$CHCl_3$) [lit.[17] mp 150–151 °C; [α] +116° ($CHCl_3$)].

Halogenation Reagent System C. A mixture of methyl α-D-glucopyranoside (**22**) (0.40 g, 2.06 mmol), polymer-bound triphenylphosphine (1.0 g, 3.09 mmol), imidazole (0.31 g, 4.53 mmol), and iodine (0.73 g, 2.88 mmol) in toluene (50 mL) was vigorously stirred at 70 °C for 4 h. Workup (procedure c2) yielded the title compound (0.60 g, 67%).

Methyl 2,3,4-Tri-*O*-acetyl-6-deoxy-6-iodo-β-D-glucopyranoside[18] (25). Halogenation Reagent System B. Methyl β-D-glucopyranoside (**24**) (0.20 g, 1.03 mmol) was reacted in the same way as for **23**. Workup (procedure b2) yielded the title compound (0.30 g, 67%): mp 113–114 °C (crystallized once from ethanol); $[\alpha]^{22}_D$ +2° (*c* 3.0, $CHCl_3$) [lit.[18] mp 114–115 °C; [α] + 1° (methanol)].

Halogenation Reagent System C. Methyl β-D-glucopyranoside (**24**) (0.40 g, 2.06 mmol) was reacted in the same way as for **23**. Workup (procedure c2) yielded the title compound (0.54 g, 61%).

Methyl 2,3,4-Tri-*O*-acetyl-6-deoxy-6-iodo-α-D-mannopyranoside[19] (27). Halogenation Reagent System B. Methyl α-D-mannopyranoside (**26**) (0.20 g, 1.03 mmol) was reacted in the same way as for **23**. Workup (procedure b2) yielded the title compound (0.32 g, 72%): mp 90–91 °C (crystallized once form ethanol); $[\alpha]^{22}_D$ +48° (*c* 1.2, $CHCl_3$) [lit.[19] mp 91–92 °C; [α] +37° ($CHCl_3$)].

Halogenation Reagent System C. Methyl α-D-mannopyranoside (**26**) (0.40 g, 2.06 mmol) was reacted in the same way as for **23**. Workup (procedure c2) yielded the title compound (0.57 g, 64%).

Acknowledgment. We thank professors Per J. Garegg and Bengt Lindberg for their interest and the National Swedish Board for Technical Development and the Swedish Natural Science Research Council for financial support.

Registry No. 1, 1079-66-9; 2, 739-58-2; 6, 4099-85-8; 7, 38838-06-1; 8, 38838-05-0; 9, 4064-06-6; 10, 4026-28-2; 11, 38838-08-3; 12, 13100-46-4; 13, 7468-48-6; 14, 582-52-5; 15, 67337-61-5; 16, 51016-10-5; 17, 117560-27-7; 18, 71117-37-8; 19, 117605-32-0; 20, 117605-33-1; 21, 117560-28-8; 22, 709-50-2; 23, 6304-96-7; 24, 709-50-2; 25, 7511-38-8; 26, 617-04-9; 27, 50692-55-2.

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Irreversible and Highly Enantioselective Acylation of 2-Halo-1-arylethanols in Organic Solvents Catalyzed by a Lipase from *Pseudomonas fluorescens*

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Received July 1, 1988

In recent years enzymatic catalysis in organic solvents has been the subject of extensive investigations.[1] Lipases have been successfully used as transesterification catalysts for stereoselective acylation[2] and kinetic resolution of alcohols.[3] The enzymatic process, however, is reversible and often requires long reaction times and a large excess of esters as the acyl donor in order to achieve a reasonable degree of conversion.[2,3b,4]

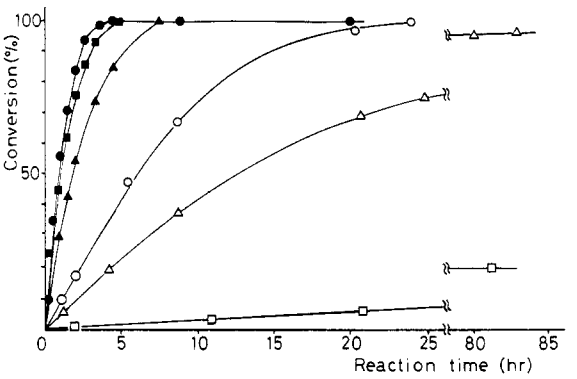
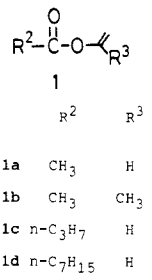


