Efficient Lipase-catalyzed Enantioselective Acylation under Reduced Pressure Conditions in an Ionic Liquid Solvent System

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Lipase-catalyzed transesterification was demonstrated using methyl esters as acyl donors under reduced pressure in an ionic liquid ([bmim]PF_6) solvent system. The transesterification of 5-phenyl-1-penten-3-ol took place smoothly under reduced pressure at 27 hPa at 40 °C when methyl phenylthioacetate was used as acyl donor in [bmim]PF_6, and we succeeded in obtaining the corresponding acylated compound in optically pure form; this makes it possible to use lipase repeatedly because there was no drop in the reaction rate despite three repetitions of the process.

Ionic liquids are a new class of solvents which have attracted growing interest over the past few years due to their unique physical and chemical properties.[1,2] We recently reported the lipase-catalyzed enantioselective transesterification of an allylic alcohol in the ionic liquid solvent such as butylmethylimidazolium hexafluorophosphate ([bmim]PF_6),[1] and demonstrated that it was possible to use the enzyme repeatedly in the [bmim]PF_6 solvent system as illustrated in Figure 1.[3]

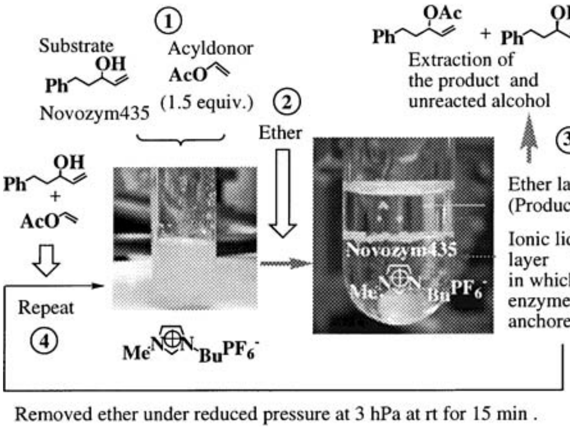
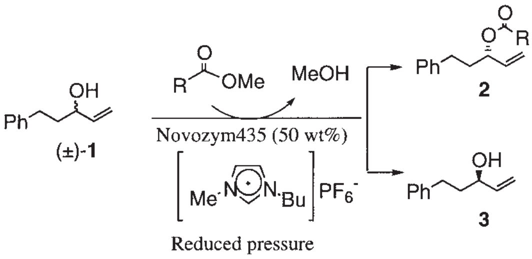


Figure 1. Lipase-catalyzed reaction system anchored to the solvent.

However, the reaction rate gradually dropped with repetition of the reaction process.[3] This drop in reactivity was assumed to be caused by the inhibitory action of acetaldehyde oligomer which was accumulated in the solvent system by ^{1}H NMR analysis.[4] One of the most important characteristics of ionic liquids is their wide temperature range for liquid phase, and ionic liquids have no vapor pressure; we therefore decided to investigate the lipase-catalyzed reaction under reduced pressure conditions in the [bmim]PF_6 solvent system. In this paper we report that the transesterification proceeds efficiently under reduced pressure[5] in an ionic liquid solvent system using methyl esters as acyl donors.

To realize transesterification under reduced pressure conditions, proper choice of the acyl donor ester is very important; it is essential to use an acyl donor ester which possesses sufficiently higher boiling temperature than the corresponding alcohol which is produced by transesterification with the substrate ester. Thus, methyl esters seem appropriate for the acyl donors of lipase-catalyzed transesterfication under reduced pressure. This is true even though ordinary methyl esters are recognized as not being suitable for lipase-catalyzed transesterification as acyl donors because reverse reaction with produced methanol takes place easily.[5] However, we would be able to avoid such difficulty when the reaction is carried out under reduced pressure even if methyl esters were used as acyl donor, because the produced methanol would be removed immediately from the reaction mixture and thus the reaction equilibrium would shift to produce the desired product (eq 1). Thus several types of methyl esters were evaluated as acyl donors for the lipase-catalyzed reaction.



(1)

We initially tested transesterification of 5-phenyl-1-penten-3-ol ((±)-**1**)[6] as a model substrate using methyl pentanoate as acyl donor at 133 hPa at 27 °C. However the reaction rate was very slow and only 7% of the product **2a** ($R = n - C_4H_9$) was obtained after 48 h reaction using 3.0 equiv. of methyl pentanoate as an acyl donor, though the desired ester **2a** was obtained with perfect enantioselectivity (Entry 1, Table 1). Fortunately the desired reaction was efficiently accomplished when the reaction was carried out using methyl nonanoate as acyl donor at 133 hPa at 32 °C (Entry 2); transesterification proceeded very smoothly and the desired ester **2b** ($R = n - C_8H_{17}$) was obtained with >99% ee. Other methyl esters can also be used as acyl donors for these reactions. Methyl phenoxyacetate[7] and methyl phenylthioacetate[7] also worked very well, and ester **2c** and **2d** were obtained with perfect enantiomeric excess, respectively (Entries 3 and 6). It was very easy to monitor the reaction course by silica gel thin layer chromatography (TLC) when phenoxyacetate or phenylthioacetate was used as acyl donor. It was also possible to reduce the amount of the acyl donor to 0.6 equiv. towards the substrate alcohol when these esters were used in the reaction; this is least recorded amount of acyl donor used in this type of lipase-catalyzed transesterification (Entries 5 and 7).

