



Ionic liquid as a recyclable and efficient medium for lipase-catalyzed asymmetric cross aldol reaction



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ABSTRACT

PPL (lipase from porcine pancreas) was found to catalyze asymmetric cross aldol reactions of aromatic and heteroaromatic aldehydes with various ketones in ionic liquid ([BMIM][PF₆]) for the first time. Interestingly, PPL exhibited high catalytic activity and excellent stereoselectivity in this efficient and recyclable room temperature ionic liquid in the presence of moderate water, similar to the results obtained in organic solvents. High yields of up to 99%, excellent enantioselectivities of up to 90% ee, and good diastereoselectivities of up to >99:1 dr were achieved.

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1. Introduction

Room temperature ionic liquids (ILs) have been regarded as potentially attractive solvents in modern organic synthesis [1,2]. ILs have low vapour pressure, low flammability, high ionic conductivity and excellent chemical and thermal stability, and they are easily recycled [3,4]. Moreover, the unique and attractive physico-chemical properties of ILs, such as viscosity, polarity and solubility, can be designed by selecting the appropriate cation and anion. Thus, ILs have been widely used in synthesis and catalysis owing to these unique properties [5,6]. Many excellent reviews have also been published in the past decade [7,8]. In biocatalysis, ILs have been used as solvents or co-solvents for enzyme-catalyzed reactions in the past decade [9,10], and several biocatalytic reactions, such as oxidation [11], hydrolysis [12], polymerization [13] and transesterification [14,15], have been achieved in ILs. Russell and co-workers first reported the enzyme-catalyzed reaction in IL [BMIM][PF₆] for the synthesis of Z-aspartame in 2000 [16]. With the rapid development of biocatalysis in ILs, Rantwijk and Sheldon published an excellent comprehensive review on the various issues associated with biocatalysis in ILs in 2007 [17]. Recently, Goto and colleagues reviewed the activation and stabilization of enzymes in ILs [18]. Yang et al. researched the specific ion effects of ILs on

enzyme activity and stability [19]. Moreover, ILs have been used for the synthesis of sugar derivatives and other special compounds, owing to the strong dissolution power of ILs [20]. In addition to their uses as reaction solvents, ILs also have many other significant applications in biocatalysis and enzyme engineering. ILs can also be utilized as extraction solvents to stabilize and extract enzymes [21] and can incorporate and covalently modify some enzymes or modify the immobilized material of enzymes [22,23]. In fact, as excellent solvents for biocatalysis, ILs provide many advantages over conventional organic solvents, including high activity and selectivity and better stability as well as better recoverability and recyclability [24]. However, few reports regarding the biocatalytic promiscuity of ILs as solvents compare to conventional biocatalysis reactions in ILs exist [25]. Thus, the combination of ILs with more biocatalysis reactions remains an important challenge.

Biocatalysis, as an eco-friendly and sustainable methodology for organic synthesis due to its high efficiency, excellent selectivity and mild reaction conditions, is widely recognized as a practical alternative to traditional organic synthesis [26,27]. However, biocatalysts exhibit specific catalytic activity for distinctly different chemical transformation of natural or non-natural substrates [28,29]. This kind of catalytic promiscuity immensely broadens the application of biocatalysts and provides an available tool for organic synthesis. Recently, several elegant studies on enzymatic promiscuity have been reported, especially with regard to hydrolases that catalyze unconventional reactions, such as aldol reaction [30,31], Mannich reaction [32], Henry reaction [33],

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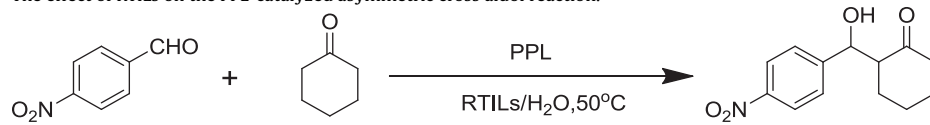
Michael additions [34,35], Ugi reaction [36] and three-component aza-Diels–Alder reaction [37]. Among these reactions, the powerful and atom economical asymmetric aldol reaction was frequently reported. Berglund and co-workers first demonstrated that wild-type lipase B from *Candida antarctica* (CAL-B) and Ser105Ala mutant CAL-B possess catalytic activity for aldol addition in cyclohexane [30]. Guan and co-workers exhibited several asymmetric aldol reactions catalyzed by different hydrolyases [38,39]. Lin and co-workers also reported an aldol condensation reaction catalyzed by acylase [40]. In our previous work, we demonstrated the first lipase-catalyzed asymmetric aldol reaction between acetone and 4-nitrobenzaldehyde greatly promoted by water [31]. However, almost all lipase-catalyzed aldol reactions were performed in the traditional organic solvents in which the enzymes were found to preserve their activities [41,42]. Hence, the search for more efficient media for biocatalytic asymmetric aldol reactions and other chemical transformations has become a considerable challenge. Recently, we found that the lipase-catalyzed stereoselective cross aldol reaction could be performed under solvent-free conditions. However, the enormously excessive ketones used as one of the substrates were not sufficiently cost-efficient [43]. An enzymatic aldol reaction in phosphate–citrate buffer was then attempted, only achieving an optimal enantioselectivity of 66% [44]. Based on these previous works, we continued to seek a more efficient biocatalytic route for asymmetric aldol reactions. We selected lipase from porcine pancreas (PPL) as a catalyst and utilized different ILs as the reaction medium in the presence of water. Surprising, we obtained similar results to those achieved in organic solvents. To the best of our knowledge, no other reports have demonstrated lipase-catalyzed asymmetric cross aldol reaction in ILs.