Figure 1. Lipase-catalyzed transesterification of 1-hexanol with vinyl acetate (●), isopropenyl acetate (○), vinyl butyrate (▲), vinyl octanoate (■), 2,2,2-trichloroethyl acetate (△), and ethyl acetate (□). Conditions: 1-hexanol (10 mmol), enol esters 1 (10.5 mmol), lipase Amano P (500 mg), dry diisopropyl ether (20 mL), 25 °C. Detection: GC (2% XE-60, 2 m, 70 °C, ethyl benzene as internal standard).

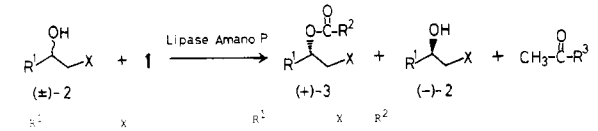
Scheme I



1

	R^2	R^3
1a	CH_3	H
1b	CH_3	CH_3
1c	n-C_3H_7	H
1d	n-C_7H_{15}	H

Scheme II



	X		R^1	X	R^2
2a	C_6H_5	Cl	3a	C_6H_5	Cl	CH_3
2b	2-$C_{10}H_7$	Br	3b	2-$C_{10}H_7$	Br	CH_3
2c	4-BrC_6H_4	Br	3c	4-BrC_6H_4	Br	CH_3
2d	4-$CH_3OC_6H_4$	Br	3d	4-$CH_3OC_6H_4$	Br	CH_3
2e	3,4-di-CH_3O C_6H_3	Cl	3e	3,4-di-CH_3O C_6H_3	Cl	CH_3
			3f	C_6H_5	Cl	n-C_3H_7
			3g	C_6H_5	Cl	n-C_7H_{15}

Recent application of vinyl or isopropenyl esters as the acylating agent to a lipase-catalyzed esterification[5] appears to offer an effective solution to this problem because the enol, product, is immediately transformed irreversibly into acetaldehyde or acetone. However, not all of the commercially available lipases are necessarily effective for transesterification with enol esters; moreover, the irreversibility (equilibrium) has not yet been clearly demonstrated, although high reactivity (reaction rate) of enol

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Table I. Stereoselective Acylation of Racemic 2-Halo-1-arylethanols 2 with Enol Esters 1 Catalyzed by Lipase Amano P[a]

	enol ester 1				S ester 3			R alcohol 2		
substr	R^2	R^3	reactn time, h	convrn,[b] %	yield,[c] %	$[\alpha]^{25}_D$, deg	ee, %	yield,[c] %	$[\alpha]^{25}_D$, deg	ee, %
2a	CH_3	CH_3	17	52	52	+73.2[d]	92[e]	44	−51.5[f]	97[e]
2a	CH_3	H	5	51	52	+74.0[d]	93[e]	51	−50.1[f]	94[e]
2a	n-C_3H_7	H	24	52	49	+66.2[g]	97[e]	46	−51.4[f]	96[e]
2a	n-C_7H_{15}	H	24	50	49	+47.9[g]	96[h]	47	−49.2[f]	92[e]
2b	CH_3	CH_3	38	50	48	+70.0[i]	95[h]	50	−38.8[j]	80[k]
2c	CH_3	CH_3	26	50	48	+56.6[l]	95[m]	51	−31.0[n]	94[k]
2d	CH_3	CH_3	30	49	48	+73.4[o]	93[m]	50	−37.7[o]	87[k]
2e[p]	CH_3	CH_3	42	50	47	+83.2[o]	97[m,q]	46	−43.1[o]	87[k,q]

