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Highly efficient dynamic kinetic resolution of secondary aromatic alcohols with low-cost and easily available acid resins as racemization catalysts

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ABSTRACT

A new and efficient dynamic kinetic resolution (DKR) process of secondary aromatic alcohols was developed with acid resins as racemization catalysts. Acid resin CD8604 was shown to have excellent racemization activity and good biocompatibility. When employing CD8604 and complex acyl donors as racemization catalyst and acyl donor, respectively, enantiomerically pure aromatic acetate was obtained with excellent yield and ee values through the DKR process. It is noteworthy that the system could be reused more than 10 times with little loss of yield and ee value.

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Dynamic kinetic resolution (DKR) is a kinetic resolution (KR) coupled with an in situ racemization of the slow-reacting substrate,[1,2] which could surpass the limitation of KR and increase the theoretical maximum yield up to 100%. For a successful DKR process, a highly selective KR of racemic mixture and an efficient racemization of unwanted enantiomer are fundamentally required.[3,4] So far, a large number of enzymes could reach the necessary selectivity of KR, while mainly two kinds of racemization catalysts were found successfully applicable in the DKR of *sec*-alcohols. The mostly reported racemization catalysts for the DKR of alcohols were transition metal catalysts,[5,6] mainly Pentaphenylcyclopentadienyl ruthenium complexes, which achieved the racemization by oxidations and reductions.[7] High ee value and excellent yield of the product often could be obtained by using this kind of racemization catalysts and lipase.[8,9] But high cost of the ruthenium complexes and sometimes requiring rigorous reaction conditions may prevent them from large-scale application.[10,11] Acid zeolite was another kind of racemization catalysts, but most of the results were only moderate. It is usually very hard to obtain both high yield and ee value of product. And byproducts of alkene were usually accompanied due to the high reaction temperature of 60 °C, thus leading to the decrease of yield.[12,13,15] Acid resins have been proven as excellent racemization catalysts in previous Letters and can be commercially available at low cost.[13,14] However, their application to DKR of *sec*-alcohols was rarely reported. In this research, acid resin with highly efficient racemization activity was screened and applied to the DKR of secondary aromatic alcohols successfully.

Several acid resins based on polyacrylate (Table 1, entries 1 and 2) and styrene–divinylbenzene copolymer (Table 1, entries 3–7) and containing either weak carboxylic acid groups (Table 1, entries 1 and 2) or strong sulfonic acid groups (Table 1, entries 3–7) were screened for their racemization activity to (*S*)-1-phenylethanol (Table 1). Two kinds of acid resins (CD550 and CD8604) showed high efficiency in the racemization of (*S*)-1-phenylethanol: the substrate was almost completely racemized in 6.5 h at 40 °C and no styrene was detected by gas chromatography under this reaction condition. It was found that a good racemization catalyst of acid resin required both strong acid group and abundant pore structure. Strong acid group could make the racemization of the substrates possible, and abundant pore structure could make the acid sites more accessible. Moreover, 1-phenylethanol acetate, the product in the DKR, would not be racemized under this condition (Table 1, entries 8 and 9). All these results showed that these two acid resins had great potential application in the DKR of *sec*-alcohols. CD8604 was chosen as the racemization catalyst in the following experiments for its higher racemization activity.

Then, CD8604 was used in the DKR of 1-phenylethanol (shown in Scheme 1) together with lipase Novozym435 at 40 °C by using vinyl acetate as an acyl donor and toluene as a solvent. The reaction can proceed smoothly with high yield, but the ee_p value of (*R*)-1-phenylethanol acetate was extremely low (Table 2, entry 1). Since the acid resin could not racemize the product, it could be reasonably presumed that the low ee_p was due to the acid resin-catalyzed transesterification of 1-phenylethanol. It was proven that the conversion of resin-catalyzed transesterification of 1-phenylethanol with vinyl acetate as the acyl donor reached above 70% while the ee_p was zero after 24 h's reaction. Further experiment showed that the ee_p would be higher if isopropenyl acetate was used as the acyl donor (Table 2, entry 2). Therefore, changing the acyl donor may be an effective method to increase the selectivity of the DKR.

