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Efficient dynamic kinetic resolution of arylamines with Pd/layered double-hydroxide-dodecyl sulfate anion for racemization

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ABSTRACT

A novel and efficient racemization catalyst, Pd/layered double-hydroxide-dodecyl sulfate anion, was prepared and used in the dynamic kinetic resolution (DKR) of arylamines. The undesired enantiomer was completely racemized at 55 °C, allowing the catalyst to be compatible with biocatalysts. DKR proceeded smoothly and showed a broad substrate scope, with good conversion and high product enantiomeric excesses (ee_p). The system could be reused more than 30 times without loss of conversion and ee_p value.

Introduction

Enantiomerically pure arylamines are important intermediates in the synthesis of pharmaceuticals, fragrances, and agrochemicals. Of the conventional preparative methods, kinetic resolution (KR) is one of the most practical[1] because of its high selectivity, mild reaction conditions, and low waste. Its main drawback is that the maximum theoretical conversion of the method is only 50%. Dynamic kinetic resolution (DKR)[2,3] which combines KR with in situ racemization of the undesired enantiomer, has potential to overcome this problem and increase conversion to 100%. In a typical process involving amines, a highly selective KR catalyst, an efficient racemization catalyst, and compatibility between these catalysts are the basic requirements.[4,5] Many efficient KR catalysts have been developed, such as Novozym 435, which has been widely used in KR reactions of alcohols and amines; however, there is a need for further research into the preparation of efficient racemization catalysts. In recent years, there has been increased investigation into catalysts for DKR of chiral amines, including Ru complexes,[6] Raney Ni,[7] Pd nanoparticles,[8] and Pt microcapsules.[9] However, high yields and enantioselectivity generally require long reaction times at high reaction temperatures, and the results can be affected by the formation of ethylbenzene (ETB) as a by-product. DKR catalysts such as Pd/C[8a,b] and Pd/$BaSO_4$[8d] are only suitable for the preparation of a few optically active amines. These racemization catalysts also still have some drawbacks such as low catalytic efficiencies and poor selectivity. The compatibilities of the racemization catalysts with enzymes are also not ideal and the substrate scope of some catalysts is narrow.

Among these racemization catalysts, Pd nanoparticles are preferred. Although many Pd catalysts have been developed for DKR of amines, most of these suffer from the drawbacks mentioned above. Parvulescu et al.[8e] showed that a basic Pd/layered double-hydroxide (LDH) catalyst could be used to racemize arylamines. Recently, LDHs have received increasing attention because of their potential applications as basic supports for transition metals in various organic transformations. In this study, based on Parvulescu's work, we developed a new efficient catalyst, namely a dodecyl-sulfate anion (DS)-embedded-LDH-supported Pd (Pd/LDH-DS),[10] to build a successful DKR system for arylamines.

Parvulescu et al.[8d] suggested that in the DKR process, racemization occurs by dehydrogenation and hydrogenation, with ETB and amine or imine condensation products as potential side products (Fig. 1).

Results and discussion

From previous research, we know that the surface acidity or alkalinity[8e] and specific surface area of the catalyst can affect the racemization of the amines. We therefore designed various catalysts to study these properties. Compared with other Pd catalysts, Pd/LDH-DS showed much better results in the racemization of (*S*)-1-phenylethylamine (Table 1). After reaction for 15 h, the amine enantiomeric excess (ee_{amine}) reached 3% when Pd/LDH-DS was used as the racemization catalyst. The efficiency of Pd/LDH-DS was higher than those of other Pd catalysts, and less ETB was

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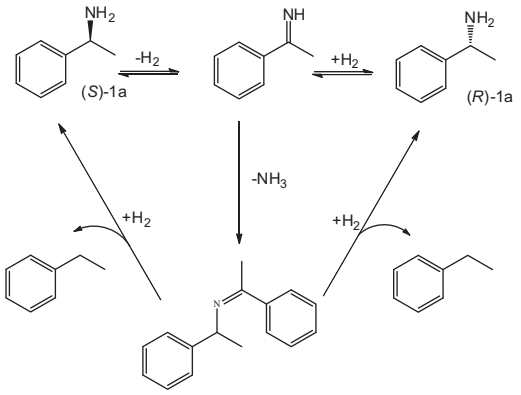


Figure 1. Mechanism of Pd/LDH-DS catalyzed racemization of (*S*)-1-phenylethylamine.

