Effects of Ionic Liquids for Lipase-Catalyzed Chiral 1,1`-binaphthyl-2-yl(phenyl)methanone *O*-acetyl Oxime Synthesis

Yongchang Zhou*[,a,b], Motohiro Takahashi[a,b], Naoto Aoyagi[a], Chunlei Li[a], Tatsuro Kijima[a] and Taeko Izumi[a]

[a]*Chemistry and Chemical Engineering, Graduate School of science and engineering, Yamagata University, Jonan 4-3-16, Yonezawa 992-8510, Japan*

[b]*Technology Department, Yonezawa Hamari Chemicals, Ltd. Hachimanpara 2-4300-18, Yonezawa 992-1128, Japan*

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Abstract: The resolution of 1,1'-binaphthyl-2-yl(phenyl)methanone O-acetyl oxime catalyzed by lipase in three different ionic liquids, 1-butyl-3-methylimidazolium hexafluoride-phosphate, [bmim][PF_6], 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim][BF_4] and N-butyl-pyridium hexafluorophosphate, [BuPy][PF_6] and organic solvents was studied. The lipase shows low activity in ionic liquids and organic solvent with ionic liquids as the additive, while the lipase coated with ionic liquids gives the best enantioselectivity as high as 95 %

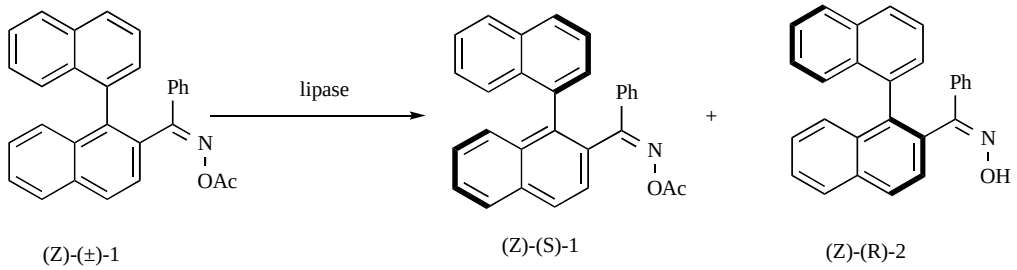
Keywords: Ionic liquids, Lipase-catalyzed, Chiral, O-acetyl oxime, Synthesis, Resolution.

INTRODUCTION

Room-temperature ionic liquids (RTILs) are known as green solvents used as reaction media in the separation process and electrochemistry and have attracted much attention in recent years because of their negligible vapor pressures. The application of ionic liquids on organic synthesis has been well documented in the reviews. Moreover, bio-catalysis in ionic liquids has also been investigated in many chemical reactions, such as transesterification, synthesis, conversion, alcoholysis, ammoniolysis, hydrolysis, epoxidation, resolution, oxidation, reduction, deracemization etc. Unlike the conventional organic solvents, the use of enzymes and substrates in ionic liquids can enhance the activity, selectivity, and stability of catalysts [1-11].

Lipase-catalyzed resolution of title compound has been reported for the synthesis of chiral oxime, but the enatioexcess is not good enough [12]. No research was conducted on the application of ionic liquids on this reaction. Therefore, it is necessary to study ionic liquids as alternative solvents for biotransformations using lipase for synthesis of chiral oxime 1 and 2.

In this paper, the effect of ionic liquids on lipase-catalyzed resolution of 1,1'-binaphthyl-2- yl(phenyl)methanone O-acetyl oxime was examined.



(Z)-(±)-1 (Z)-(S)-1 (Z)-(R)-2

Scheme 1. Lipase-catalyzed hydrolysis of (Z)-(±)-1

RESULTS AND DISCUSSION

We reported before that the optimal condition of enzyme-resolution was carried out at 60 ˚C, so we wanted to find a suitable ionic liquid, whose melting point is above 60 ˚C. N-butyl-pyridium hexafluoride phosphate ([Bupy][PF_6]) is the suitable one since its melting point is 68 ˚C.

The successful approach involved the enzymatic resolution of (±)-1 under hydrolysis condition, using lipase preparations according to Scheme **1**.

