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Dynamic kinetic resolution of amines by using palladium nanoparticles confined inside the cages of amine-modified MIL-101 and lipase

Sen Xu, Meng Wang, Bo Feng, Xinchen Han, Zijie Lan, Huajun Gu, Hexing Li, Hui Li *

The Education Ministry Key Lab of Resource Chemistry and Shanghai Key Laboratory of Rare Earth Functional Materials, Shanghai Normal University, Shanghai 200234, PR China

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ABSTRACT

Dynamic kinetic resolution (DKR) of amines is an important strategy for the synthesis of chiral drugs and their building blocks; however, improving the matchability of metal-catalyzed racemization and enzymatic resolution is still a task. In this paper, Pd nanoparticles (NPs) were encapsulated inside the cages of ethylenediamine-grafted MIL-101 (ED-MIL-101), giving highly efficient catalysts (Pd/ED-MIL-101) for the racemization of primary amines. The racemization can be combined with lipase-catalyzed resolution in a one-pot DKR of *rac*-1-phenylethylamine leading to optically pure product (>99% *ee* value) with an excellent conversion and selectivity up to 99% and 93%, respectively, superior to other catalysts, such as Pd/MIL-101, Pd/MCM-41 and commercially available Pd/C. Furthermore, the heterogeneous chemoenzymatic catalyst combination can be recovered and recycled 8 times without significant loss of efficiency. The enhance catalytic performances were found to depend on the amine modification of MIL-101 that not only endows the surface of its cages with basic property, but also enables efficiently confining Pd NPs in the cages. In addition, the matchability of such chemoenzymatic catalyst combination can be further enhanced by conducting the DKR process under microwave irradiation.

1. Introduction

There is an ever increasing requirement for chiral amines, primarily for use as pharmaceuticals, but also for use as important key intermediates in fine chemical and agrochemical industries [1]. Despite great achievements in catalytic asymmetric synthetic transformations [2–4], kinetic resolution (KR) of racemic starting materials is still the most common approach to obtaining enantiomerically pure amines in industrials [5]. The enzyme-aided KR is one of the most widely utilized methods for the synthesis of chiral amines [6]. However, the resolution process is generally limited to a maximum yield of 50%. The combination of KR and *in situ* racemization of the remaining enantiomer results in a dynamic kinetic resolution (DKR) process (Scheme 1), which is an option to tackle this problem. This modification increases the theoretical yield to 100% of a single enantiomer starting from a racemic mixture [7–11]. Furthermore, one-pot DKR that combining of racemization catalyst and enzyme into a single reaction vessel usually increases the profitability and efficiency of the process by reducing costs, time, as well as labor efforts [12]. In general, racemization of amines is difficult to achieve and requires harsh reaction conditions, resulting in the rate-determining racemization step in one-pot DKR process. To ensure the matchability of the racemization reaction with the enzyme-aided KR, a sufficiently high racemization rate is demanded for the continuous feed of the faster-reacting enantiomer to the enzyme catalyst. Several racemization methods have been developed using basic catalysts, enzymes, or transition-metal catalysts [13]. The former two kinds of racemization are relatively infrequent and thus, not applied in DKR process. In the development of one-pot DKR processes for amines, homogeneous Shvo-type ruthenium complexes played a key role. The most efficient DKR applications utilizing homogenous Ru-based racemization catalysts have been pioneered by the group of Bäckvall [14,15]. However, homogeneous transition-metal catalysis also presents a number of drawbacks, particularly including the catalyst reusability and the environmental pollution from heavy metallic ions [16,17]. The development of heterogeneous racemization catalysis system with high efficiency is preferred due to the easier work-up protocols, simple product isolation, as well as catalyst recycling [18]. The first example of heterogeneous DKR of amine was reported by Reetz and Schimossek using Pd/C for the racemization and lipase (CALB, Novozym® 435) for the enzymatic resolution [19]. This combination required long reaction time (8 days) to provide excellent *ee* value (99%) and moderate yield (75–77%) in the one-pot DKR of 1-phenylethylamine. Generally, the activity

* Corresponding author.
E-mail address: lihui@shnu.edu.cn (H. Li).

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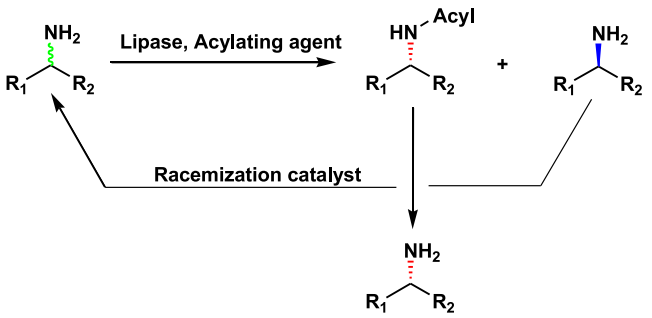
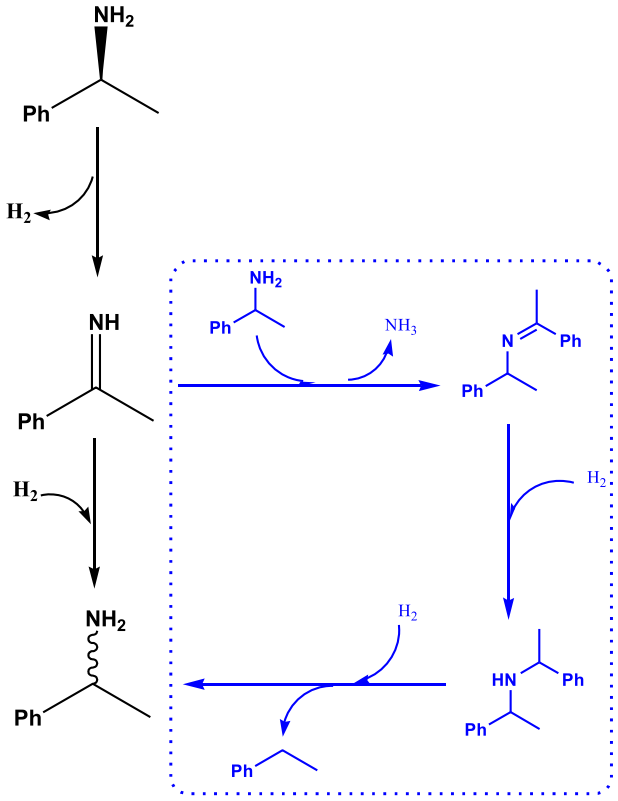