Table 1
Racemization of (*S*)-1-phenylethylamine over Pd catalysts

Entry	Catalyst	Specific surface area (m^2/g)	ee_{amine} (%)	$Sel._{ETB}$ (%)
1	Pd/C	55	60	15
2	$Pd/BaSO_4$	2.967	8	11
3	$Pd/CaCO_3$	0.945	10	12
4	Pd/AlO(OH)	9.872	44	12
5	$Pd/BaCO_3$	2.353	31	2
6	Pd/LDH[8e]	73	8	13
7	Pd/LDH-DS	69.389	3	2

Reaction conditions: 0.33 mmol of (*S*)-1-phenylethylamine, 4 ml of toluene, 40 mg of Pd catalysts, 55 °C, 15 h, 0.03 MPa H_2, catalyst loading 5 wt % Pd on support.

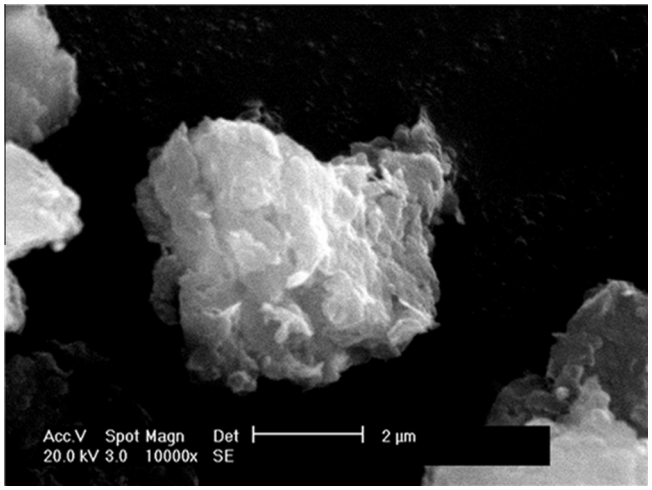


Figure 2. SEM image of Pd/LDH-DS.

detected after racemization, showing that the side reaction was effectively suppressed.

These results show that the new catalyst features several significant improvements. First, the alkaline environment prevents hydrogenolysis of C–N bonds on Pd,[11] so that side reactions are suppressed. Second, the intercalation of DS improves the lipophilicity of the catalyst,[10] making it easier for the substrate to react on the catalyst surface. Third, the intercalation of DS enlarges the surface area, and this improves the efficiency by adding more reaction sites. The SEM image (Fig. 2) shows that the catalyst has layered structure which increases its surface area. And in Figure 3, the curve of Pd/LDH-DS has three Pd crystal characteristic peaks

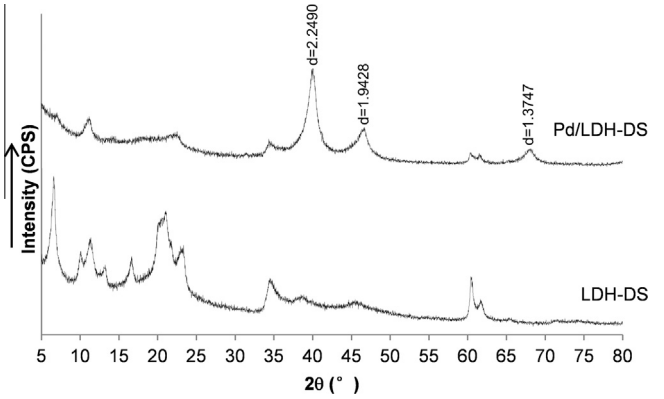


Figure 3. XRD pattern of Pd/LDH-DS.

