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Enantioselective preparation of *N*-chirogenic tertiary amine oxides

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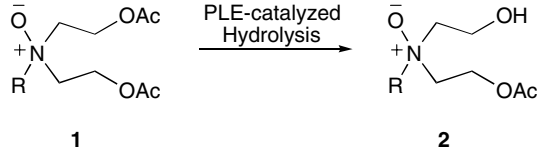
Abstract—We found that PLE can be used as an efficient catalyst for desymmetrization of prochiral tertiary amine N-oxides and demonstrated that they were hydrolyzed by PLE efficiently to afford *N*-chirogenic tertiary amine oxides up to 99% ee in moderate to good yields.

Chiral sulfoxide and phosphoxides having unsymmetrically substituted heteroatom centers have attracted a great deal of attention, and their preparation and utilization have been extensively studied because of their usefulness in recent enantioselective syntheses.[1] On the other hand, *N*-chiral amine oxides, which are nitrogen analogues of these compounds, have been much less investigated in spite of their great potential for chiral ligands of transition metal catalysts and for asymmetric organocatalysts.[2,3] The reason why much less attention has been paid to *N*-chiral amine oxides is the lack of practical methods for preparing chiral N-oxides in a highly enantioselective manner. After Meisenheimer obtained enantio-pure *N*-chiral amine oxides by recrystallization of diastereomeric salts between racemic amine oxides and chiral organic acids, several methods have been investigated to resolve racemic amine oxides, including HPLC techniques.[4] However, these separation methods are not always efficient and are therefore applicable to only a limited range of amine oxides. Oxidation of tertiary amine using chiral oxidants, such as percamphoric acid and *O*,*O*-dibenzoyl pertartaric acid, has also been studied, but chiral amine oxides could be obtained in only low enantioselectivities.[5] To our knowledge, the most efficient method for preparing chiral N-oxides is BSA-catalyzed oxidation reaction, by which chiral amine oxides were obtained in up to 66% ee.[6] In our research project for developing efficient organocatalysts, we are interested in Lewis/Brønsted basicity of N-oxides and their high acceptability of hydrogen bonding. In this communication, we report that PLE-catalyzed desymmetrization of prochiral amine oxide **1** afforded *N*-chiral amine oxide **2** in good to excellent enantioselectivity (Fig. 1).

Typical methods for preparing N-oxides are shown in Scheme 1. Diethanolamine was treated with benzyl bromide and Et_3N in $CHCl_3$ to give *N*-benzyl diethanolamine, which was acetylated by using AcCl and Et_3N in benzene to yield a diacetate in 87% yield (two steps). The resulting diacetate was oxidized to N-oxide **1a** by MCPBA in 95% yield. Other N-oxides **1b–n** were also obtained in good to excellent yields by using this method. For N-oxides **1c** and **1d**, commercially available *N*-phenyl diethanolamine and *N*-methyl diethanolamine were used as starting materials.

First, we screened several enzymes for their ability to hydrolyze N-oxide **1a**. N-Oxide **1a** and an enzyme were dissolved in phosphate-buffer solution (pH 7.2) and the mixture was reacted at 25 °C. The products were separated by reversed-phase silica gel (Merck, Silica gel 60 silanaized) column chromatography to monoacetate **2a** and diol **3a**, which was formed by hydrolysis of **2a**. Enantiomeric excesses of **2a** were determined by ^1H



1 **2**

Figure 1. PLE-catalyzed desymmetrization of prochiral amine oxide **1**.