[a] Conditions: substrate 2 (4.0–13 mmol), enol ester 1 (2.0 equiv of 2), dry lipase Amano P (2.0–6.5 g), dry diisopropyl ether (20–65 mL), 25 °C. [b] Determined by HPLC(hexane/AcOEt). [c] Isolated yield based on racemic 2. [d] c 2.0, acetone. [e] Determined by comparison of the observed specific rotations with the reported value.[10] [f] c 2.0, cyclohexane. [g] c 1.0, acetone. [h] Determined by HPLC analysis (column, CHIRALCEL OB, hexane/propan-2-ol) of 1-phenylethanol or 1-(2-naphthyl)ethanol derived from 3 ($LiAlH_4$, THF, 0 °C, 2 h), respectively. [i] c 3.0, $CHCl_3$. [j] c 2.5, $CHCl_3$. [k] Determined by ^1H NMR, ^{19}F NMR, or HPLC analysis of the corresponding MTPA ester. [l] c 3.4, $CHCl_3$. [m] Determined by ^1H NMR in the presence of chiral shift reagent, Eu(hfc)$_3$. [n] c 2.9, $CHCl_3$. [o] c 1.0, $CHCl_3$. [p] The reaction was conducted in a mixture of dry diisopropyl ether (10 mL) and dry toluene (10 mL). [q] Absolute configuration was not determined.

esters has been established.[5a,c] We screened a number of commercial lipases and found lipase Amano P[6] from *Pseudomonas fluorescens* to be more effective in transesterification of the enol esters **1a–d** with 1-hexanol (Scheme I). The time course of the reaction (Figure 1) showed that the reaction was fast and irreversible,[7] attaining 100% conversion in each case. Moreover, the lipase catalyzed the reaction with **1a–d** more effectively than that with 2,2,2-trichloroethyl acetate, which has been frequently used as a reactive acyl donor in lipase-catalyzed transesterification.[3a,c,8] Based on this observation, we have investigated the kinetic resolutions of racemic 2-halo-1-arylethanols **2** using lipase Amano P from *P. fluorescens* (Scheme II).

Optically active **2**, a versatile synthetic intermediate for compounds of pharmaceutical interest,[9] was obtained by several methods including enzymatic hydrolysis,[10] microbial hydrolysis,[11] and reduction;[12] however, lipase-catalyzed stereoselective acylation of **2** in organic solvents is an additional method not yet reported. Thus, racemic **2** was allowed to react with 2 molar equiv of **1** in the presence of lipase Amano P in dry diisopropyl ether (Scheme II).[13] The reaction virtually ceased when a half mole of **2** was consumed.[14] After the enzyme powder was removed by filtration, evaporation of solvent and chromatographic separation gave the product esters **3** and the unreacted alcohols **2** in high optical and chemical yields (Table I). Absolute configurations and enantiomeric excesses (ee) of the esters **3a,f,g** derived from **2a** were determined by comparison with the reported optical rotation values of the corresponding optically pure *R* esters **3a,f,g**.[10] The reaction of **2a** with vinyl acetate (**1a**) was terminated in 5 h; the reaction rate with **1a** was much faster than that of isopropenyl acetate (**1b**), vinyl butyrate (**1c**), and vinyl octanoate (**1d**). No differences were noted in the reactivity or stereoselectivity between **1c** and **1d**. The absolute configurations of bromoethyl esters **3b**, **3c**, and **3d** were established by reduction to the corresponding 1-arylethanols[15,16] with $LiAlH_4$ followed by optical rotation comparison and/or HPLC analysis. In each case the lipase was found to acylate the *S* isomer of 2-halo-1-arylethanols **2** exclusively, irrespective of the structure of both **2**[17] and enol esters **1** used.

In summary, lipase Amano P was shown to be as an excellent catalyst for transesterification of alcohols with the enol esters **1a–d**, permitting rapid and irreversible acylation of alcohols under mild conditions. The kinetic resolution of racemic 2-halo-1-arylethanols **2** was also successfully achieved with almost complete stereoselection by this enzymatic reaction. Considering the broad substrate specificity of the lipase, the present enzymatic system is expected to provide a versatile and synthetically useful method for stereo- and regioselective acylation of alcohols under mild conditions.