($2\theta = 40.1°$, $2\theta = 46.6°$, $2\theta = 68.0°$), which do not exist in the curve of LDH-DS, indicating that Pd was successfully loaded on the LDH-DS surface.

In this study, a model reaction using Novozym 435 as the catalyst for enantioselective acylation, 1-phenylethylamine as the model substrate, 4-chlorophenyl valerate as an acyl donor for amine acylation, and toluene as the solvent was combined with the racemization catalyst Pd/LDH-DS to build a successful DKR system for 1-phenylethylamine.

As a lipase, the optimum temperature of Novozym 435 is low, such that high reaction temperatures may reduce its efficiency. However, the high catalytic efficiency of Pd/LDH-DS allows the reaction to be performed at low temperature. The optimal reaction temperatures for racemization using catalysts such as Ru complexes[6], $Pd/BaSO_4$,[8d] and $Pd/CaCO_3$[8d] are as high as 90 °C, and racemization using Pd/AlO(OH) requires a temperature of 70 °C. However, we achieved nearly 100% product *ee* (ee_p) at 100% conversion (Table 2, entry 1) at a lower temperature (55 °C), shows that the new racemization catalyst had better compatibility with the enzyme.

We then expanded the substrate scope to build successful DKR systems for other arylamines. The results are shown in Table 2.

The results in Table 2 show that DKR was successful with most arylamines using Pd/LDH-DS as the racemization catalyst. Quite a few of the reactions achieved nearly 100% ee_p at 100% conversion. From the results, we can also conclude that the reaction proceeded more efficiently when electron-donating groups were substituted on the benzene ring. When the substituents were electron-withdrawing groups, the conversion and ee_p values of the reaction were low (Table 2, entries 7–11).

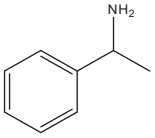
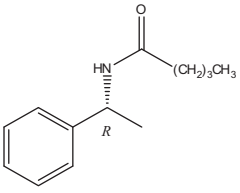
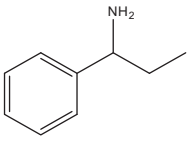
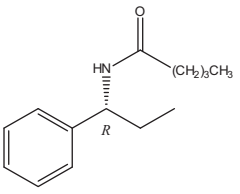
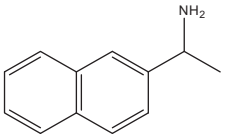
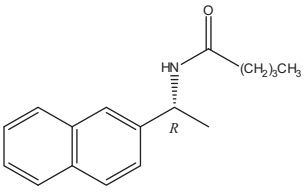
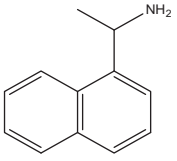
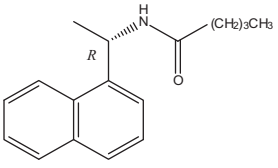
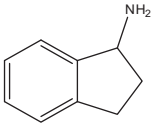
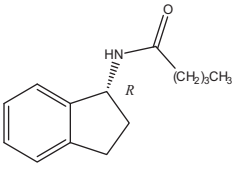
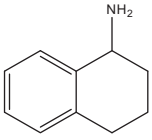
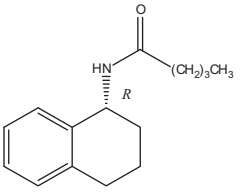
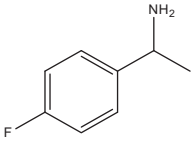
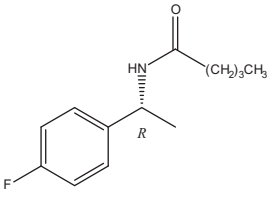
The ee_p values of some arylamines did not reach 100% during the DKR process. Decreased selectivity of the enzyme may be the reason for the reduced ee_p. The KR of the arylamines with 4-chlorophenyl valerate as an acyl donor was then investigated. The results in Table 3 show that ee_p values cannot reach 100% after reaction under the same condition, suggesting that the catalyst for the enantioselective acylation reaction, that is the lipase, was the reason for the decrease in ee_p values in DKR.