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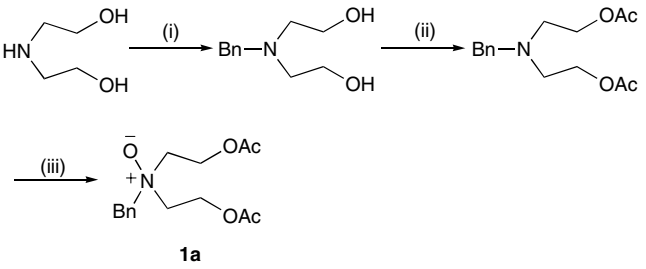


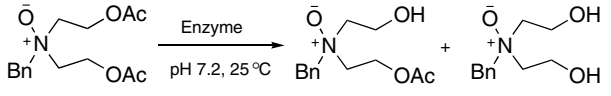
1a

Scheme 1. Preparation of N-oxide **1a**. Reagents and conditions: (i) $PhCH_2Br$, $Et_3N/CHCl_3$, rt, 12 h. (ii) AcCl, Et_3N/benzene, 0 °C, 3 h, 87% (two steps). (iii) MCPBA/$CHCl_3$, 0 °C, 0.5 h, 95%.

NMR using (*R*)-BINOL (6–10 equiv) as a chiral solvating agent (CSA)[7] and the results are summarized in Table 1.

When PLE and lipase AS AMANO were used, hydrolysis of **1a** proceeded to give **2a** (entries 1–4 and 6), whereas other enzymes did not work as catalysts for the desymmetrization reactions (entries 5 and 7–11). Since PLE gave a better result with respect to the enantioselectivity rather than lipase AS AMANO (entries 1 and 6), we further optimized reaction conditions by using PLE. Since over-hydrolyzed product **3a** was obtained when the reaction was carried out for 24 h (entry 1), the reaction time was shortened to 12 h. In this case, **3a** was not formed at all; however, recovery of **1a** increased to 44% and the yield and enantiomeric excess of **2a** were not greatly improved (entry 2). The enantiomeric purity of **2a** was enhanced up to 99% ee when the reaction was conducted for 48 h, though the yield of **2a** was lowered to 28% with increase in **3a** (entry 3). In these reactions, the enantioselectivity was enhanced with increase in **3a**. This fact indicates that the minor enantiomer of **2a** suffered over-hydrolysis faster than did the major enantiomer. When the reaction was conducted at a higher concentration, **2a** was obtained in 67% yield (90% ee) without over-hydrolyzed product **3a** along with the recovery of **1a** (entry 4). Since PLE was proved to be the best catalyst amongst enzymes tested, we next examined desymmetrization reactions of other substrates and the results are presented in Table 2.

Table 1. Enzyme-catalyzed desymmetrizations of N-oxide **1a**



1a 2a 3a

Entry	Enzyme	Time (h)	Yield[c] (%)		
			Recovery	**2a**	**3a**
1	PLE[a]	24	24	48 (93)	19
2	PLE[a]	12	44	51 (91)	0
3	PLE[a]	48	9	28 (>99)	32
4	PLE[a,d]	24	25	67 (90)	0
5	PPL[a]	66	>95	0	0
6	Lipase AS[b]	24	12	49 (60)	0
7	Lipase AYS[b]	66	>95	0	0
8	Lipase PS[b]	66	>95	0	0
9	Lipase M[b]	66	>95	0	0
10	Lipase G[b]	66	>95	0	0
11	Lipase F-AP[b]	66	>95	0	0

960 Units of an enzyme and 0.43 mmol of **1a** were mixed in 20 mL of phosphate-buffer solution (pH 7.2) and the reaction was conducted for indicated time at 25 °C.

[a] PLE and PPL were purchased from Sigma–Aldrich.

[b] Lipases were purchased from Amano Enzyme Inc.

[c] Values in parentheses indicate enantiomeric excesses determined by ^{1}H NMR using (*R*)-BINOL as a CSA.

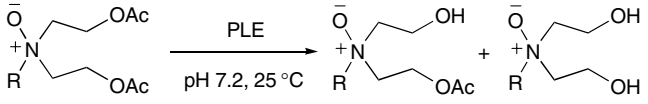
[d] 20 mg PLE (480 units) and 0.43 mmol of **1a** were mixed in 10 mL of phosphate-buffer solution (pH 7.2) and the reaction was performed for indicated time at 25 °C.

