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Enantiomerically pure *N*-aryl-β-amino alcohols by enzymatic resolution

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Abstract

N-Aryl-β-amino acetates, obtained by opening epoxides with aromatic amines followed by acetylation of the hydroxyl group, were resolved using crude pig liver esterase (PLE) enzyme in DMSO in high enantiomeric excess.

Enantiomerically pure β-amino alcohols are an important class of organic compounds which have found much use in asymmetric synthesis[1–4] and medicinal chemistry.[5] The most common method for synthesis of this class of compounds is via reduction of optically active α-amino acids.[6] Thus, the availability of α-amino acids becomes a limiting factor in the synthesis of these amino alcohols. This prompted organic chemists to develop a more flexible approach where optically active amino alcohols were synthesized by opening epoxides with amines using chiral Lewis acids; however, so far not much success has been achieved with this approach.[7] As part of our program towards the synthesis of β-amino alcohols via enantioselective epoxide opening with amines, we discovered that $Cu(OTf)_2$ and $Sn(OTf)_2$ can efficiently catalyze epoxide opening reactions with aromatic amines.[8] Since we too could not obtain much success (in terms of enantiomeric excesses) in epoxide opening reactions with amines where chiral ligands were complexed with these metal salts, we directed our attention towards an enzymatic approach to the synthesis of enantiopure β-amino alcohols. The kinetic resolution of racemic acetates with pig liver esterase (PLE) enzyme has been very well studied.[9,10] Although a variety of substrates have been resolved using PLE enzyme, the resolution of (±)-β-amino acetates, to the best of our knowledge, has not been reported.[11] In this paper, we report our findings in this direction.

A variety of (±)-β-amino acetates were synthesized from corresponding amino alcohols[8] which, in turn, were obtained by epoxide opening reactions with amines. The amino acetates were treated with crude PLE enzyme obtained[12] from fresh pig liver at pH 8.0 (KH_2PO_4/K_2HPO_4; 15 mL aq. buffer) in DMSO (2.5 mL) at 25°C and the reactions were monitored by TLC. After approximately 50% hydrolysis (by TLC), the reaction was stopped and the products were isolated. The absolute stereochemistry of

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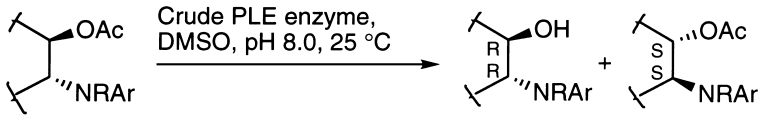
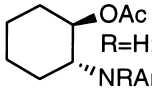
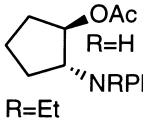
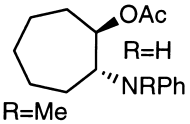
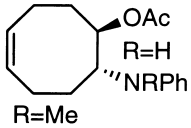
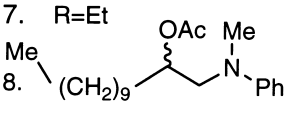
Table 1
Enantiomerically pure *N*-aryl-β-amino alcohols by kinetic resolution of (±)-amino acetates with crude PLE enzyme in DMSO at room temperature



Entry	Amino acetate (±)	Time	Amino alcohol Yield[a]	% ee[b]	Amino acetate Yield[a]	% ee[c]	E[d]
1.	 R=H; Ar=Ph	7 h	48	>99	50	91	>637
2.	R=Me; Ar=Ph	5 h	47	>99	51	80[b]	>477
3.	R=H; Ar=C_6H_4-*m*-Br	4 h	38	>99	61	57	>425
4.	R=H; Ar=C_6H_4-*p*-Cl	4.5 h	46	>99	49	96	>989
5.	R=H; Ar=C_6H_4-*p*-NO_2	15 h	32	94	63	57	57
6.	R=H; Ar=C_6H_4-*p*-OMe	5 h	52	79	46	97	39
7.	R=H; Ar=C_6H_4-*o*-Me	32 h	37	73	56	42	10
8.	R=H; Ar=β-naphthyl	7 h	34	>99	62	52	>335
9.	R=Et; Ar=Ph	12 h	32	95	51	51	65
10.	 R=H	3 h	60	65	40	87	13
11.	R=Et	3.5 h	50	52	48	68	6
12.	 R=H	7 h	45	92	52	99	126
13.	R=Me	21 h	33	94	64	68	67
14.	R=Et	21 h	38	>99	55	70	>419
15.	 R=H	21 h	34	89	52	57	22
16.	R=Me	12 h	25	>99	50	39	>292
17.	R=Et	240 h	25	>99	73	37	>295
18.		50 h	46	39	53	33	3