Scheme 1. DKR of *rac*-amine.

of Pd is primarily determined by its dispersion, thus the synthesis of Pd nanoparticles (NPs) on a few nanometer scale is of great important. Kim et al. [20] reported an improved process using a modified lipase-Pd combination, in which Pd NPs in the range of 2–3 nm entrapped in aluminum hydroxide [21], Pd/AlO(OH), was employed as the racemization catalyst. The racemization of (*S*)-1-phenylethylamine by Pd/AlO(OH) proceeded much more rapidly compared to the commercially available Pd/Al_2O_3, most likely because of the high dispersion of the metallic Pd active sites. The one-pot DKR of 1-phenylethylamine was done by the combination of Pd/AlO(OH) and CALB in the presence of molecular sieves, giving a good yield (92%) and a high optical purity (98% *ee*) at shorter reaction time (3 days) [20]. Jacobs [22] and De Vos [23] utilized $Pd/BaSO_4$ in combination with CALB for the DKR of 1-phenylethylamine, obtaining good conversion (91%) and selectivity (94%) with high *ee* value (99%) of the acetylated amine product within a more shorter reaction time (24 h). Another important aspect of one-pot DKR of amines is the control of selectivity towards the target products. Jacobs and De Vos found the main byproducts in amine racemization to be a result of competing condensation reactions to secondary amine and its subsequent hydrogenolysis to ethylbenzene (EB) (Scheme 2) [22,23]. Such side product formation could be strongly suppressed when alkaline earth salts were used as supports for Pd [22,23]. In their next work, Pd on amine-functionalized silica proved to be more selective for the racemization of 1-phenylethylamine relative to Pd on bare silica [24]. They demonstrated that the acid-base properties of the supports for Pd catalysts evidently influences the formation of by-products and should be modestly basic to enable suppress the formation of byproducts [24]. By incorporating alkalic salt, Jin et al. [25] prepared K_2CO_3-modified Pd catalysts, which could efficiently suppress side reactions during the racemization and thus enhance the yield in the DKR of 1-phenylethylamine in combination with Novozym® 435; however, their stability was unclear due to the lack of durability studies. Recently, several multifunctional hybrid materials containing Pd NPs loaded on basic support and enzymes were constructed, and served as catalysts for one-pot DKR of amines [26,27], whereas the stability or efficiency is still an open task. Despite these advances, one-pot DKR protocols with efficient catalysts would be highly desirable.

Presently, metal-organic frameworks (MOFs) have drawn tremendous attention owing to their abundant diversity in structure and composition and thus specific applications [28–30]. In the domain of catalysis, besides the well-demonstrated catalytic activity of pure MOFs, these materials are also attractive candidates for catalyst supports because of their unique porous features [31–33]. In previous work, we have used MIL-101 as support to encapsulate Pd NPs in its cages and applied the as-prepared Pd/MIL-101 for one-pot indole synthesis from 2-iodoaniline and phenylacetylene in aqueous media [34]. Our results exemplified the superiority of Pd/MIL-101 over other conventional Pd catalysts,



Scheme 2. Reaction mechanism for racemization of (*S*)-1-phenylethylamine.

both in terms of activity and durability. The enhanced catalytic performances of Pd/MIL-101 were found to depend on the specifical texture of MIL-101 matrix which impeded the agglomeration of Pd NPs while maintaining efficient substrate transport owing to the porous nature of the material. Additionally, Férey and coworkers conferred basic properties to MIL-101 by grafting amine groups onto the chromium(III) coordinatively unsaturated sites (CUSs) in their mesoporous cages and, then, used the resulting modified solid as a host for further loading of Pd NPs in the internal pores [35]. In the present work, Pd NPs were encapsulated inside the cages of both the bare and the the amine-grafted MIL-101 via a facile incipient wetting procedure followed by reduction with hydrogen, giving highly efficient racemization catalysts for primary amines. The racemization can be combined with enzymatic KR in a one-pot process leading to optically pure products from racemic amines, showing superior catalytic efficiency when compared to other catalysts, such as Pd/MCM-41 and commercial Pd/C. On the basis of various characterizations, the correlation of catalytic observations to the structural characteristics has been tentatively established, especially, getting an insight into the effect of amine modification of MOFs on catalytic performances.

2. Experimental section

2.1. Catalyst preparation

All of the chemicals used in this experiment were obtained from commercial sources and used without any other treatments. Novozym® 435 (immobilized lipase B from *Candida antarctica*), (±)-1-phenylethylamines, (*S*)-1-phenylethylamines, and 1%-Pd/C were purchased from Sigma-Aldrich Inc. (USA). Other reactants were purchased from Aladdin Industrial Co., Ltd. (Shanghai, China).

MIL-101 was synthesized following the method reported by Férey et al. [36]. Ethylenediamine (ED) grafted MIL-101 were