Due to the large difference in boiling points between methyl

Table 1. Lipase-catalyzed enantioselective transesterification under reduced pressure conditions in an liquid solvent system[a]

Entry	Acyl donor R	Run	Conditions Temp/pressure	Time /h	%ee of **2** /%Yield[b]	%ee of **3** /%Yield[b]	Conv. /c	Rata[c]	E value[9]
1	n-C_4H_9	1	27 °C/133 hPa	24 + 24[d]	>99 (6)	7 (77)	0.06	0.13	>200
2	n-C_8H_{17}	1	32 °C/133 hPa	8.5	>99 (43)	72 (57)	0.42	8.4	>420
3	$PhOCH_2$	1	40 °C/133 hPa	9	>99 (35)	72 (64)	0.42	4.7	>430
4	$PhOCH_2$[e]	1	40 °C/133 hPa	7	>99 (38)	87 (62)	0.47	6.7	>570
5	$PhOCH_2$[f]	1	40 °C/133 hPa	28	>99 (29)	73 (48)	0.42	1.5	>430
6	$PhSCH_2$	1	40 °C/27 hPa	13	>99 (30)	86 (40)	0.46	3.5	>530
7	$PhSCH_2$	2	40 °C/27 hPa	13	>99 (35)	80 (42)	0.44	3.4	>530
8	$PhSCH_2$	3	40 °C/27 hPa	14	>99 (35)	88 (40)	0.47	3.4	>470
9	$PhSCH_2$[f]	1	40 °C/27 hPa	18	>99 (37)	86 (40)	0.46	2.6	>540

[a] The reaction was carried out using [bmim]PF_6 (0.2 M) in the presence of 1.5 equiv. of the acyl donor ester.

[b] Isolated yield. Enantiomeric excess was determined by capillary GC analysis using a chiral column (Chiraldex G-TA); >99% ee means that no isomer is detected in the analysis conditions. [c] Rate: %conv./ reaction time (h).

[d] Additional methyl pentanoate (1.0 equiv.) was added when the reaction was started for 24 h. [e] The reaction was carried out under concentrater conditions (0.2 M). [f] 0.6 equiv. of acyl donor was used.

phenylthioacetate with methanol, this ester was indeed useful for the lipase recycling system. The transesterification took place smoothly under reduced pressure at 27 hPa at 40 °C when 1.5 equivalent of methyl phenylthioacetate was used as acyl donor, and we were able to obtain ester **2d** in optically pure form. Repetition with this process three times showed no drop in the reaction rate (Entries 6–8).[8]

In conclusion, we demonstrated the lipase-catalyzed enantioselective transesterification of an allylic alcohol in the [bmim]PF_6 solvent system under reduced pressure conditions and showed that it was possible to use the enzyme repeatedly in this system. It is assumed that a good acyl donor must be selected depending on the substrate. We do believe, however, that this might be a very important means of lipase-catalyzed enantioselective acylation in the ionic liquid solvent system. Further investigation of the scope and limitations of this reaction, especially optimization of the reaction conditions for the lipase recycling system in the ionic solvent system, will make it even more beneficial.

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

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4 In addition, the ionic solvent was sometimes acidified significantly and dropped to less than pH 2 due to partial hydrolysis of the salt by the moisture. We developed two good methods of restoration: the solvent is washed with a mixture of hexane and ethyl acetate (1 : 1) and treated with ionic exchange resin IRA 400, or is washed with the same mixed solvent followed by treatment with neutral alumina activate type I.

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8 Typically, the reaction was carried out as follows: To a mixture of lipase (25 mg) in the ionic liquid (1.5 ml) were added racemic 5-phenyl-1-penten-3-ol ((±)-**1**) (50 mg, 0.30 mmol) as a model substrate and methyl phenylthioacetate (82 mg, 0.45 mmol, 1.5 equiv.) as the acyl donor. The resulting mixture was stirred at 40 °C at 27 hPa for 13 h. The reduced pressure was broken and the reaction was stopped by the addition of 3 ml of ether to the reaction mixture to form the biphasic state. The desired products and unreacted alcohol were quantitatively extracted from the ether. To the remaining ionic liquid phase, which was placed under reduced pressure for 15 minutes to remove the ether, a mixture of the substrate and methyl phenylthioacetate was again added. This mixture was stirred at 40 °C at 27 hPa. The optical purities of the acetate (*S*)-**2** produced and the remaining alcohol (*R*)-**1** were determined by capillary GC analysis using a chiral column (Chiraldex G-TA).

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