According to previous Letter, if bulkier acyl-transfer reagents, such as vinyl butyrate and vinyl octanoate were used in the DKR

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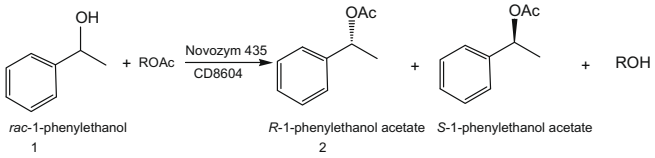
Table 1
Catalytic activity of resins in racemization of (*S*)-1-phenylethanol and (*R*)-1-phenylethanol acetate

Entry[a]	Resin[c]	Acid group	BET surface area (m^2/g)	BJH desorption average pore diameter (nm)	Reaction time (h)	$ee_{alcohol}$ (%)
1	D113	–COOH	1.40	41.0	48	>99
2	116	–COOH	2.18	3.07	48	>99
3	CD550	$-SO_3H$	31.15	35.7	6.5	16.3
4	CD8604	$-SO_3H$	31.46	39.4	6.5	12.5
5	001*7	$-SO_3H$	~0	<0.35	48	60.4
6	001*8	$-SO_3H$	1.71	<0.35	48	58.3
7	001*10	$-SO_3H$	0.26	<0.35	48	81.8
8[b]	CD550	$-SO_3H$	31.15	35.7	6.5	>99[d]
9[b]	CD8604	$-SO_3H$	31.46	39.4	6.5	>99[d]

[a] Reaction conditions: 2 mL toluene, 80 mg resin, 118 mmol/L (*S*)-1-phenylethanol at 40 °C under stirring.
[b] Reaction conditions: 2 mL toluene, 80 mg resin, 100 mmol/L (*R*)-1-phenylethanol acetate at 40 °C under stirring.
[c] Acid resins were commercially available from Zhejiang Zhengguang Industrial Co., Ltd.
[d] ee_{ester}.



Scheme 1. The dynamic kinetic resolution of 1-phenylethanol by acid resin and lipase coupling catalysis.

Table 2
The DKR of 1-phenylethanol catalyzed by CD8604 and Novozym435 with different acyl donors[a]

Entry	Acyl donor	Time (h)	Yield (%)	ee_P (%)
1	Vinyl acetate	3	>99	24.2
2	Isopropenyl acetate	3	>99	31.1
3	3-Chlorophenyl acetate	3	94.3	82.1
4	4-Chlorophenyl acetate	3	92.6	71.0
5	2,3-Dichlorophenyl acetate	3	>99	70.9
6	2,4-Dichlorophenyl acetate	3	>99	66.0
7	2,6-Dichlorophenyl acetate	24	>99	28.3
8	2,4,5-Trichlorophenyl acetate	3	92.0	91.7
9	2,4,6-Trichlorophenyl acetate	3	98.2	68.4
10	4-Methoxybenzyl acetate	24	77.2	88.8
11	4-Nitrophenyl acetate	3	95.4	52.9
12	1,2-Diacetoxybenzene	3	96.2	93.2
13	1,3-Diacetoxybenzene	24	>99	95.8
14	1,4-Diacetoxybenzene	3	>99	80.5
15	3,5-Dimethyl phenyl acetate	24	>99	54.4

[a] Reaction conditions: 2 mL toluene, 20 mg/mL resin, 10 mg/mL Novozym435, 100 mmol/L 1-phenylethanol, 3 equiv acyl donor at 40 °C under stirring.

