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Chemoenzymatic Dynamic Kinetic Resolution of β-Halo Alcohols. An Efficient Route to Chiral Epoxides

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Enzymatic resolution of β-chloro alcohols in combination with ruthenium-catalyzed alcohol isomerization led to a successful dynamic kinetic resolution (conversion up to 99% and ee up to 97%). The efficiency of the DKR is dramatically reduced when β-bromo alcohols are used. The presence of the bromo substituent causes decomposition of the ruthenium catalysts, which triggers the progressive deactivation of the enzyme. The synthetic utility of this procedure has been illustrated by the practical synthesis of different chiral epoxides.

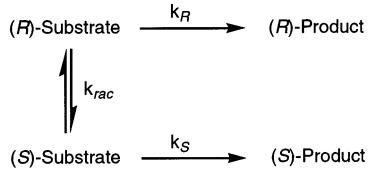
Introduction

Dynamic kinetic resolution (DKR) has become an active and important area of research in organic synthesis.[1] DKR is a powerful tool to prepare enantiomerically enriched compounds in high yields that overcomes the limitation of the maximum 50% yield in the traditional kinetic resolution (Scheme 1).[2] We have recently developed an easy approach to perform DKR on alcohols in which the traditional enzymatic kinetic resolution is combined with an in situ racemization of the substrate using a ruthenium−hydrogen-transfer catalyst.[3]

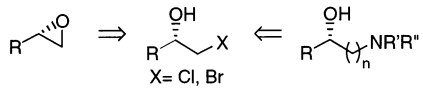
In the past few years, we and others have applied this DKR approach to the preparation of different functionalized alcohols (i.e., hydroxy esters,[4] hydroxy nitriles,[5] azido alcohols,[6] allylic alcohols[7]) that would lead to interesting building blocks for the synthesis of high-value compounds (e.g., pharmaceuticals, natural products, etc.).

Chiral β-halo alcohols are important structural elements for asymmetric catalysis. Thus, a wide range of different compounds are accessible due to the versatility conferred by the presence of the halogen that can readily act as a good leaving group. The possible transformations

SCHEME 1. Dynamic Kinetic Resolution (DKR)



SCHEME 2



includes among others the formation of chiral epoxides and β- and γ-amino alcohols, widely used as adrenergic receptor blockers and immune stimulants (Scheme 2).[8] Previous attempts to use β-halo alcohols in DKR were unsuccessful and gave only moderate ee's and yields.[3b,9] We now report our investigations toward the efficient synthesis of enantiopure β-halo acetates from β-halo alcohols **1** via DKR.

Results and Discussion

Kinetic Resolution. A primary requirement for a successful DKR is that the KR conditions are compatible with the racemization process. Therefore, we screened different commercially available lipases in the kinetic resolution of 2-chloro-1-phenylethanol **1a** under different reaction conditions. 4-Chlorophenyl acetate **3** was used as acyl donor since it is known to be compatible with ruthenium-catalyzed racemization of alcohols. The use of vinyl acetate, commonly used as acyl donor, results in

(1) For recent reviews on DKR, see: (a) El Gihani, M. T.; Williams, J. M. J. *Curr. Opin. Chem. Biol.* **1999**, *3*, 11. (b) Strauss, U. T.; Felfer, U.; Faber, K. *Tetrahedron: Asymmetry* **1999**, *10*, 107. (c) Azerad, R.; Buisson, D. *Curr. Opin. Biotechnol.* **2000**, *11*, 565. (d) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321.

(2) Faber, K. *Biotransformations in Organic Media*, 3rd ed.; Springer: Graz, Austria, 1996.

(3) (a) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1211. (b) Persson, B. A.; Larsson, A. L. E.; LeRay, M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645.

(4) (a) Huerta, F. F.; Laxmi, Y. R. S.; Bäckvall, J.-E. *Org. Lett.* **2000**, *2*, 1037. (b) Huerta, F. F.; Bäckvall, J.-E. *Org. Lett.* **2001**, *3*, 1209. (c) Runmo, A.-B. L.; Pàmies, O.; Fabert, K.; Bäckvall, J.-E. *Tetrahedron Lett.* **2002**, *43*, 2983. (d) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, 67, 1261.