N-Oxide **1b**, which has a larger substituent on nitrogen, was hydrolyzed slowly to yield **2b** only in 27% yield along with 38% recovery of **1b**, and the enantioselectivity of the reaction was moderate (63% ee). When N-oxide **1c** was treated with PLE in phosphate-buffer solution, enantiomeric excess of **2c** reached to 99% ee, but the yield was 34% due to instability of **2c**, which was gradually decomposed at room temperature even in buffer solution. It is noteworthy that N-oxide **1d** was not hydrolyzed at all and was recovered almost completely. It seems reasonable to assume that the lower lipophilicity of N-oxide **1d** compared to that of other N-oxides tested prevents incorporation of **1d** to the hydrophobic reaction site of PLE. On the other hand, N-oxide **1e** possessing a highly lipophilic cyclohexyl group on nitrogen was consumed completely in 24 h and afforded **2e** in 55% along with 34% of **3e**. These results indicate that the efficiency of the PLE-catalyzed hydrolysis is considerably dependent on a substituent on the nitrogen atom, and we further investigated the PLE-catalyzed hydrolysis of **1f–n**, and the results are summarized in Table 3. N-Oxides having an *ortho*-substituted benzyl group on nitrogen exhibited 88–99% ee (entries 1, 4, 7 and 9), whereas in the case of *para*-substituted N-oxides, to our surprise, the enantioselectivity was only 6–13% ee (entries 3, 6 and 8).[8] For *meta*-substituted **1g** and **1j**, while **1g** gave **2g** in 92% ee, **1j** afforded **2j** in only 36% ee. With respect to reaction rates, considering the recovery of diacetate **1**, *ortho*-substituted N-oxides **1f**, **1i**, **1l** and **1n** were smoothly hydrolyzed to give monoacetate **2f**, **2i**, **2l** and **2n**, respectively, while *para*-substituted **1h**, **1k**, **1m** and *meta*-substituted **1g** and **1j** reacted more slowly and larger amounts of starting diacetates remained unreacted than the case of using *ortho*-substituted N-oxides.

To determine the absolute configuration of N-oxides, we first tried to obtain single crystals of the N-oxides **2a–n** in the presence or absence of chiral acids, such as camphoric acid, camphorsulfonic acid, MTPA and (*R*)-BINOL; however, none of them afforded crystals fine enough for X-ray crystallographic analysis. Furthermore, we also attempted to convert **2a–n** to diastereomeric esters with the chiral acids mentioned above, but these efforts have been all failed due to low reactivity of **2a–n**.

In conclusion, we found that PLE can be used as an efficient catalyst for desymmetrization of prochiral N-oxides and demonstrated that N-oxides **1** were hydrolyzed by PLE efficiently to afford *N*-chirogenic tertiary amine N-oxides up to 99% ee in moderate to good yields.

Table 2. PLE-catalyzed desymmetrization reactions of **1b–e**



1b: R = 2-naphthylmethyl
1c: R = Ph
1d: R = Me
1e: R = Cyclohexyl

2b-2e **3b-3e**

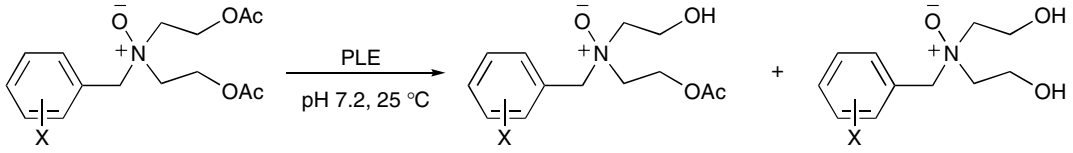
Entry	R	Yield[a] (%)		
		Recovery	**2**	**3**
1	2-Naphthylmethyl (**1b**)	38	27 (63), $[\alpha]_D^{24}$ +2.05 (*c* 0.95, $CHCl_3$)	9
2	Phenyl (**1c**)	0	34 (99)	0
3	Methyl (**1d**)	>95	0	0
4	Cyclohexyl (**1e**)	0	55[b], $[\alpha]_D^{23}$ +3.02 (*c* 1.00, $CHCl_3$)	34

40 mg PLE (960 units) and 0.43 mmol of **1a** were mixed in 20 mL of phosphate-buffer solution (pH 7.2) and the reaction was conducted for 24 h at 25 °C.