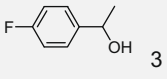
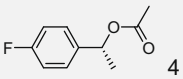
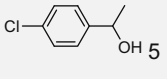
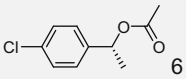
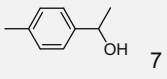
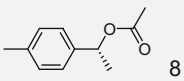
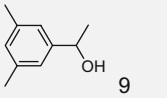
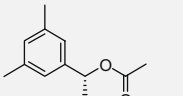
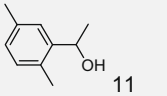
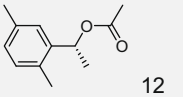
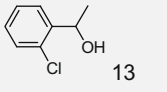
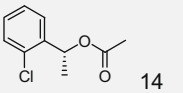
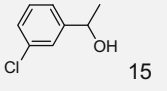
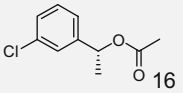
process, the ee_p would be increased.[15] Moreover, using 4-chlorophenyl acetate instead of common acyl donors could help to stop the side-reaction in ruthenium–enzyme catalyzed the DKR of 1-phenylethanol, and increased the yield and the ee_p.[16] So it was reasonable that complex acyl donor might help to inhibit or decrease the acid resin-catalyzed transesterification. The strategy is to change the alcohol part of the acyl donor. Then a series of phenyl acetate derivatives were synthesized and investigated for increasing the ee_p. Before the DKR of 1-phenylethanol with different acyl donors, the KR with these acyl donors were studied first. Despite the different reaction rate, it was pleased that complex acyl donors did not affect the enantioselectivity of Novozym435 (E >200) at all.

Later on, the DKR of 1-phenylethanol with different acyl donors was studied and the results are summarized in Table 2. It was shown that the ee_p was greatly improved by using complex acyl donors. When 1,3-diacetoxybenzene was used as the acyl donor, good yield (>99%) and high ee value of product (95.8%) were obtained (Table 2, entry 13). Generally speaking, the acyl donors with electron-donating groups on the benzene ring gave higher ee values than those with electron-attracting groups, but longer reaction time was needed. Resin-catalyzed transesterifications with different acyl donors were also investigated and the experiment results indicated that complex acyl donors could slow down the transesterification rate. For instance, the conversion of resin-catalyzed transesterification of 1-phenylethanol with 1,3-diacetoxybenzene as acyl donor decreased to below 5% while the ee_p was zero after 24 h's reaction. The results were in good agreement with those of DKR with different acyl donors. Therefore, the selectivity of the DKR could be successfully enhanced by using more complex acyl donors to inhibit the acid resin-catalyzed transesterification.

To expand the application area of the results, several substrates with different substitution groups on its benzene ring were tested with vinyl acetate. To our disappointment, none of the ee_P values could exceed 50%. Considering the good performance in DKR of 1-phenylethanol, 1,3-diacetoxybenzene was selected as the acyl donor for expectation of better results and the results are summarized in Table 3. It was shown that the reactions could proceed smoothly and give excellent yields and high ee_p values when electron-withdrawing group was substituted on its *para* position of the benzene ring (Table 3, entries 1 and 2). Moderate results were obtained when electron-donating group was substituted on its *para* position (Table 3, entry 3). But when groups were substituted on other position of the benzene ring, especially with electron-withdrawing group on its *ortho* and *meta* position (Table 3, entries 6 and 7), longer time was usually needed and unsatisfied results were obtained. A plausible explanation was that the acyl donor may inhibit the lipase-catalyzed transesterification more than the resin-catalyzed transesterification. And then we found that if 1,3-diacetoxybenzene was used as acyl donor, the lipase-catalyzed resolution of 1-(2-chlorophenyl)ethanol and 1-(3-chlorophenyl) ethanol at 40 °C should be performed at least 72 h to obtain 46.9% and 47.7% conversion, respectively. So it could be considered that 1,3-diacetoxybenzene was not the appropriate acyl donor for all of these substrates.

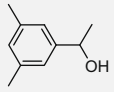
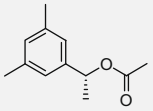
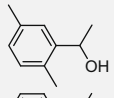
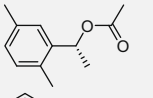
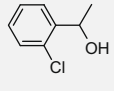
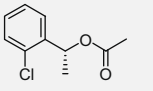
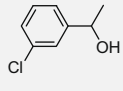
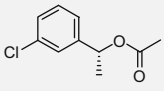
When substrate changed, the rate of lipase-catalyzed transesterification, resin-catalyzed transesterification, and racemization also changed, so did the appropriate acyl donor. Considering the slow reaction of these substrates, what we need should be an acyl donor that could accelerate the lipase-catalyzed transesterification reaction. Then, 4-chlorophenyl acetate was selected as a new acyl donor. It was exciting that all of the reactions were improved and the results are listed in Table 4. It was shown that the reaction could proceed more quickly and give excellent yields and high ee_p values when electron-donating groups were substituted on the benzene ring. But when electron-withdrawing groups were on its *ortho* or *meta* position, steric effect and electronic effect of the substituent would make combined effects on the lipase-cata-