(5) (a) Pàmies, O.; Bäckvall, J.-E. *Adv. Synth. Catal.* **2001**, *343*, 726. (b) Pàmies, O.; Bäckvall, J.-E. *Adv. Synth. Catal.* **2002**, *344*, 947.

(6) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2001**, 66, 4022.

(7) Lee, D.; Huh, E. A.; Kim, M.-J.; Jung, H. M.; Koh, J. H.; Park, J. *Org. Lett.* **2000**, *2*, 2377.

(8) Powell, J. R.; Waimer, I. W.; Drayer, D. E. In *Drug Stereochemistry Analytical Methods and Pharmacology*; Marcel Dekker: New York, 1998.

(9) Kinetic resolution of β-halo alcohols with *Candida antarctica* lipase B (CALB) has been reported to proceed with low selectivity: Rotticci, D.; Haefner, F.; Orrenius, C.; Norin, T.; Hult, K. *J. Mol. Catal. B: Enzym.* **1998**, *5*, 267.

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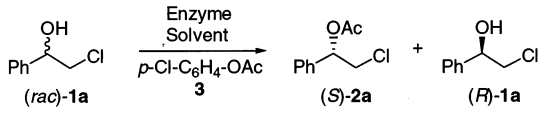
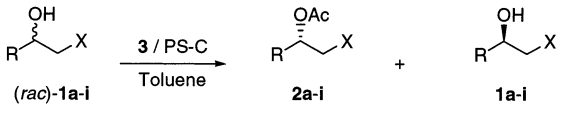
TABLE 1. Kinetic Resolution of 1a[a]



entry	enzyme	solvent	% **2**[b]	% ee of **2a**[c]	% ee of **1a**[c]	E[d]
1	PS-C	toluene	42	98	71	210
2	N-435	toluene	11	99	16	230
3	AK	toluene	23	98	18	115
4	PS-C	cyclohexane	47	92	82	60
5	PS-C	DIPE[e]	50	92	91	75
6	PS-C	TBME[f]	50	95	93	130

[a] Reactions were carried out on a 0.2 mmol scale with 20 mg of enzyme and 3 equiv of **3** in 2 mL of solvent at 60 °C for 5 h. [b] Determined by NMR. [c] % ee determined by GC. [d] Enantiomeric ratio. [e] Diisopropyl ether. [f] *tert*-Butyl methyl ether.

TABLE 2. Lipase-Catalyzed Kinetic Resolution of *rac*-1[a]



entry	substrate	R	X	% yield of **2**[b]	% ee of **2**[c]	% ee of **1**[c]	E[d]
1	**1a**	Ph	Cl	42	98	71	210
2	**1b**	*p*-OMeC$_6$H$_4$	Cl	46	97	87	185
3	**1c**	*p*-FC$_6$H$_4$	Cl	47	95	85	105
4	**1d**	Ph	Br	43	97	72	140
5	**1e**	*p*-OMeC$_6$H$_4$	Br	41	96	77	115
6	**1f**	benzyl	Cl	46	88	74	35
7	**1g**	PhOCH$_2$	Cl	54	82	97	40
8	**1h**	1-naphthyl-OCH$_2$	Cl	55	83	99	55
9	**1i**	(^{i}Pr)OCOCH$_2$	Cl	56	65	86	1

[a] Conditions: 0.2 mmol of *rac*-**1**, 0.6 mmol of **3**, 20 mg of *Pseudomonas* sp. lipase (PS-C) in 2 mL of toluene at 60 °C. [b] Yield determined by NMR after 5 h. [c] Optical purity measured by GC or HPLC. [d] Enantiomeric ratio.

the formation of acetaldehyde after the acyl transfer process, which interferes with the ruthenium−hydrogen-transfer catalysts usually employed in the DKR.[10] The results are summarized in Table 1.

Although the enzyme *Candida antarctica* lipase B (N-435) showed the highest enantiomeric ratio (entry 2), the best combination of activity and selectivity was obtained using *Pseudomonas* sp. lipase (PS-C) (entry 1).[11] The use of *Pseudomonas fluorescens* lipase (AK) show low activity and selectivity under our conditions (entry 3).[12] Moreover, the results showed that the selectivity is very dependent on the solvent. Thus, the best selectivity was observed in toluene (entry 1), while the transesterification in ethers and cyclohexane proceeded with significantly lower enantiomeric ratios (entries 4−6).