In order to compare the effect of ionic liquids, we do the lipase-catalyzed resolution with methyl tertiary-butyl ether (MTBE) as a solvent only at the very beginning. As shown in Table **1**, entry 1, 36% yield is obtained for (Z)-(R)-2 and 83% yield for enatio-excess (ee) after 22 h reaction.

*Address correspondence to this author at the Technology Department, Yonezawa Hamari Chemicals, Ltd. 2-4300-18, Hachimanpara, Yonezawa-city 992-1128, Yamagata, Japan; Tel: +81-238-28-3809;
E-mail:yczhou97@hotmail.com

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Table 1. Resolution of (Z)-(±)-1 by Lipase Catalyst

Entry[a]	Ionic liquids	Type [b]	Ratio [c]	Time (h)	Ketoxime		O-acetyl ketoxime		*E* [f]
					Yield % [d]	e.e. % [e]	Yield % [d]	e.e. % [e]	
1	-	MTBE	-	22	36	83	64	54	19
2	[BMIM][PF_6]	IL	-	24	1	-	99	0	-
3	[BMIM][PF_6]	additive	1:5	26	2	87	98	0	-
4	[HMIM][BF_4]	additive	1:1	27	7	93	93	8	3
5	[BuPy][Tf_2N]	additive	1:1	24	-	-	recovery	-	-
6	[Bupy][PF_6]	ILCE	1:10	32	12	91	88	7	23
7	[Bupy][PF_6]	ILCE	1:7.5	22	22	95	78	28	47
8	[Bupy][PF_6]	ILCE	1:7.5	117	31	82	69	40	15
9	[Bupy][PF_6]	ILCE	1:5	22	21	81	79	21	12
10	[Bupy][PF_6]	ILCE	1:2.5	22	9	57	91	3	4
11	[Bupy][PF_6]	ILCE	1:7.5	24	-	-	recovery	-	-

[a]Entry 1~10 were carried out by Novozym 435, entry 11 was carried out by Novozym 525L. The temperature of entry 8 was 55 ˚C, and the others were 60 ˚C.
[b]Additive means that the ionic liquids were added as co-solvent for lipase-catalyzed reaction; IL= ionic liquids; ILCE=ionic liquids coated Lipase.
[c]The ratio is the mass ratio of lipase and ionic liquids.
[d]Determined by internal standard method of HPLC using ODS-2(254nm, 0.8mL/min, $CH_3CN:H_2O$=8:2).
[e]Determined by HPLC using Chiralcel OG (254nm, 0.5mL/min, n-Hexane:IPA=8:2).
[f] $E = \ln\left[(ee_p(1-ee_S))/(ee_p+ee_S)\right]\Big/\ln\left[(ee_p(1+ee_S))/(ee_p+ee_S)\right]$ see ref [16].

Then the lipase-catalyzed hydrolysis of (Z)-(±)-1 is carried out in ionic liquids, but only 1 % of product of (Z)-(±)-2 is detected with no ee. The reason may be that the active point of the enzyme 435 was covered by ionic liquid.

Then ionic liquids as a co-solvent in the lipase-catalyzed hydrolysis of (Z)-(±)-1 are carried out for three kinds of ionic liquids. The results show that the reaction rate is very slow (entries 3 and 4) because of the high viscosity of ionic liquids, but it is still better than that of in ionic liquids only (entry 1). No reaction with [Bupy][Tf2N] as co-solvent (entry 5) proceed.

We investigated the activity of Ionic liquid-coated enzyme at different ratio of lipase and ionic liquids. The preparation of ionic liquids coated with Lipase/ enzyme (ILCE) is similar to known procedure [13]. It is said that the amount of ionic liquids varied depending upon the type of enzyme used, but it is preferably between 5 and 20 g per 1g of enzyme according to the reference [13].

We examine wide varieties of weight of ionic liquid per 1 g of enzyme as shown in Table **1**.

The ILCE-catalyzed hydrolysis of 1 proceeded with better enantioselectivity than that catalyzed by enzyme 435 only. The catalytic activity of ILCE varied with different weight ratio of lipase to ionic liquids. The activity is changing with the weight ratio from 1:2.5 to 1:10. The ratio of 1:7.5 give the most effective selectivity for hydrolysis (entries 6~10). Although the activity of hydrolysis reaction catalyzed by ILCE proceeded at a slight yield, the enantioselectivity is relatively high (95% ee, 22% yield, entry 7) as shown in Fig. (**1**).