As a heterogeneous catalyst, Pd/LDH-DS can be easily separated from the system, and the reaction system showed good operational stability. The catalyst can be reused more than 30 times without any loss of conversion and ee_p value (Fig. 4). This reusability makes the catalyst suitable for the preparation of optically active amines.

Conclusions

In summary, an efficient heterogeneous catalyst, Pd/LDH-DS, was designed for racemization of arylamines, giving high ee_p

Table 2
The DKR of arylamines with long carbon-chain esters as acyl donor

Entry	Substrate	Product	ee_P (%)	Conv. (%)
1	 1a	 2a	>99	>99
2	 1b	 2b	>99	>99
3	 1c	 2c	>99	94
4	 1d	 2d	>99	89
5	 1e	 2e	>99	>99
6	 1f	 2f	>99	>99
7	 1g	 2g	88.2	98

(*continued on next page*)

Table 2 (*continued*)

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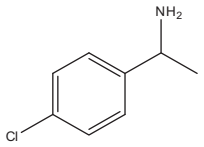
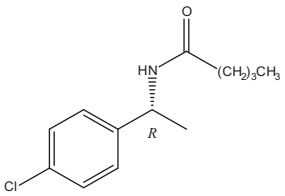
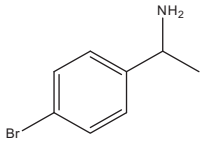
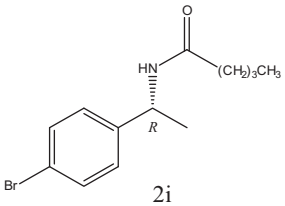
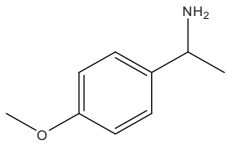
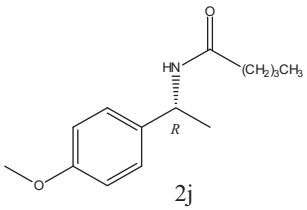
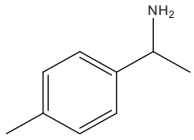
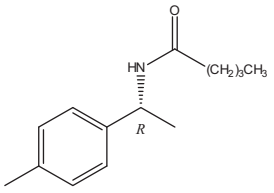
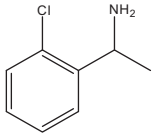
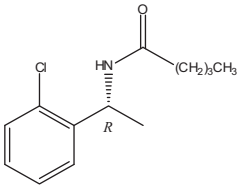
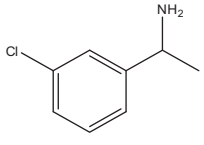
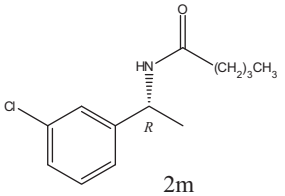
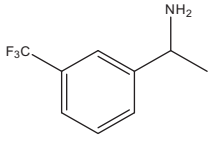
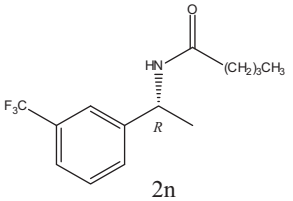
8	 1h	 2h	92.7	95
9	 1i	 2i	93	>99
10	 1j	 2j	95	>99
11	 1k	 2k	>99	>99
12	 1l	 2l	94.3	92.9
13	 1m	 2m	93.4	93
14	 1n	 2n	>99	>99

