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THE EFFICIENT RESOLUTION OF PROTECTED DIOLS AND HYDROXY ALDEHYDES BY LIPASES: STERIC AUXILIARY APPROACH AND SYNTHETIC APPLICATIONS.

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Abstract: 1,*n*-Diols (*n* = 2 - 5) and 2-hydroxy aldehydes protected with a steric auxiliary are transformed by *Pseudomonas* lipases with high enantioselectiivity, thus allowing the efficient resolution of these molecules and the synthesis of related derivatives with high optical purity.

Introduction

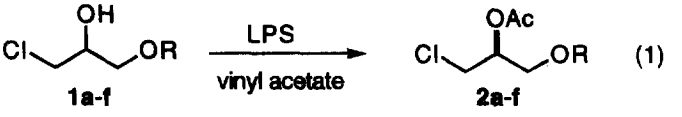
Enantioselective transformations based on enzymatic catalysis now provide useful alternatives to the chemical methods in the synthesis of optically active molecules.[1-6] Lipases are among the enzymes that have been the most intensively used in the enantioselective transformations.[1-4] They accept a broad range of substrates but show variable enantioselectivity. The recent studies by us[7] and others[8-10] have revealed that the enantioselectivity in lipase-catalyzed transformations of secondary alcohols and their acyl derivatives can be significantly enhanced by increasing the difference in size between two substituents at the stereocenter of substrates by the addition of a large group to one side. The large group, to be effective as a steric auxiliary, should be stable during the enzymatic tranformations and readily removable after the enzymatic transformations are complete. In this work, we explored the lipase-catalyzed transformations of protected diols and hydroxy aldehydes with two objectives: first, to search for the best steric auxiliaries for the efficient resolution of these molecules; second, to demonstrate the utility of lipase-catalyzed transformations employing steric auxiliary in organic synthesis. We herein describe that 1,*n*-diols, when protected with *t*-butyl or trityl group, and 2-hydroxy aldehydes, when protected with 1,2-benzenedimethanol, are transformed by *Pseudomonas* lipases with high enantioselectivity, allowing the enantioselective synthesis of these molecules and related derivatives, including (*S*)-1-*O*-*t*-butylisoserinol, (*R*)-3-azido-1,2-propanediol, (*S*)-4-*O*-*t*-butyl-1,2,4-butanetriol, (*S*)-3-phenyl-1,2-propanediol, (*S*)-3-thiophenoxy-1,2-propanediol, and (*S*)-2-methylpyrrolidine.

Results and Discussions

Lipase-catalyzed transformations employing steric auxilaries. The protecting groups such as *t*-butyl and trityl were previously used as the steric auxiliaries of some 1,2-diols in lipase-catalyzed reactions.[7,10] However, no systematic study was done for the comparison of these groups in terms of enantioselectivity and scope. For the comparison of the protecting groups in enhancing the enantioselectivity, 3-chloro-1,2-propanediol protected with several different groups ($ClCH_2CHOHCH_2OR$, **1a-f**) were tested as the substrates of lipase PS (LPS) from *Pseudomonas cepacia* in transesterification. In a typical experiment, each substrate was subjected to the LPS-catalzyed transesterification in the presence of vinyl acetate (eqn. 1). The reaction was carried to approximately 50% completion. The acetylated products and the unreacted substrates were isolated by silicagel chromatography. The opticaly purity was determined by ^1H NMR

spectroscopy in the presence of chiral shift reagents. The results from the LPS-catalysed transesterifications are listed in Table 1. Data of Table 1 indicate that the ability in enhancing the enantioselectivity increases significantly with an order of *t*-Bu ~ Tr > Ph > Ph-*o*-Me > Ph-*p*-OMe > *i*-Pr. Accordingly, these results suggest that *t*-Bu and Tr are the best steric auxiliary of choice for 1,2-diols. It is noted that both groups are readily removable by the treatment with acids.

Table 1. The results from the LPS-catalyzed transesterification of 3-chloro-1,2-propanediol monoethers **1a-f** in the presence of vinyl acetate.