We then applied this procedure to a series of β-halo alcohols. The results are given in Table 2. The kinetic resolution of different para-substituted 2-chloro-1-phenyl alcohol derivatives **1a**−**c** indicated that the presence of different substituents in the para position of the aromatic ring influence the enantiomeric ratio and therefore the efficiency of the process (entries 1−3). The effect of the halogen group at the β-position was investigated comparing substrates **1a** and **1b** with **1d** and **1e**, containing chloro and bromo substituents at the β-positions, respectively. The results indicate that the enzyme is more selective for the chloro substrates than for the bromo substrates. For the benzyl (**1f)** and aryloxymethyl derivatives (**1g** and **1h)**, the kinetic resolution proceed with low enantiomeric ratios (entries 6−8). The KR of the isopropyl 4-chloro-3-hydroxybutanoate **1i** proceed with very low enantioselectivity (entry 9), probably due the similar size of both substituents.

SCHEME 3

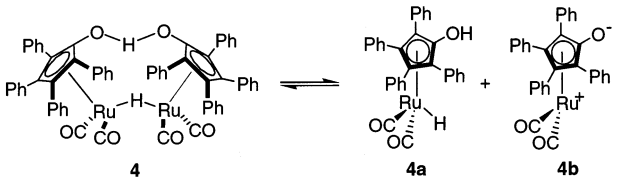
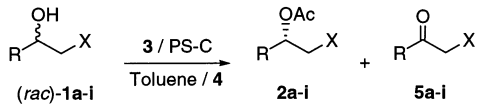


TABLE 3. Dynamic Kinetic Resolution of *rac*-1[a]



entry	substrate	R	X	T (°C)	t (h)	% yield of **2**[b]	% ee[c]	% **5**[b]
1	**1a**	Ph	Cl	60	48	74	96	9
2	**1a**	Ph	Cl	70	48	85	95	3
3	**1a**	Ph	Cl	80	48	79	95	2
4	**1a**	Ph	Cl	70	72	93 (85)[d]	95	3
5	**1b**	*p*-OMeC$_6$H$_4$	Cl	70	72	69 (58)[d]	96	1
6	**1c**	*p*-FC$_6$H$_4$	Cl	70	72	>99 (91)[d]	93	<1
7	**1d**	Ph	Br	70	72	63	97	9
8	**1e**	*p*-OMeC$_6$H$_4$	Br	70	72	39[e]	95	5
9[f]	**1f**	benzyl	Cl	70	72	82 (74)[d]	91	2
10[g]	**1g**	PhOCH$_2$	Cl	70	72	87	85	0
11[g]	**1h**	1-naphthyl-OCH$_2$	Cl	70	72	98	87	0

[a] Conditions: 0.2 mmol of *rac*-**1**, 0.6 mmol of **3**, 4 mol % of **4**, 20 mg of PS-C lipase, and 2 mL of toluene. [b] Yield measured by NMR. Isolated yields in parentheses. [c] Enantiomeric excess measured by GC or HPLC. [d] Reaction performed at 0.6 mmol scale. [e] 61% of unreacted starting material. [f] 5 mg of enzyme used. [g] 2.5 mg of enzyme used.

Dynamic Kinetic Resolution. On the basis of our preliminary results on KR, we combined the KR of β-halo alcohols **1** using PS-C and the acyl donor **3** with a ruthenium-catalyzed racemization process via hydrogen transfer with catalyst **4**. A feature of this catalyst is that no addition of external base is needed as a co-catalyst, since one of the coordinating sites of the ligand acts as a basic center (Scheme 3).[13] This is an important advantage to other potential ruthenium/base racemization catalytic systems, since the presence of an external base could induce cyclization of the substrates to epoxides. The results are summarized in Table 3. In all cases, small amounts of ketone **5**, formed during the hydrogen-transfer process, were observed.

Under "standard" conditions (i.e., 60 °C and 4 mol % of **4**), good enantioselectivity (96% ee) was achieved for substrate **1a**. However, the racemization proceeded slowly,

(10) Bäckvall, J.-E.; Chowdhury, R. L.; Karlsson, U.; Wang, G. Z. In *Perspectives in Coordination Chemistry*; Williams, A. F., Floriani, C., Merbach, A. E., Eds.; Helvetica Chimica Acta: Basel, 1992; p 463.