Table 2 (*continued*)

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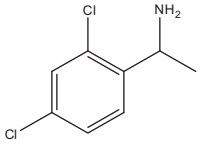
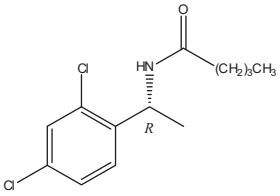
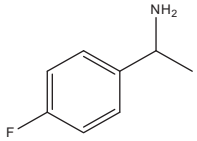
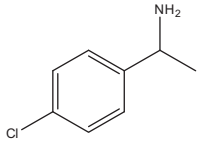
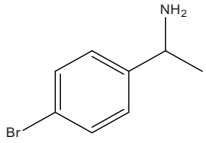
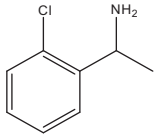
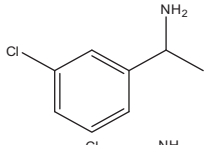
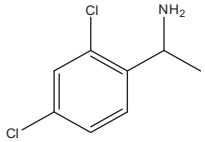
15	 1o	 2o	90.2	>99

Reaction condition: 4 ml of toluene, 0.33 mmol of 1-phenylethylamine, 0.35 mmol of 4-chlorophenyl valerate, 40 mg of Pd/LDH-DS, 100 mg of Novozym 435, 0.03 MPa H_2, 55 °C, rotation speed 200 r/min, 15 h for each reaction run.

Table 3
The KR of arylamines with 4-chlorophenyl valerate as acyl donor

Entry	Substrate	ee_p (%)	Yield (%)
1		>99	50
2		>99	50
3		92.7	53.5
4		94	51.2
5		92	53.5
6		88	54.1

KR reaction conditions: 4 ml of toluene, 0.33 mmol of 1-phenylethylamine, 0.35 mmol of 4-chlorophenyl valerate, 100 mg of Novozyym 435, 0.03 MPa H_2, 55 °C, rotation speed 200 r/min.

values and excellent conversions. The unwanted enantiomer could be completely racemized after a short reaction time of 15 h at a low reaction temperature of 55 °C, which is a sufficiently mild temperature for a lipase. Side reactions were suppressed, and DKR was successful for most arylamines using Pd/LDH-DS as the racemization catalyst. This system can be reused more than 30 times without any loss of conversion and ee_p value.

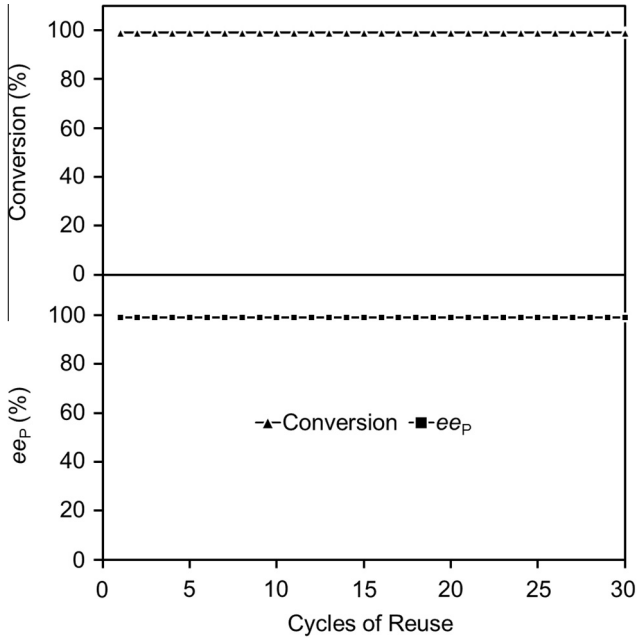


Figure 4. Catalyst reuse with 4-chlorophenyl valerate as acyl donor (▲ conversion, ■ ee_p).

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