Experimental Section

General Methods. ^1H NMR spectra were measured in $CDCl_3$ at 60 or 200 MHz. HPLC analyses were carried out on a silica gel column (NUCLEOSIL 50-5, 4 mm × 25 cm, Chemco Pak, hexane/AcOEt) or a cellulose column (CHIRALCEL OB, 4.6 mm × 25 cm, hexane/propan-2-ol) for the analyses of enantiomers. The products were isolated by bulb-to-bulb distillation on a Büchi Kugelrohr apparatus or by preparative flash column chromatography on silica gel [Kieselgel 60 (230–400 mesh), Merck Co., Ltd.].

(6) Lipase Amano P from the bacterium *Pseudomonas fluorescens* was kindly provided by Amano Pharmaceutical Co., Ltd., Nagoya, Japan.

(7) When a mixture of 1-hexyl acetate (10 mmol) and acetone (10 mmol) or acetaldehyde (10 mmol) in dry diisopropyl ether (20 mL) in the presence of lipase (500 mg) was incubated at 25 °C for 50 h, neither isopropenyl acetate nor vinyl acetate was detected by GC, indicating that the equilibrium was located by far to the side of 1-hexyl acetate.

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(13) Diisopropyl ether was our choice for solvent because the reaction proceeded rapidly and the lipase was very stable in this solvent. Hexane and cyclohexane were also good solvents for this enzymatic reaction; however, the substrates were much less soluble in these nonpolar solvents. Diethyl ether was less suitable because it is rather volatile, although the reaction proceeded as well in this solvent as in diisopropyl ether. Diisopropyl ether has also been used as solvent for lipase-catalyzed reactions with rather good results. (a) Zaks, A.; Klibanov, A. M. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 3192–3196. (b) Yamamoto, K.; Nishioka, T.; Oda, J. *Tetrahedron Lett.* **1988**, *29*, 1717–1720. In addition, diethyl ether was reported to competitively inhibit a lipase in some cases. (c) Kim, K. H.; Kwon, D. Y.; Rhee, J. S. *Lipids* **1984**, *19*, 975–977. (d) Brockerhoff, H. *Arch. Biochem. Biophys.* **1969**, *134*, 366–371.

(14) A half mole of **1** was also used in the resolution of **2a**. Racemic **2a** (12.8 mmol), isopropenyl acetate (6.4 mmol), and lipase Amano P (600 mg) in diisopropyl ether (15 mL) for 3 days at 25 °C afforded (*S*)-**3** [45% yield, $[\alpha]^{25}_D$ +77.5° (c 5.1, acetone), 97% ee] and (*R*)-**2a** [45% yield, $[\alpha]^{25}_D$ −34.1° (c 1.7, acetone), 64% ee]. The conversion was 41% because some loss of **1** was caused by adventitious moisture, thus an excess of **1** was used throughout the experiments listed in Table I.

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(17) Absolute configuration of (−)-**2e** was not determined.

Diisopropyl ether, dimethoxyethane (DME), and toluene were distilled over CaH_2 and stored over 4-Å molecular sieves. THF was dried by distillation from sodium metal immediately before use. Enol esters 1 were all commercially available (Tokyo Chemical Industry Co., Ltd.) and purified by distillation before use. The purity of 1 was ascertained by GC and NMR. 2,2,2-Trichloroethyl acetate was prepared by mixing 2,2,2-trichloroethanol and an equimolar amount of acetic anhydride in the presence of concentrated H_2SO_4 (room temperature, 12 h) and purified by distillation [bp 62–72 °C (oven temperature)/14 mmHg, 91% yield; ^1H NMR δ 2.24 (s, 3 H), 4.85 (s, 2 H)]. Lipase powder (Amano P) was dried in a desiccator over P_2O_5 under reduced pressure (room temperature, 3 days).

(±)-2-Chloro-1-phenylethanol (2a); Standard Procedure. To a stirred solution of chloromethyl phenyl ketone (15.5 g, 100 mmol) in methanol (50 mL) was added sodium borohydride (1.90 g, 50 mmol) portionwise to maintain the temperature of the solution below 0 °C. The mixture was stirred at 0 °C for 30 min and then at room temperature for a further 30 min. The reaction mixture was acidified with 2 N HCl (50 mL) at 0 °C, and methanol was removed by evaporation. The resulting aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL) and the combined extracts were washed with saturated NaCl (3 × 30 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was distilled to afford **2a** as a colorless oil, 14.07 g (90%): bp 105–115 °C (oven temperature)/3 mmHg. The ^1H NMR spectral data agreed with the literature values.[10] Compounds **2b–d** were prepared by the same procedure. Only the purification method, physical state, yield, and ^1H NMR data are given.