(11) PS-C lipase has been already successfully used in the KR of β-halo alcohols; see: Bevinakatti, H. S.; Banerji, A. A. *J. Org. Chem.* **1991**, *56*, 5372.

(12) As an example of AK lipase transesterification of β-halo alcohols, see: Hiratake, J.; Inagaki, M.; Nishioka, T.; Oda, J. *J. Org. Chem.* **1988**, *53*, 6130.

(13) Pàmies, O.; Bäckvall, J.-E. *Chem. Eur. J.* **2001**, *7*, 5052.

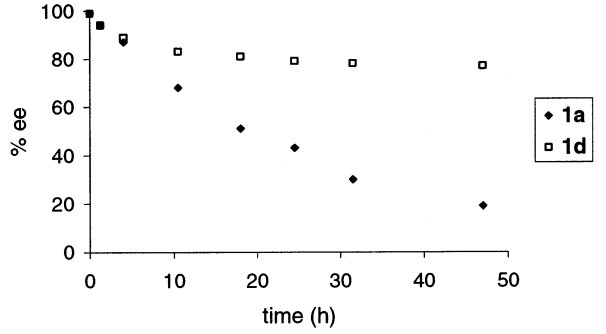


FIGURE 1. Racemization of (*S*)-**1a** and (*S*)-**1d** vs time.

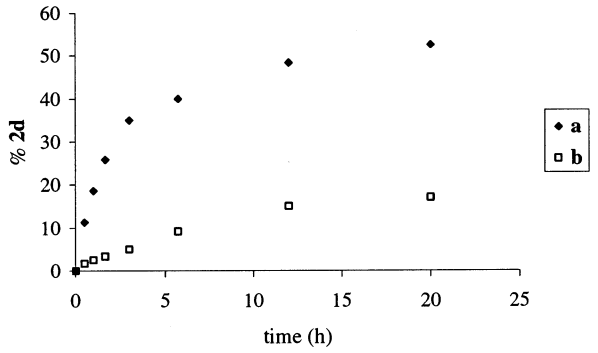


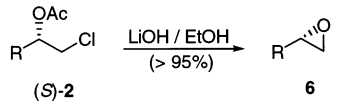
FIGURE 2. Formation of acetate **2d** under DKR conditions: (a) acyl donor **3** immediately added; (b) acyl donor **3** added after 24 h.

resulting in a moderate yields of **2a** after 48 h (entry 1). In previous studies, we have shown that increasing the temperature led to a significantly higher racemization rate.[6] Therefore, we performed the DKR at higher temperatures (entries 2 and 3). At 70 °C, the activity was better; however, at 80 °C, the activity was similar to that at 60 °C. This can be explained by the partial deactivation of the enzyme at this temperature.[14] Interestingly, smaller amounts of ketone **5a** were formed at 70 and 80 °C than at 60 °C.

The introduction of a methoxy substituent in the para position of the phenyl moiety has a negative effect on the efficiency of the process (entry 5). However, the presence of a fluoro substituent in the para position has a slightly positive effect on the outcome of the reaction (entry 6). This is most likely due to the faster racemization of the latter substrate.

The efficiency of the DKR is severely reduced when the chloro substituent is replaced by a bromo substituent (entries 4 and 5 vs 7 and 8). A possible explanation can be found in the lower racemization rates of β-bromo alcohols compared to β-chloro alcohols. Figure 1 suggests that the presence of a bromo substituent at the β-carbon results in decomposition of the racemization catalyst **4**. However, this cannot explain why acetate **2d** is obtained in a better ee than **2a**, since the enzymatic KR proceeds with better enantiopreference for **1a** than **1d**. Also, it is difficult to rationalize why the KR limit of 50% is not reached for substrate **1e**. A likely explanation of these results is that the enzyme undergoes deactivation. To learn more about the causes of the deactivation, we first investigated if the substrate poisons the enzyme. For this purpose, we premixed the substrate with the enzyme in toluene at 70 °C during 24 h and studied the kinetic resolution of substrate **1d** after addition of the acyl donor **3**. Comparison of this with the normal kinetic racemization indicates that the enzyme is not poisoned by the substrate. We then studied if the decomposition of the ruthenium catalyst **4** can affect the enzyme. For this purpose, we premixed the substrate **1d** with the enzyme and the ruthenium catalyst **4** in toluene at 70 °C during 24 h and studied the formation of acetate **2d** after addition of the acyl donor **3**. Comparison of this with the formation of acetate **2d** under normal DKR conditions clearly indicates that the decomposition of the ruthenium catalyst is responsible for the progressive deactivation of the enzyme (Figure 2).