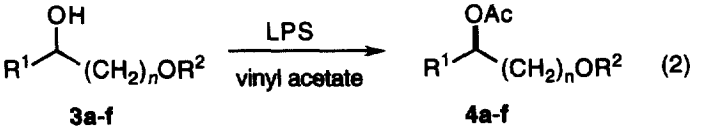
1a-f **2a-f** (1)

	R	yield, %	ee, %	E
a	^{t}Bu	40	>98	>290
b	Tr	43	>98	>210[a]
c	Ph	47	88	70
d	Ph-*o*-Me	52	85	45
e	Ph-*p*-OMe	52	74	24
f	^{i}Pr	49	62	18

[a]Ref. 7.

To see if other diols protected with *t*-Bu and Tr also are transformed by LPS with high enantioselectivity, three additional *t*-butyl 1,2-diols **3a-c** and three additional trityl 1,*n*-diols (n = 2 - 4) **3d-f** were prepared and tested as the substrates of LPS in transesterification (eqn. 2). It was observed that all the *t*-butyl and trityl diols tested were transformed with high enantioselectivity (E = >270) (Table 2). Accordingly, this observation indicates that *t*-Bu and Tr are the steric auxiliaries applicable to a broad range of diols for high stereoselection in lipase-catalyzed reactions.

Table 2. The results from the LPS-catalyzed transesterification of 1,*n*-diol monoethers **3a-f** in the presence of vinyl acetate.

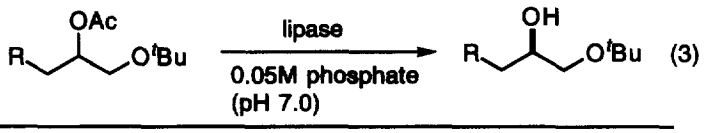


3a-f **4a-f** (2)

	n	R^1	R^2	yield, %	ee, %	E
a	1	$BrCH_2$	^{t}Bu	44	>98	>320
b	1	N_3CH_2	^{t}Bu	45	>98	>270
c	1	CH_2=$CHCH_2$	^{t}Bu	38	97	300
d	2	Me	Tr	49	>98	>400
e	3	Me	Tr	46	>98	>400
f	4	Me	Tr	41	>98	>400

Next, we examined some acetylated *t*-butyl 1,2-diols as the substrates of two bacterial lipases, LPS and LAK (lipase AK from *Pseudomonas* sp.), in hydrolysis to see if they are hydrolyzed with the same high enantioselectivity as observed in the transesterification reactions described above. It was observed that all the substrates tested were hydrolyzed by both enzymes with high enantioselectivity (E = >390) (Table 3). The comparision of data from Tables 1-3 indicates that even higher level of stereoselection is achieved in hydrolysis than in transesterification.

Table 3. The results from the LPS-catalyzed hydrolysis of acetylated *t*-butyl 1,2-diols.

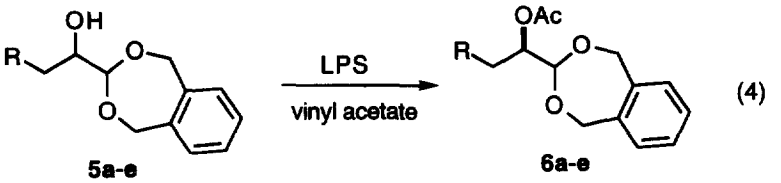


(3)

	R	lipase	yield, %	ee, %	E
2a	Cl	LPS	39	>98	>400
		LAK	36	>98	>400
4b	N_3	LPS	45	>98	>390
		LAK	43	>98	>400
4c	CH_2=CH	LPS	45	>98	>400
		LAK	36	>98	>400

The high stereoselection observed in the lipase-mediated resolutions of diols protected with *t*-Bu or Tr encouraged us to search for a steric auxiliary for the efficient resolution of protected 2-hydroxy aldehydes in lipase-catalyzed transesterification. We envisaged that 1,2-benzenedimethanol would be a useful steric auxiliary for the protection of 2-hydroxy aldehydes because it can be easily incorporated into aldehydes to give acetals and readily removed from acetals under mild conditions.[11] Several 2-hydroxy aldehydes (**5a-e**) protected with 1,2-benzenedimethanol were prepared and tested as the substrates of LPS in transesterification

Table 4. The results from the LPS-catalyzed transesterification of 2-hydroxy acetals **5a-e** in the presence of vinyl acetate.