When adding more ionic liquid into the 1 g of enzyme, for example, 10g of ionic liquid, the yield and enantioselectivity become relatively low (91% ee, 12% yield, entry 6). On the contrary, the added ionic liquid changes from 7.5 times to 5.0 and 2.5 times, the yield also becomes lower from 22% to 21% and 9% respectively (entries 7,9 and 10). Enantioselectivity has the same trend. The reason may be that when the weight of ionic liquid is 7.5 times greater than that of lipase, the activity point was covered by ionic liquid. The coating effect is insignificant if the weight of IL is less than 7.5 times in the case where Novozym 435 is used. If Novozym 525L is used instead, there is no reaction when IL is 7.5 times the weight of lipase.

The effect of temperature is also examined. The results show that the temperature can affect the yield and enantio-selectivity as shown in Fig. (**2**). The hydrolysis of (Z)-(±)-1 at 60 ˚C proceeded to 22 % yield after 22 h (entry 7), while for the reaction carried out at 55 ˚C, 31% yield was obtained after 117 h with enantio-selectivity of 82% (entry 8). When the reaction temperature is at 65 ˚C (at the melting point of ionic liquid), no reaction take place. So the [BuPy] anion is prohibited at liquid state for hydrolysis of substrate (Z)-(±)-1 (entries 5, 10 and 11).

CONCLUSION

In summary, both the added quantities of ionic liquid per weight of enzyme and reaction temperature have an effect on the ionic liquids coated lipase catalyzed hydrolysis reactions of O-acetyl binaphthyl ketoximes. The optimum condition is 7.5 g of ionic liquid per gram of enzyme 435, and the best reaction temperature is at 60 ˚C.

ACKNOWLEDGEMENT

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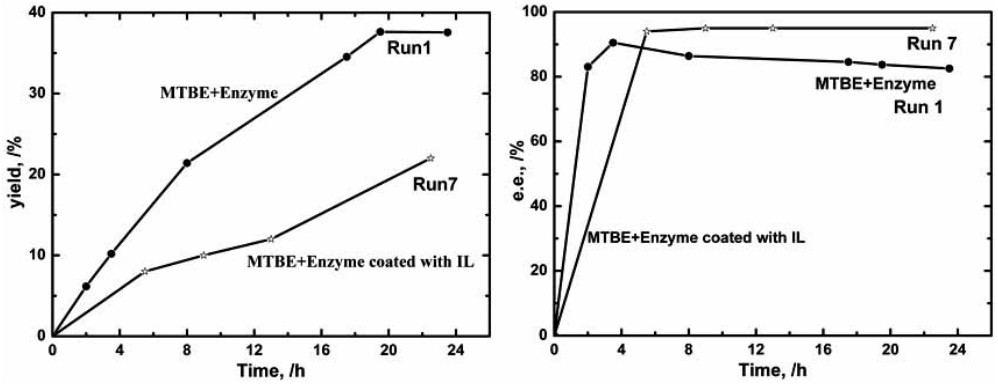


Fig. (1). The effect of ionic liquid on reactions.

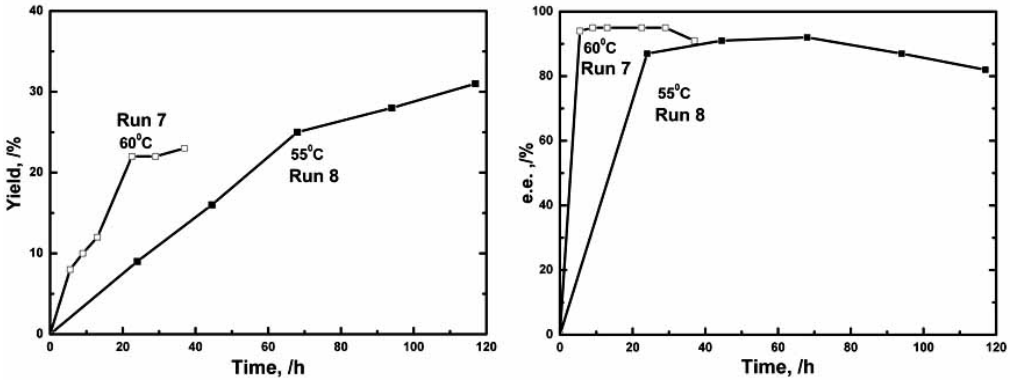
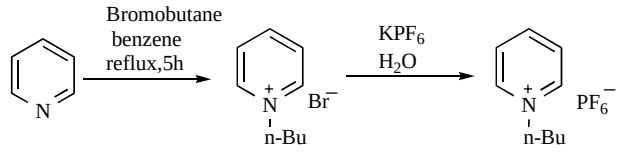