TABLE 4. Epoxide Formation



(*S*)-**2** **6**

entry	substrate	R	% ee[b]
1	**2a**	Ph	95
2	**2b**	*p*-OMeC$_6$H$_4$	94[c]
3	**2c**	*p*-FC$_6$H$_4$	92
4	**2f**	benzyl	90
5	**2g**	PhOCH$_2$	83
6	**2h**	1-naphthyl-OCH$_2$	86

[a] Conditions: 0.5 mmol of (*S*)-**2**, 3 equiv of LiOH, and 5 mL of ethanol (95%) at room temperature. [b] Enantiomeric excess measured by chiral GC or HPLC. [c] % ee measured on the corresponding 1-(4-methoxyphenyl)ethanol obtained by reaction of **6c** with LiAlH$_4$.[15]

For the benzyl (**1f**) and aryloxymethyl (**1g** and **1h**) derivatives, the DKR under the conditions used for **1a** (i.e., 100 mg PS-C/mmol product, 70 °C, 4 mol % **4**) gave the acetates in moderate enantioselectivity (around 70% ee for **1f** and **1g** and around 60% ee for **1h**). This is due to the lower enantiopreference of the enzyme for these substrates (vide infra). To obtain better enantioselectivity, we took full advantage of the DKR. Thus, by reducing the enzyme/ruthenium catalyst ratio, the enzymatic acylation became the rate-determining step and the enantioselectivity was therefore substantially improved (entries 9−11).

Synthetic Applications. A wide range of synthetic applications of this dynamic kinetic resolution procedure can be envisaged. For instance, the hydrolysis of acetates **2** with LiOH in ethanol gave the corresponding epoxides **6** almost quantitatively (yields > 95%) in good enantiomeric excess. The results are summarized in Table 4. The absolute stereochemistry of (*S*)-**6a** was established by comparison with a commercially available sample of (*S*)-phenylethylene oxide. Independently, the absolute stereochemistry of **6b** was established by derivatization to the corresponding (*R*)-1-(4-methoxyphenyl)ethanol.[15]

The synthetic utility of chiral epoxides is well-known. Thus, for instance, they can be stereoselectively opened by azides,[16] cyanide derivatives,[17] and amines,[18] giving easy access to aziridines and β-and γ-amino alcohols.

(14) The optimum performance of the PS-C is set to 50−60 °C. PS-C product sheet from Amano Pharmaceutical Co., Ltd.

(15) Nieduzak, T. R.; Margolin, A. L. *Tetrahedron*: *Asymmetry* **1991**, *2*, 113.

Chiral aziridines are important intermediates in organic synthesis[19] and are present in several in bioactive molecules (e.g., radiation sensitizers and enzyme inhibitors).[20] Chiral β- and γ-amino alcohols are important structural elements in chiral ligands for asymmetric catalysis[21] as well as in biologically active compounds (e.g., β-adrenergic receptor blockers and immune stimulants).[22]

