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Kinetic resolution of cyanohydrins via enantioselective acylation catalyzed by lipase PS-30

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ABSTRACT

By using lipase PS-30 as catalyst, the kinetic resolution of a series of racemic cyanohydrins has been achieved via enantioselective acylation. The values of kinetic enantiomeric ratio (*E*) reached up to 314. Substituent effect is also briefly discussed.

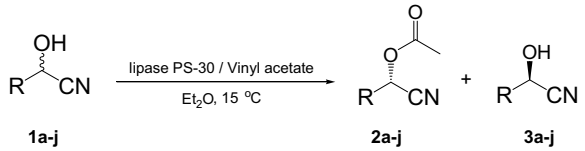
Enantiomerically pure (or enriched) cyanohydrins are versatile synthetic intermediates as they bear a hydroxyl group and a cyano group on one chiral carbon. They therefore provide a wide space for transformation into a large number of chiral molecules, which are important in the synthesis of biologically active molecules. Asymmetric formation of cyanohydrins has been an extensively investigated topic and several excellent reviews have appeared.[1] The methods for their formation can roughly be divided into three major categories: (1) hydrocyanation of aldehydes or ketones catalyzed by chemical catalyst, (2) hydrocyanation of aldehydes or ketones catalyzed by biological catalyst, and (3) enantioselective acylation or hydrolytic deacylation of racemic cyanohydrins or racemic cyanohydrin esters catalyzed by esterase or lipase, namely, simple kinetic resolution (KR) and dynamic kinetic resolution (DKR).

In the KR, a cyanohydrin racemate is treated by an acylating reagent in the presence of a lipase or an esterase to enantioselectively obtain an acylated enantiomer and an unreacted enantiomer,[2] or alternatively, an acylated racemic cyanohydrin racemate is enantioselectively hydrolyzed in the presence of a lipase or an esterase to give a hydrolyzed enantiomer and an unreacted enantiomer.[2b,3] The theoretical yield of this method is 50% and, in the ideal cases, both of the two enantiomers can be obtained simultaneously in high ee values.

As a continuation of our previous investigation of asymmetric synthesis of cyanohydrin catalyzed by plant originated catalysts,[4] we are now undertaking a study on the stereoselective formation of cyanohydrins by alternative methods. Here we report our KR results.

Cyanohydrin racemate was treated with vinyl acetate in the presence of lipase PS-30 (Amano) in diethyl ether to afford the (*S*)-cyanohydrin acetates and the unreacted (*R*)-cyanohydrin (Scheme 1). After the reaction proceeded by about 50%, the reaction was stopped and worked up for enantiomeric excess (ee) value analysis. The kinetic enantiomeric ratio (*E*) was calculated based on the measured ee values according to the equation defined in Ref. 5.

Table 1 summarizes the results. As can be seen from the data in Table 1, the ee values can be altered by adjusting the conversion through changing the reaction time to obtain the desired product with high ee value and reasonable yield. Among the observed ten substrates, seven (entries 1, 2, 3, 5, 6, 9, and 10) gave satisfactory *E* values, which are close to or higher than 100. According to Schneider et al.,[3a] values of *E* >50 are sufficient for the production



1a-j 2a-j 3a-j

Scheme 1.

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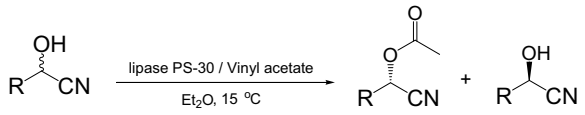
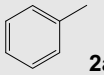
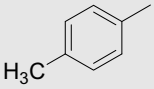
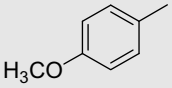
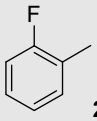
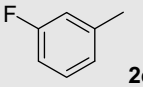
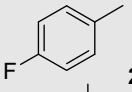
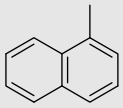
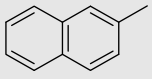
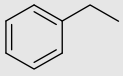
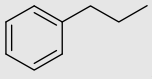
Table 1
Stereoselective acetylation of cyanohydrins **1a–j** with vinyl acetate in diethyl ether at 15 °C catalyzed by lipase PS-30



1a-j **2a-j** **3a-j**

Entry	R	ee_E (**2**)[a] (%)	ee_A (**3**)[b] (%)	E[c]	C[c] (%)	Reaction time (h)
1	 **2a**	98.3	71.1	249	42	24
2	 **2b**	98.3	48.6	191	33	23.5
3	 **2c**	98.7	47.1	244	32	29
4	 **2d**	94.3	31.3	46	25	25
5	 **2e**	98.6	47.8	228	33	27
6	 **2f**	92.8	93.6	94	50	50
7	 **2g**	87.2	36.5	21	30	25
8	 **2h**	72.8	82.3	17	54	24
9	 **2i**	94.1	82.6	85	47	20
10	 **2j**	98.4	80.7	314	45	24

[a] ee_E stands for enantiomeric excess of cyanohydrin acetate of the fast reacted enantiomer of the cyanohydrin. Analysis was performed on Chiralcel OJ-H or OD-H column with hexane/*i*PrOH in varying ratios to afford ee values.

[b] ee_A stands for enantiomeric excess of the slow reacted enantiomer of the cyanohydrin, which was obtained after the cyanohydrin was converted into the corresponding acetate (but into its propionate for **3g** and **3h** for HPLC baseline separation) then subjected to chiral HPLC analysis on Chiralcel OD-H column with hexane/*i*PrOH in varying ratios.

[c] $E = \ln[1 - C(1 + ee_E)]/\ln[1 - C(1 - ee_E)]$, where $C = ee_E/(ee_E + ee_A)$ as defined in Ref. 5.

of the desired cyanohydrin acetates in good chemical yield and enantiomeric purity. Data in Table 1 show that the bulky aryl group (entries 7 and 8) and the aryl group bearing a strong electronegative substituent (fluorine) (entries 4 and 6) decrease the *E* values remarkably probably due to their weaker interaction with the enzyme. However, fluorine substituted on *meta* position of the phenyl group (entry 5) appears to be of not much influence. 4-F- (entry 6) substitution in the benzene ring requires considerably longer reaction time (50 h) to achieve about 50% conversion. Differing from the aromatic cyanohydrins in Table 1, compounds **2i** and **2j** (entries 9 and 10) are aliphatic cyanohydrins with phenyl group substituted on the β or Y carbon atom, which also gave high *E* values.

Configuration assignment of the KR products was made by comparing the observed optical rotation with those reported in the literatures[2i,4a,6–8,2c] (for details, see Table 2 in Supplementary data). As a result, the acetates have an *S* configuration, while the unreacted cyanohydrins have an *R* configuration.

In conclusion, we have achieved the kinetic resolution of ten racemic cyanohydrins via enantioselective acylation by using lipase PS-30 as the catalyst. Majority of the substrates gave *E* values close to or higher than 100.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.090.

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