Table 3
The DKR of various *sec*-alcohols with 1,3-diacetoxybenzene as acyl donor[a]

Entry	Substrate	Product	Time (h)	Yield (%)	ee_P (%)
1	 3	 4	24	>99	93.1
2	 5	 6	24	91.6	91.6
3	 7	 8	3	98.9	83.3
4	 9	 10	3	66.9	80.1
5	 11	 12	3	86.7	87.9
6	 13	 14	24	17.2	87.6
7	 15	 16	24	19.4	93.6

[a] Reaction conditions: 2 mL toluene, 20 mg/mL resin, 10 mg/mL Novozym435, 100 mmol/L substrate, 3 equiv acyl donor at 40 °C under stirring.

Table 4
The DKR of various *sec*-alcohols with 4-chlorophenyl acetate as acyl donor[a]

Entry	Substrate	Product	Time (h)	Yield (%)	ee_P (%)
1			3	>99	98.6
2			3	>98	94.7
3			24	61.6	97.7
4			24	91.5	70.8

[a] Reaction conditions: 2 mL toluene, 20 mg/mL resin, 10 mg/mL Novozym435, 100 mmol/L substrate, 3 equiv acyl donor at 40 °C under stirring.

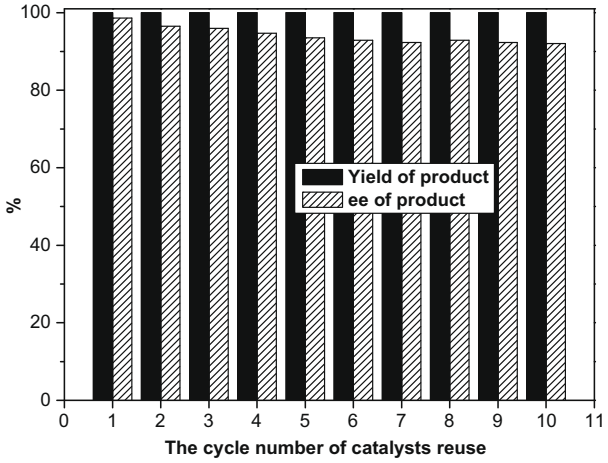


Figure 1. The repeated use of resin and lipase in the DKR of 1-(3,5-dimethylphenyl)ethanol with 4-chlorophenyl acetate as acyl donor (a, b). (a) Reaction condition was the same as in Table 4; (b) the resin and lipase were washed with toluene for five times before the next use.

lyzed transesterification reaction, thus only moderate yields were obtained.

To investigate the reusability of the resin–lipase coupled catalysis system, the repeated use of CD8604 and Novozym435 in the DKR of 1-(3,5-dimethylphenyl) ethanol with 4-chlorophenyl acetate as acyl donor was studied. As shown in Figure 1, after 10 cycles, the ee_p decreased a little (from 98.6% to 92%), while the yields were kept nearly unchanged (>99%). In a word, both resin and lipase had shown good operation stability, high efficiency, and great application potential.

In summary, a highly efficient DKR of secondary aromatic alcohols using acid resin as racemization catalysts coupled with enzymatic KR has been developed. During the process, acid resin CD8604 was found efficient and stable enough to be racemization catalyst. And using complex acyl donors instead of simple acyl donor to inhibit the acid resin-catalyzed transesterification could greatly increase the ee value of the product. This reaction system has been proved to be applicable for several substrates and also showed good operation stability and great potential application in industry. So a highly efficient way to enantiomerically pure substances indeed has been established.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, analytical methods and characterization data for chief compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.152.

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