Experimental Section

General Experimental Procedures. All reactions were carried out under dry argon atmosphere using standard Schlenck techniques. Solvents were purified by standard procedures. Solvents for HPLC use were spectrometric grade. All other reagents are commercially available and were used without further purification. Racemic β-halo alcohols **1b**−**e**,**i** were obtained from the corresponding commercially available halo ketones **5** by reduction with sodium borohydride under standard conditions. β-Halo alcohols **1f**−**h** were prepared by ring opening of the corresponding epoxide by LiCl and $CuCl_2$ in THF.[23] Racemic β-halo acetates **2** were obtained from the corresponding alcohols by reaction with acetic anhydride under standard conditions. Acyl donor **3** was prepared according to a literature procedure.[3b] Ruthenium catalyst **4** was synthesized according to a literature procedure[4a] and recrystallized from CH_2Cl_2/pentane prior to use. Lipases PS-C type II and AK were a generous gift from Amano Pharmaceutical Co. Ltd.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. Solvents for extraction and chromatography were technical grade and distilled before chromatography was performed with Merck 60 silica gel. The enantiomeric excess of compounds **1a**−**f**,**i** and **2a**−**f** was determined by analytical GC employing a CP−Chirasil-Dex CB column using racemic compounds as references. The enantiomeric excess of all the other compounds was determined by GC analysis on a Daicel, Chiracel OD-H column using racemic compounds as references (Table 5).

General Procedure for the KR of Halo Alcohols. (*S*)-1-Chloro-2-acetoxy-2-phenylethane ((*S*)-2a). In a typical experiment, PS-C lipase (20 mg) was added to a solution of **1a** (31.2 mg, 0.2 mmol) and **3** (102 mg, 0.6 mmol) in dry toluene (2 mL) under argon. The resulting reaction mixture was stirred at 60 °C for 5 h. The enzyme was then filtered off and washed with toluene (3 × 5 mL). The combined toluene phases were evaporated, and the residue was analyzed. The product (*S*)-**2a** was obtained in 45% conversion and in 98% ee. The ^{1}H NMR data are in agreement with those previously reported.[12] ^{13}C NMR δ 21.2, 46.7, 75.3, 126.8, 128.9, 129.3, 137.4, 170.1.

TABLE 5. Methods Used to Assay Enantiomeric Excess.

substrate	ee assay	conditions[a]	$t_R(R)$	$t_R(S)$
1a	GC	A	23.5	23.3
2a	GC	A	21.9	22.4
1b	GC	A	25.1	25.3
2b	GC	A	24.8	25.0
1c	GC	A	23.7	23.5
2c	GC	A	22.2	22.6
1d	GC	A	24.2	24.0
2d	GC	A	23.1	23.4
1e	GC	A	25.8	25.7
2e	GC	A	25.4	25.5
1f	GC	A	23.6	23.7
2f	GC	A	23.1	23.3
1g	HPLC	B	31.1	18.5
2g	HPLC	B	12.3	13.4
1h	HPLC	B	32.2	34.1
2h	HPLC	B	18.7	16.9
1i	GC	C	26.5	26.6
2i	GC	C	26.9	27.0

[a] Conditions A: 110 °C, 20 min; 20 °C/min to 200 °C. Conditions B: hexane/2-propanol = 9:1, 0.5 mL/min. Conditions C: 80 °C, 20 min; 10 °C/min to 200 °C.

(*S*)-1-Chloro-2-acetoxy-2-(*p*-methoxyphenyl)ethane ((*S*)-2b).[24] ^{1}H NMR δ: 2.11 (s, 3H), 3.67 (dd, 1H, $^2J_{H-H}$ = 11.6 Hz, $^3J_{H-H}$ = 4.8 Hz), 3.77 (dd, 1H, $^2J_{H-H}$ = 11.6 Hz, $^3J_{H-H}$= 8.0 Hz), 3.80 (s, 3H), 5.89 (dd, 1H, $^3J_{H-H}$ = 8.0 Hz, $^3J_{H-H}$ = 4.6 Hz), 6.90 (m, 2H), 7.25 (m, 2H). ^{13}C NMR, δ: 21.2, 46.6, 55.5, 75.0, 114.3, 128.3, 129.5, 160.1, 170.2.

(*S*)-1-Chloro-2-acetoxy-2-(*p*-fluorophenyl)ethane ((*S*)-2c). The ^{1}H NMR data are in agreement with those previously reported.[15] ^{13}C NMR, δ: 21.1, 46.5, 74.5, 115.8 (d, J_{C-F} = 28 Hz), 128.8 (d, J_{C-F} = 11.2 Hz), 133.2, 162.5 (d, J_{C-F} = 286.2 Hz), 170.0.