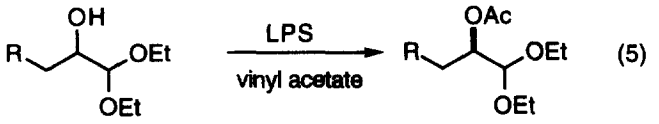
5a-e **6a-e**

(4)

	R	yield, %	ee, %	E
a	H	34	>98	>310
b	Cl	55	95	150
c	N_3	39	94	150
d	Me	46	>98	>400
e	$NCCH_2$	49	>98	>400

(eqn. 4). It was observed that all the cyclic acetals tested were transformed with high enantioselectivity (E = ≥150) (Table 4). In separate experiments, acyclic acetals **7a-d** were tested as the substrates of LPS in transesterification for comparison (eqn. 5). It was observed that all the acyclic acetals tested except **7d** were transformed with lower enantioselectivity (E = 31 - 120) (Table 5). The combined data from Tables 4 and 5 clearly indicate that 1,2-benzenedimethanol is the steric auxiliary of choice for the protection of 2-hydroxy aldehydes in LPS-catalyzed transesterification.[12]

Table 5. The results from the LPS-catalyzed transesterification of 2-hydroxy acetals 7a-d in the presence of vinyl acetate.



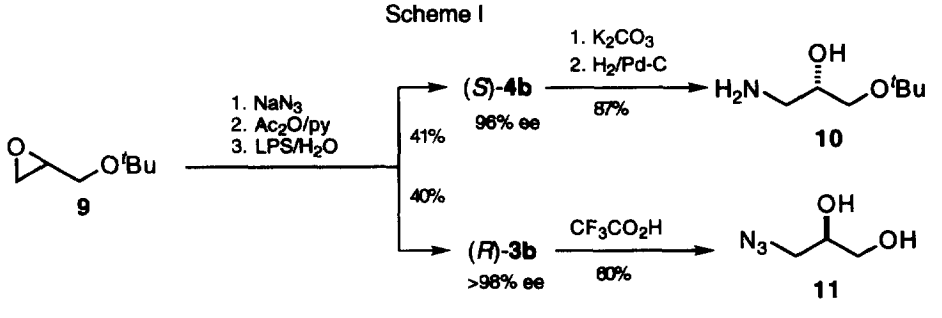
(5)

7a-d **8a-d**

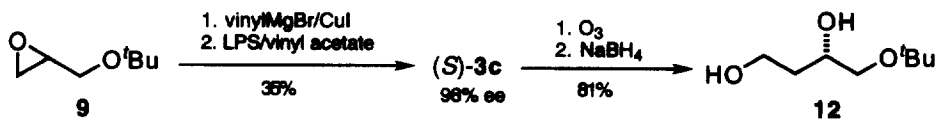
	R	yield, %	ee, %	E
a	H	50	75	31
b	Cl	49	85	60
c	Me	45	95	120
d	CH_2=CH	38	>98	>400

Synthetic Applications. The studies described above have demonstrated that *t*-butyl 1,2-diols and their acetates are efficiently resolved by LPS and LAK. A variety of *t*-butyl 1,2-diols are readily available from *t*-butyl glycidyl ether **9** by the nucleophilic ring-opening reactions. Accordingly, the integrations of the chemical and the enzymatic transformations should provide a wide range of protected and unprotected diols in the optically pure forms from racemic **9**. As illustrative examples, regioselectively protected isoserinol **10**[13] and unprotected diol **11**[14] were synthesized in four to five steps from **9** (Scheme I). Regioselectively protected triol **12**,[15] which would be a useful chiral building block in asymmetric synthesis, was synthesized in four steps from **9** (Scheme II). Larger 1,2-diols of high optical purity, (*S*)-3-phenyl-1,2-propanediol (**13**) and (*S*)-3-thiophenoxy-1,2-propanediol (**14**),[16] were synthesized, respectively, from (*S*)- and (*R*)-**9**, which in turn were obtained by the four-step chemoenzymatic resolution of racemic **9** including the LAK-catalyzed hydrolysis of **2a** (Scheme III).