As a part of our continuing research on enzyme promiscuity, we wish to report a lipase-catalyzed the asymmetric cross aldol reaction between aromatic aldehydes and cyclic ketones under mild conditions using an IL medium. Interestingly, we also observed that the presence of water greatly promoted the catalytic activity and selectivity of PPL, which was consistent with our previous report [31]. High yields and good enantioselectivities and diastereoselectivities were also obtained while simultaneously investigating a wide variety of substrates. Meanwhile, the good reusability of ILs as the medium for PPL was also observed.

2. Results and discussion

It is well known that enzyme activity is strongly affected by reaction medium [42,45]. The feasibility of using ILs as efficient solvents for biocatalysis is well documented. However, ILs are rarely used in enzyme-catalyzed promiscuous reactions, such as aldol reaction. Therefore, we endeavored to find a more efficient medium combination with biocatalysis to meet the criteria of sustainable conscious development. Recently, we reported a lipase-catalyzed asymmetric aldol reaction in cyclohexanone, which is one of the substrates [43]. Although the reaction produced good yield and high selectivity, the excessive ketones were not sufficiently cost-efficient. Furthermore, we continued to attempt this enzymatic aldol reaction in phosphate–citrate buffer considering that lipase could maintain good activity in aqueous solvents [44]. However, the best enantioselectivity achieved was only 66% ee. Thus, we employed efficient ILs as the medium for the asymmetric aldol reaction catalyzed by PPL. The aldol reaction between 4-nitrobenzaldehyde and cyclohexanone was used as a model reaction. The initial experiments were performed in various pure ILs, including five tetrafluoroborate ILs (Table 1, entries 1–5), three hexafluorophosphate ILs (Table 1, entries 6–8) and two chiral ILs (Table 1, entries 9 and 10). Unfortunately, PPL showed extremely poor catalytic activity in all of the tested RTILs, as the products were difficult to detect by thin-layer chromatography (TLC) or high-performance liquid chromatography (HPLC). The most likely reason for such low yields was that the high viscosity of the IL systems might be limiting the mass transfer of substrates and products to and from the active site of the enzyme [46]. In principle, high viscosity could be overcome through the addition of small amounts of other solvents as additives to the IL medium. According to our previous research, water plays an important role in lipase-catalyzed promiscuous aldol reaction. For most reaction systems, a water content of approximately 10% has produced the best results. Thus, we added 10% water to the ILs to investigate the optimal IL for this reaction. To our surprise, when 10% water was added to the ILs, we detected the aldol product in several ILs. As shown in Table 1, PPL exhibited good catalytic activity in all tested ILs. For the most utilized ILs, both hexafluorophosphate and tetrafluoroborate ILs showed that ILs with shorter alkyl chains on their cations promoted better enzyme activity. The two chiral ILs also induced high activity, and 1-butyl-3-methylimidazolium

Table 1
The effect of RTILs on the PPL-catalyzed asymmetric cross aldol reaction.^a



Entry	RTILs	Catalyst	Yield% ^b	dr(anti/syn) ^b	ee%(anti) ^b
1	[EMIM][BF ₄]	PPL	80	80:20	57
2	[BMIM][BF ₄]	PPL	77	83:17	58
3	[HMIM][BF ₄]	PPL	71	79:21	53
4	[OMIM][BF ₄]	PPL	68	79:21	53
5	[EOMIM][BF ₄]	PPL	55	78:22	68
6	[BMIM][PF ₆]	PPL	63	86:14	80
7	[HMIM][PF ₆]	PPL	45	64:36	38
8	[OMIM][PF ₆]	PPL	39	85:15	77
9	[BMIM][LTar]	PPL	84	48:52	8
10	[BMIM][LLac]	PPL	76	47:53	3
11	[BMIM][PF ₆]	Bovine serum albumin (BSA)	5	–	–
12	[BMIM][PF ₆]	No enzyme	1	–	–
13	[BMIM][PF ₆]	Denatured PPL ^c	1	–	–

^a Conditions: 4-nitrobenzaldehyde (0.1 mmol), cyclohexanone (1.0 mmol), and PPL (10 mg) in RTILs with deionized water (10%, water/([BMIM][PF₆] + water), v/v) at 50 °C for 24 h.

^b Yield, ee, and dr were determined by HPLC using AD-H chiral column.

^c Pretreated with guanidine hydrochloride solution (6 mol/L).

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