(*S*)-1-Bromo-2-acetoxy-2-phenylethane ((*S*)-2d).[24] ^{1}H NMR, δ: 2.08 (s, 3H), 3.59 (dd, 1H $^2J_{H-H}$ = 10.8 Hz, $^3J_{H-H}$ = 4.8 Hz), 3.65 (dd, 1H, $^2J_{H-H}$ = 10.8 Hz, $^3J_{H-H}$= 8.0 Hz), 5.97 (dd, 1H, $^3J_{H-H}$ = 8.0 Hz, $^3J_{H-H}$ = 4.8 Hz), 7.46 (m, 5H). ^{13}C NMR, δ: 21.2, 34.5, 75.1, 126.8, 128.9, 129.0, 137.9, 170.1.

(*S*)-1-Bromo-2-acetoxy-2-(*p*-methoxyphenyl)ethane ((*S*)-2e). The ^{1}H NMR data are in agreement with those previously reported.[12] ^{13}C NMR, δ: 22.2, 45.2, 55.5, 74.8, 114.3, 128.2, 129.9, 160.2, 170.1.

(*S*)-1-Chloro-2-acetoxy-3-phenylpropane ((*S*)-2f).[25] ^{1}H NMR, δ: 2.06 (s, 3H), 2.98 (d, 2H, $^3J_{H-H}$ = 6.8 Hz), 3.50 (dd, 1H, $^2J_{H-H}$ = 11.6 Hz, $^3J_{H-H}$ = 5.0 Hz), 3.62 (dd, 1H, $^2J_{H-H}$ = 11.6 Hz, $^3J_{H-H}$ = 4.2 Hz), 5.21 (m, 1H), 7.28 (m, 5H). ^{13}C NMR, δ: 21.2, 37.7, 44.9, 73.6, 127.1, 128.8, 129.6, 136.3, 170.5.

(*S*)-1-Chloro-2-acetoxy-3-phenoxypropane ((*S*)-2g).[26] ^{1}H NMR, δ: 2.11 (s, 3H), 3.77 (dd, 1H, $^2J_{H-H}$ = 11.6 Hz, $^3J_{H-H}$ = 5.2 Hz), 3.85 (dd, 1H, $^2J_{H-H}$ = 11.6 Hz, $^3J_{H-H}$= 4.8 Hz), 4.16 (m, 2H), 5.32 (m, 1H), 6.92 (m, 2H), 6.99 (m, 1H), 7.28 (m, 2H). ^{13}C NMR, δ: 21.1, 42.7, 66.1, 71.3, 114.8, 121.7, 129.8, 158.4, 170.4.

(*S*)-1-Chloro-2-acetoxy-3-(1-naphthoxy)propane ((*S*)-2h).[11] ^{1}H NMR, δ: 2.14 (s, 3H), 3.83 (dd, 1H, $^2J_{H-H}$ = 11.6 Hz, $^3J_{H-H}$ = 5.2 Hz), 3.90 (dd, 1H, $^2J_{H-H}$ = 11.6 Hz, $^3J_{H-H}$ = 4.8 Hz), 4.30 (m, 2H), 5.41 (m, 1H), 7.17 (m, 2H), 7.36 (m, 1H), 7.46 M, 1H), 7.76 (m, 4H). ^{13}C NMR, δ: 21.2, 42.8, 66.3, 71.3, 107.3, 118.8, 124.2, 126.8, 127.0, 127.9, 129.5, 129.8, 134.6, 156.4, 170.4.

(16) See, for instance: (a) Hamamoto, H.; Mamedov, V. A.; Kitamoto, M.; Hayashi, N.; Tsuboi, S. *Tetrahedron*: *Asymmetry* **2000**, *11*, 4485. (b) He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **1998**, *63*, 5696. (c) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **1999**, *64*, 6094.

(17) See, for example: (a) Wade, P. A.; Bereznak, J. F.; Palfey, B. A.; Carroll, P. J.; Dailey, W. P.; Sivasubramanian, S. *J. Org. Chem.* **1990**, *55*, 3045. (b) Mitchell, D.; Koenig, T. M. *Synth. Commun.* **1995**, *25*, 1231.

(18) See, for instance: (a) Chini, M.; Crotti, P.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 5939. (b) Prabhakaran, E. N.; Rajesh, V.; Dubey, S.; Iqbal, J. *Tetrahedron Lett.* **2001**, *42*, 339. (c) Chuang, T.-H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555. (d) Tremblay, M. R.; Wentworth, P.; Lee, G. E.; Janda, K. D. *J. Comb. Chem.* **2000**, *2*, 698.