[a] Values in parentheses indicate enantiomeric excess.

[b] Enantiomeric excess could not be determined by ^1H NMR techniques.

Table 3. PLE-catalyzed desymmetrization of N-oxides **1f–n**



1f - 1n **2f - 2n** **3f - 3n**

Entry	N-oxide	Yield[a] (%)		
		Recovery	**2**	**3**
1	**1f** (X = 2-nitro)	5	74 (99)[b], $[\alpha]_D^{23}$ +25.6 (*c* 1.00, $CHCl_3$)	12
2	**1g** (X = 3-nitro)	36	33 (92), $[\alpha]_D^{23}$ +8.9 (*c* 1.00, $CHCl_3$)	10
3	**1h** (X = 4-nitro)	50	31 (6), $[\alpha]_D^{23}$ −1.42 (*c* 0.70, $CHCl_3$)	2
4	**1i** (X = 2-methoxy)	6	49 (88), $[\alpha]_D^{22}$ −13.2 (*c* 1.13, $CHCl_3$)	18
5	**1j** (X = 3-methoxy)	32	36 (36), $[\alpha]_D^{22}$ −1.61 (*c* 1.33, $CHCl_3$)	19
6	**1k** (X = 4-methoxy)	27	50 (13), $[\alpha]_D^{23}$ +1.38 (*c* 1.10, $CHCl_3$)	10
7	**1l** (X = 2-chloro)	14	64 (89), $[\alpha]_D^{20}$ +1.82 (*c* 1.40, $CHCl_3$)	21
8	**1m** (X = 4-chloro)	41	30 (8), $[\alpha]_D^{23}$ +0.23 (*c* 1.28, $CHCl_3$)	9
9	**1n** (X = 2-fluoro)	15	60 (88), $[\alpha]_D^{24}$ −1.86 (*c* 1.00, $CHCl_3$)	15

20 mg PLE (480 units) and 0.43 mmol of **1** were mixed in 10 mL of phosphate-buffer solution (pH 7.2) and the reactions were conducted for 24 h at 25 °C.

[a] Values in parentheses indicate enantiomeric excesses of **2**.

[b] Enantiomeric excess was determined by ^1H NMR using (*R*)-1,1′-binaphthyl-2,2′-dicarboxylic acid as a CSA instead of (*R*)-BINOL, which was not effective for determining enantiomeric purity of **2f**.

Although absolute configurations of these N-oxides have not been elucidated, these findings should provide an attractive strategy for designing chiral organocatalysts and ligands for enantioselective reactions.

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7. Wenzel, T. J.; Wilcox, J. D. *Chirality* **2003**, *15*, 256–270, We screened several optically active chiral acids, such as camphorsulfonic acid, MTPA and BINOL, for their ability to distinguish two enantiomers of **2a** in the ^{1}H NMR spectrum. When 10 equiv of (*R*)-BINOL was used, methyl (acetyl) signals of the both enantiomers were separated and appeared at 1.89/1.84 ppm, respectively, in ^{1}H NMR (500 MHz, $CDCl_3$) at 25 °C.
8. Similar results were also reported for PLE-catalyzed transesterification of *trans*-2,5-disubstituted pyrrolidines. In the report, contrary to our results, *N*-benzyl pyrrolidines derivatives having *para*-substituted phenyl group exhibited better enantioselectivity than those bearing *ortho*- and *meta*-substituents in PLE-catalyzed transesterification reactions. See Ref.: Kawanami, Y.; Iizuna, N.; Maekawa, K.; Maekawa, K.; Takahashi, N.; Kawada, T. *Tetrahedron* **2001**, *57*, 3349–3353.