Fig. (2). The effect of temperature.

EXPERIMENTAL SECTION

Analytical-grade solvents and all chemicals were purchased from TCI Ltd. ^{1}H- and ^{13}C-NMR spectrum were measured with a JNM-ECS400 NMR spectrometer at 400 megahertz by using TMS as an internal standard ($CDCl_3$ as solvent). The melting point was determined by MFB-595-030G digital thermometer apparatus.

Racemic mixtures of 1,1'-binaphthyl-2-yl(phenyl)methanone O-acetyl oxime (Z)-(±)-1 were prepared according to known literature.4 The ionic liquids were synthesized by known scheme and the preparation of Ionic liquid-coated enzyme (ILCE) is illustrated as Scheme **2** [13].



Scheme 2. Synthesis of N-butylpyridinium hexafluorophosphate.

Synthesis of N-butylpyridinium hexafluorophosphate [14,15]

Mixtures of 1-bromobutane and pyridine in a molar ratio 1:1.1 were heated for 3 h at 150°C. The wax-like solids were recrystallized once in ether-ethanol (5:1) and three times in acetone and finally dried under vacuum for 48 h at 105°C. The resulting off-white solid was dissolved in H_2O and then cooled to 0°C in an ice bath. Potassium hexafluorophosphate (1.1 eq) was added slowly with rapid stirring. The resulting biphasic mixture was stirred for 2 h, then the upper layer, aqueous phase was decanted. The lower layer, ionic liquid phase was washed with water, and then extracted with dichloromethane (400 mL). The organic phase was dried over $MgSO_4$, filtered, the solvent was removed under reduced pressure and the ionic liquid dried for 6 h at 70°C in vacuum. 85% yield is obtained.

A colorless solids; mp 65-67 ˚C;^{1}H-NMR(400MHz, $CDCl_3$):δ0.94-0.98(3H,t,CH_3), 1.38-1.47(2H,m,CH_2), 2.00-2.08(2H,m,CH_2),4.99-5.03 (2H, t,N-CH_2), 8.15-8.23 (2H,m, ArH), 8.52-8.57(1H,d, ArH), 9.54-9.5(2H,d,ArH); ^{13}C-NMR (400MHz, $CDCl_3$): δ=13.6, 19.4, 33.9, 61.9, 128.6, 145.2

Preparation of IL-Coated Enzyme [13]

Ionic liquids [Bupy][PF_6] (1 g) was heated above 75 °C in a flask to get a liquid phase, and then a fixed quantity of lipase is added. The resulting heterogeneous solution is stirred for 30 min and then cooled to room temperature to yield ILCE in a solidified solution. The solid ILCE is crushed with a mortar and used for enzyme reaction.

General Procedure of Lipase Catalyzed Resolution

In a typical experiment, Novozym 435 (40 mg) and n-butanol (0.0672 mmol) were added to a solution of O-acetylketoxime (Z)-(±)-1 (28 mg, 0.0672 mmol)] and

2`-acetonaphthone (1.0 mg, standard substance) in tert-butyl methyl ether (6 mL) (MTBE). The resulting mixture was stirred at 60˚C. The reaction conversion and enantiomeric excess were determined by using HPLC (column, Daicel Chiralcel OG; mobile phase, hexane/2-propanol=50:1; flow rate, 0.58 mL/min; UV detection at 254 nm). Evalues were calculated according to the literature [16].

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