(19) Deyrup, J. A. In *The Chemistry of Heterocyclic Compounds*; Hassner, A., Ed.; John Wiley & Sons: New York, 1993.

(20) (a) Tomasz, M.; Jung, M.; Verdine, G.; Nakanishi, K. *J. Am. Chem. Soc.* **1984**, *106*, 7367. (b) Danishefsky, S.; Ciufolini, M. *J. Am. Chem. Soc.* **1984**, *106*, 6424.

(21) (a) Blasser, H.-U. *Chem. Rev.* **1992**, *92*, 935. (b) Kolb, H. C.; Van Nieeuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (c) Pfaltz, A. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: Greenwich, CT, 1995.

(22) (a) Powell, J. R.; Waimer, I. W.; Drayer, D. E. In *Drug Stereochemistry Analytical Methods and Pharmacology*; Marcel Dekker: New york, 1998. (b) C. P. Kordik, A. B. Reitz, *J. Med. Chem.* **1999**, *42*, 181.

(23) Hoff, B. H.; Anthosen, T. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1401.

(24) Cozens, L.; O′Neill, M.; Bogdanova, R.; Schepp, N. *J. Am. Chem. Soc.* **1997**, *119*, 10652

(25) Kim, M. J.; Cho, H. *J. Chem. Soc., Chem. Commun.* **1992**, 1411.

(26) Hoff, B. H.; Anthosen, T. *Chirality* **1999**, *11*, 760.

(*S*)-Isopropyl 4-Chloro-3-hydroxybutanoate ((*S*)-2i).[26] ^{1}H NMR, δ: 1.22 (d, 6H, $^3J_{H-H}$= 6.4 Hz), 2.06 (s, 3H), 2.68 (dd, 1H, $^2J_{H-H}$ = 16.0 Hz, $^3J_{H-H}$ = 6.8 Hz), 2.73 (dd, 1H, $^2J_{H-H}$ = 16.0 Hz, $^3J_{H-H}$ = 6.0 Hz), 3.68 (dd, 1H, $^2J_{H-H}$ = 11.6 Hz, $^3J_{H-H}$ = 4.8 Hz), 3.74 (dd, 1H, $^2J_{H-H}$ = 11.6 Hz, $^3J_{H-H}$ = 4.8 Hz), 5.02 (sp, 1H, $^3J_{H-H}$ = 6.4 Hz), 5.38 (m, 1H). ^{13}C NMR, δ: 21.0, 21.9, 36.9, 45.2, 68.6, 69.5, 169.3, 170.1.

General Procedure for the DKR of Halo Alcohols. (*S*)-1-Chloro-2-acetoxy-2-phenylethane ((*S*)-2a). Ruthenium catalyst **4** (32.5 mg, 4 mol %) and PS-C lipase (60 mg) were placed in a Schlenk flask under argon. A solution of **1a** (93.9 mg, 0.6 mmol) and **3** (306 mg, 1.8 mmol) in dry toluene (6 mL) under argon (2 min of argon bubbling) was transferred to the ruthenium catalyst and the enzyme. The resulting reaction mixture was stirred at 70 °C for 72 h. The enzyme was then filtered off and washed with toluene (3 × 5 mL), the solvent was evaporated, and the product was purified by flash chromatography (pentane/ethyl acetate 15/1) to yield 101 mg (85%) of (*S*)-**2a** in 95% ee.

General Procedure for the Epoxide Formation. (*S*)-Phenylethylene Oxide ((*S*)-6a). To a solution of (*S*)-**2a** (89 mg, 0.5 mmol) in ethanol 95% (5 mL) was added LiOH (36 mg, 1.5 mmol). The resulting reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with H_2O (25 mL), the ethanol was evaporated, and the product was extracted with ether (5 × 20 mL). The organic layer was dried over Na_2SO_4 and concentrated to yield 59 mg (98%) of (*S*)-**6a** in 95% ee. The absolute stereochemistry of (*S*)-**6a** was established by comparison with a commercially available sample of (*S*)-phenylethylene oxide.

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