[a]Isolated yield. [b]%ee was determined by derivatizing the -OH group with Mosher acid chloride and running high field ^{1}H NMR spectra. [c]%ee was based on specific rotation of the corresponding amino alcohols. [d]Enantiomeric ratio (E) was calculated according to Sih equation.[13]

amino alcohols for entries 1 and 2 (Table 1) was established by comparing their sign of rotation with that of literature values.[7] The absolute stereochemistry of other amino alcohols was assigned with the above analogy.

In most cases, except for 5-membered amino acetate and acyclic terminal amino acetate, we obtained very high enantioselectivity (up to 99% enantiomeric excess) in the hydrolysis reaction (Table 1). The cases in which we obtained lower enantioselectivity were due to over hydrolysis and the enantiomeric excess can be improved by optimizing the conditions. The reaction was also tried in other solvents such as

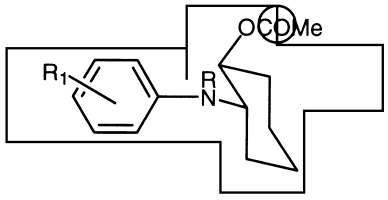


Figure 1.

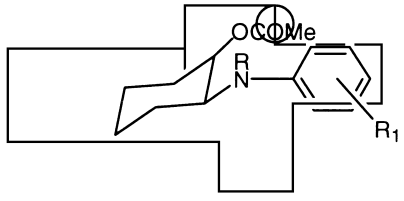


Figure 2.

DMF, MeOH, EtOH, hexane, acetone and ether,[14] but only DMSO gave the maximum enantioselectivity. The unusual aspect of this kinetic resolution was that it worked only when an aromatic group was present on the 'N' atom of the amino group. The enzymatic hydrolysis reaction failed in the case of *N*-butyl and *N*-benzyl substrates. This was confirmed from the results of the hydrolysis reaction of a mixture of *N*-phenyl and *N*-benzyl substrates, where only the former was hydrolyzed and the latter remained intact. This kind of result, to the best of our knowledge, is quite unprecedented in kinetic resolutions using crude PLE enzyme.

The kinetic resolution using PLE enzyme in the above reaction could be explained using the cubic active site model proposed by Jones and co-workers.[15] The catalytically important region which is denoted by a circle is a serine moiety which initiates the acetate hydrolysis. The model has two hydrophobic sites, one large on the left and one small on the right (Figs. 1 and 2). The hydrolysis will proceed only if the acetate is in the proximity of the serine moiety. Fig. 1 depicts the favorable binding mode for the (*R*,*R*)-amino acetate–enzyme complex where a large aromatic ring is in the large hydrophobic pocket. It is this mode which gives (*R*,*R*)-β-amino alcohols. The other binding mode (Fig. 2) where the aromatic ring is in the small pocket is less favored because the size of the pocket is small, thus (*S*,*S*)-β-amino acetate remains unhydrolyzed. It was observed that if the aromatic ring is *ortho*-substituted, the hydrolysis is very slow and the enantiomeric excesses are not very high. This could be because the *ortho*-substituted aromatic ring was unable to fit comfortably even in the large pocket, thus making the hydrolysis reaction less selective. *Meta*- and *para*-substituted aromatic rings did not create much steric hindrance in the large hydrophobic pocket. Although some rationale has been drawn from these models, there are several aspects of the reaction left unclear relating to the specificity of enzymes involved in the hydrolysis reactions.

In conclusion, we have synthesized a variety of enantiomerically pure *N*-aryl-β-amino alcohols which should find a use in organic synthesis.

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