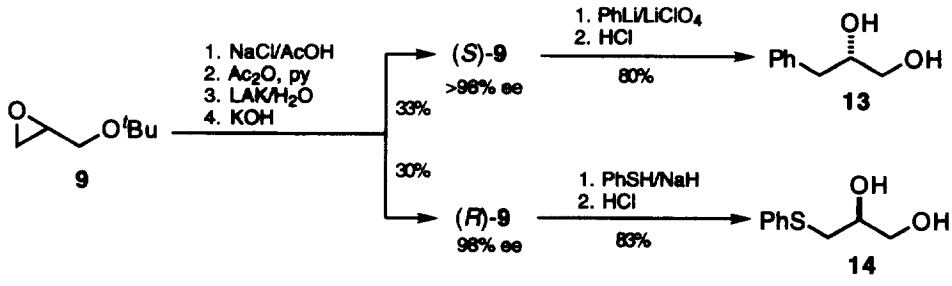
Scheme I



Scheme II

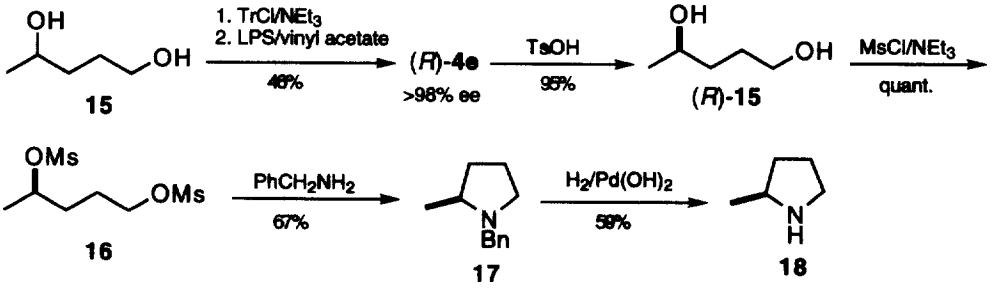


Scheme III



To show the use of the lipase-catalyzed transesterification of trityldiols in asymmetric synthesis, (*S*)-2-methylpyrrolidine **18** was synthesized from 1,5-hexanediol **15** (Scheme IV). The starting material was protected by the treatment with TrCl/Et_3N, followed by LPS-catalyzed transesterification, to give acetate (*R*)-**4e**. The (*R*)-acetate was deacetylated and detritylated at the same time by the treatment with TsOH in MeOH to yield (*R*)-**15**. The diol (*R*)-**15** was then converted to **17** in two steps (i. MsCl/Et_3N; ii. benzylamine). The protected pyrrolidine **17** was finally deprotected by catalytic hydrogenation to afford **18**.[17]

Scheme IV



In summary, this work has demonstrated that the substrates carrying a proper steric auxiliary are transformed by *Pseudomonas* lipases with high enantioselectivity. *t*-Butyl and trityl group are recommended as the steric auxiliary for 1,*n*-diols and 1,2-benzenedimethanol for 2-hydroxy aldehydes. These groups are readily added to the substrate system, stable during the enzymatic transformations, and readily removed after the enzymatic transformations or further chemical transformations. This work has also shown that the integration of the enzyme-catalyzed and chemical transformations provides efficient routes to diols and related derivatives of high optical purity.

Acknowledgements
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References and Notes

1. Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114.
2. Chen, C.-S. and Sih, C. J. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 695.
3. Xie, Z. F. *Tetrahedron: Asymmetry* **1991**, *2*, 733.
4. Boland, W.; Frossl, C.; Lorenz, M. *Synthesis* **1991**, 1049.
5. Santaniello, E.; Fetrizia, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, 92, 1071.
6. Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994.
7. Kim, M.-J.; Choi, Y. K. *J. Org. Chem.* **1992**, *57*, 1605.
8. Kazlauskas, J. J.; Weissfloch, A. W. E.; Rapport, A. T.; Cuccia, L A. *J. Org. Chem.* **1991**, *56*, 2656.
9. Gupta, A. K.; Kazlauskas, R. J. *Tetrahedron: Asymmetry* **1993**, *4*, 879.
10. Goergens, U.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1064 and 1066.
11. Oi, R.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 2095 and references therein.
12. For previous examples of lipase-mediated resolution of hydroxy aldehyde acetals, see Pederson, R. L.; Liu, K. K.-C.; Rutan, J. E.; Chen, L.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 4897; Bianchi, D.; Cesti, P.; Golini, P. *Tetrahedron* **1989**, *45*, 869.
13. **10**: $[\alpha]^{25}_{D}$ -13.2° (*c* 2.01, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 3.66 (*m*, 1 H), 2.77 (*m*, 2 H), 1.77 (*bs*, 3 H), 1.20 (*s*, 9 H); ^{13}C NMR ($CDCl_3$, ppm) 73.0, 71.5, 64.0, 44.6, 27.4.
14. **11**: $[\alpha]^{25}_{D}$ +12.9° (*c* 0.3, MeOH) [lit.[18] -10.8° (*c* 0.98, EtOH) for (*S*)-enantiomer].
15. **12**: $[\alpha]^{25}_{D}$ -15.4°(*c* 2.20, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 3.92 (*m*, 1 H), 3.82 (*t*, *J* = 5.69 Hz, 2 H), 3.38 (*dd*, *J* = 8.98 and 3.83 Hz, 1 H), 3.27 (*dd*, *J* = 8.98 and 7.31 Hz), 2.64 (*bs*, 2 H); ^{13}C NMR ($CDCl_3$, ppm) 73.3, 70.5, 65.8, 60.9, 35.3, 27.5.
16. **13**: mp 52-54°C, $[\alpha]^{25}_{D}$ - 31.5° (*c* 1.1, EtOH) [lit.[19] - 21.0° (*c* 1, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.38-7.15 (*m*, 5 H), 3.93 (*m*, 1 H), 3.67 (*dd*, *J* = 3.7, 12.3 Hz, 1 H), 3.50 (*dd*, *J* = 7.7, 12.3, 1 H), 2.69-2.82 (*m*, 2 H), 1.96 (*bs*, 2 H); ^{13}C NMR ($CDCl_3$, ppm) 137.7, 129.3, 128.7, 128.3, 126.6, 73.0, 60.1, 39.8.

    14: mp 80-82°C (lit.[20] 79-81°C), $[\alpha]^{25}_{D}$ + 22.0° (*c* 1.1, EtOH) [lit.[20] + 21.3° (*c* 1.03, EtOH); ^{1}H NMR ($CDCl_3$, ppm) 7.19-7.42 (*m*, 5 H), 3.72-3.85 (*m*, 2 H), 3.58 (*dd*, *J* = 6.2, 11.2 Hz), 3.12 (*dd*, *J* = 5.2, 15.5 Hz, 1 H), 3.00 (*dd*, *J* = 8.8, 15.5 Hz, 1 H), 2.67 (*bs*, 1 H), 1.93 (*bs*, 1 H); ^{13}C NMR ($CDCl_3$, ppm,) 134.9, 130.1, 129.1, 126.8, 69.9, 65.2, 37.7.
17. **18**: $[\alpha]^{25}_{D}$ +33.6 (*c* 2.1, hexane) [lit.[21] -31.2 (*c* 1.0, hexane) for (*R*)-**14**]; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 2.98-3.12 (*m*, 2 H), 2.77-2.88 (*m*, 1 H), 2.0 - 2.1 (*br*, 1 H), 1.62-1.93 (*m*, 4 H), 1.15 (*d*, *J* = 6.24 Hz, 3 H); ^{13}C NMR ($CDCl_3$, ppm) 55.1, 47.3, 34.3, 26.3, 21.8.
    18•HCl: m.p. 59 - 62°C. **18**•picrate: m.p. 74 - 75°C [lit.[21] m.p. 73°C].
18. Sato, T.; Mizutani, T.; Okumura, Y.; Fujisawa, T. *Tetrahedron Lett.* **1989**, *30*, 3701.
19. Parida, S.; Dordick, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 2253.
20. Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 5413.
21. Kostyanovsky, R. G.; Gella, I. M.; Markov, V. I.; Samojlova, Z. E. *Tetrahedron* **1974**, *30*, 39.

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