material.[2]

Herein we report that the racemisation of the α-bromo ester **1** is significantly faster than for the corresponding α-bromo acid **2** under appropriate conditions. Thus, competition experiments between enantiomerically enriched ester **1** and acid **2** show that the ester racemises more quickly (Scheme 1 and Table 1).†

Scheme 1

Table 1 Racemisation of ester **1** and acid **2** with bromides

		Ee of **1** (%)		Ee of **2** (%)	
Bromide	*t*/h	Initial	Final	Initial	Final
KBr	18	38	28	34	34
CsBr	18	80	77	35	35
Bu_4NBr[a]	4	80	0	64	35
Bu_4PBr	18	80	4	33	31
$C_{16}H_{33}P^+Ph_3Br^-$	6	55	5	38	36
Wang polymer-$CH_2P^+Ph_3Br^-$	2	43	0.5	61	58

[a] Performed in H_2O–MeOH (5:1).

We rationalise that the racemisation of the ester **2** occurs *via* S_N2 displacement by bromide (Fig. 1), which is enhanced by the neighbouring carbonyl function (π* C=O). However, under the reaction conditions, the carboxylic acid will be deprotonated, and the carboxylate is less willing to assist the adjacent S_N2

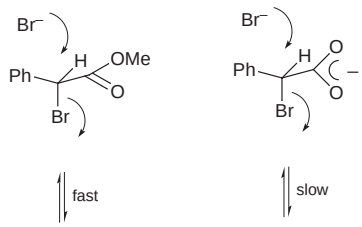
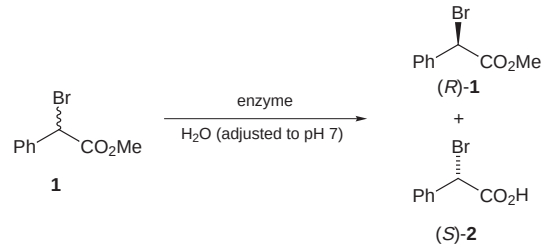


Fig. 1 Preferential racemisation by SN2 bromide displacement of an α-bromo ester.

process. We have not ruled out the possibility that racemisation occurs by simple enolisation, but the racemisation of the ester is not qualitatively dependent on pH (5–8)

The preferred sources of bromide were quaternary ammonium bromides and quaternary phosphonium bromide. In particular, the phosphonium salt produced by heating brominated Wang resin with PPh_3 in toluene for 10 h provided a particularly convenient bromide source.[3] Simple salts such as KBr were significantly less effective for the racemisation of either ester or acid.

We chose to use an enzymatic procedure for the selective hydrolysis of the bromo ester, which has some literature precedent.[4] Thus, ester **1** was hydrolysed by various enzymes in water, using a autotitrater to maintain a constant pH (7.0). A representative selection of these enzymes in a simple kinetic resolution reactions are shown in Scheme 2 and Table 2.



Scheme 2

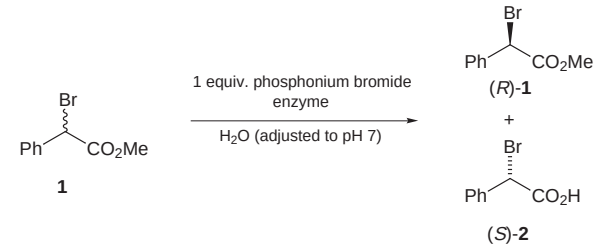
Table 2 Kinetic resolution of ester **1**[a]

Enzyme	*t*/h	Conversion (%)	Ee of **1** (%)	Ee of **2** (%)
CRL[b]	18	42	69	74
Altus 17[c]	2.5	47	81	80
Altus 20[d]	144	32	51	65

[a] Performed in H_2O. [b] *Candida rugosa* lipase. [c] CLEC-CRL - cross linked enzyme crystal (*Candida rugosa* lipase) [d] CLEC-PCL - cross linked enzyme crystal (*Pseudomonas cepacia* lipase). In this case the *R* enantiomer of acid was formed preferentially.

We favoured the commercially available cross-linked enzyme crystal, Altus 17 (*Candida rugosa* lipase, cross-linked),[5] which provided a fast reaction with reasonably good enantioselectivity in the resolution.

By combining the selective racemisation procedure with simple kinetic resolution, we proceeded to investigate the dynamic kinetic resolution reaction (Scheme 3 and Table 3). Gratifyingly, the combination of the Wang phosphonium



Scheme 3

Table 3 Dynamic kinetic resolution of ester **1**

Bromide	*t*/h	Yield of **2** (%)[a]	Ee of **1** (%)	Ee of **2** (%)
Bu_4PBr	6	26 (30)[b]	26	22
$C_{16}H_{33}P^+Ph_3Br^-$	7	65 (70)	6	68
Wang polymer-$CH_2P^+Ph_3Br^-$	4.5	78 (80)	26	79

[a] Isolated yields. Figures in parentheses are conversions. [b] Performed in H_2O–MeOH (5 : 1).

bromide with Altus-17 afforded an effective dynamic resolution procedure. Thus at 80% conversion, the product **2** was obtained with good enantioselectivity (79% ee, essentially the same as for the simple kinetic resolution). The starting material, although not racemic, was clearly undergoing slow racemisation under the reaction conditions. Presumably the larger phosphonium salts (R^1 = $C_{16}H_{33}$) and the immobilised phosphonium salts are unable to interfere with the immobilised enzyme, which is beneficial in an effective dynamic resolution where both the enzyme and bromide source must co-exist.

In conclusion, we have shown that an α-bromo ester can be successfully racemised in the presence of an α-bromo acid (carboxylate). This provides the basis for a dynamic kinetic resolution procedure using a combination of a hydrolytic enzyme with a source of bromide. Further work extending the range of substrates will shortly be underway.

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Notes and references

† Enantiomeric excess was determined by chiral HPLC. Chiralcel OD, hexane–Pr^iOH–formic acid (240:10:1), 1 ml min^{-1}, methyl ester (**1**): 5.6 min (*R*) and 6.2 min (*S*), acid (**2**): 9.4 min (*R*) and 11.7 min (*S*).

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2 P. M. Dinh, J. A. Howarth, A. R. Hudnott, W. Harris and J. M. J. Williams, *Tetrahedron Lett*., 1996, **37**, 7623; J. V. Allen and J. M. J. Williams, *Tetrahedron Lett*., 1996, **37**, 1859.
3 Brominated Wang resin contains a benzyl bromide function, and was purchased from Novo Biochem. See also; I. Hughes, *Tetrahedron Lett*., 1996, **37**, 7595.
4 For examples, see; P. Kalariitis, R. W. Regenye, J. J. Partridge and D. L. Coffen, *J. Org. Chem*., 1990, **55**, 812; G. Kirchner. M. P. Scollar and A. M. Klibanov, *J. Am. Chem. Soc*., 1985, **107**, 7072; S. K. Dahod, Eur. Pat., 1988, EP257716.
5 CLEC enzymes were purchased from Altus Biologics Inc., 40 Allston St., Cambridge, MA 02139-4211, USA.

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