(±)-2-Bromo-1-(2-naphthyl)ethanol (2b): crystallization from Et_2O–light petroleum; yield, 2.56 g (85%); mp 65–66 °C; ^1H NMR (200 MHz) δ 2.72 (br s, 1 H, OH), 3.62 (dd, 1 H, J_1 = 10.4, J_2 = 8.7 Hz, CH_2), 3.73 (dd, 1 H, J_1 = 10.4, J_2 = 3.5 Hz, CH_2), 5.10 (dd, 1 H, J_1 = 8.7, J_2 = 3.4 Hz, CH), 7.42–7.58 and 7.78–7.91 (m, 7-H).

(±)-2-Bromo-1-(4-bromophenyl)ethanol (2c): yield, 4.48 g (89%); bp 122–130 °C (oven temperature)/0.2 mmHg; ^1H NMR (200 MHz) δ 2.73 (br s, 1 H, OH), 3.48 (dd, 1 H, J_1 = 10.5, J_2 = 8.4 Hz, CH_2), 3.60 (dd, 1 H, J_1 = 10.5, J_2 = 3.6 Hz, CH_2), 4.88 (dd, 1 H, J_1 = 3.6, J_2 = 8.4 Hz, CH), 7.20–7.30 and 7.45–7.54 (m, 4-H).

(±)-2-Bromo-1-(4-methoxyphenyl)ethanol (2d): flash chromatography (hexane/AcOEt, 4:1) giving colorless oil; yield, 7.05 g (70%); ^1H NMR (200 MHz) δ 2.40 (br s, 1 H, OH), 3.51 (dd, 1 H, J_1 = 10.6, J_2 = 8.4 Hz, CH_2), 3.60 (dd, 1 H, J_1 = 10.6, J_2 = 4.0 Hz, CH_2), 3.80 (s, 3 H, OMe), 4.88 (dd, 1 H, J_1 = 8.4, J_2 = 4.0 Hz, CH), 6.82–6.98 and 7.22–7.39 (m, 4-H).

(±)-2-Chloro-1-(3,4-dimethoxyphenyl)ethanol (2e). A mixture of chloromethyl 3,4-dihydroxyphenyl ketone (3.00 g, 16.1 mmol), dimethyl sulfate (6.76 g, 53.6 mmol), and anhydrous K_2CO_3 powder (4.44 g, 32.2 mmol) in dry acetone (40 mL) was refluxed for 7 h under an argon atmosphere. The reaction mixture was filtered over Celite, and the filtrate was evaporated. The residue was diluted with AcOEt (50 mL), washed with 2 N HCl (40 mL), saturated $NaHCO_3$ (40 mL), and saturated NaCl (40 mL), and then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was dissolved in methanol and then diluted with Et_2O to afford chloromethyl 3,4-dimethoxyphenyl ketone as an amorphous powder, 1.79 g (52.0%): ^1H NMR (200 MHz) δ 3.94 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 4.66 (s, 2 H, CH_2Br), 6.90 (d, 1 H, J = 8.2 Hz, 5-H_{Ar}), 7.53 (d, 1 H, J = 2.0 Hz, 2-H_{Ar}), 7.56 (dd, 1 H, J_1 = 8.2, J_2 = 2.0 Hz, 6-H_{Ar}). According to the standard procedure, chloromethyl 3,4-dimethoxyphenyl ketone was reduced with sodium borohydride to give **2e** quantitatively as a colorless oil. The purity was ascertained by TLC and the product **2e** was used without further purification, 1.76 g: ^1H NMR (200 MHz) δ 2.64 (d, 1 H, J = 3.0 Hz, OH), 3.62 (dd, 1 H, J_1 = 11.2, J_2 = 8.4 Hz, CH_2), 3.72 (dd, 1 H, J_1 = 11.2, J_2 = 3.8 Hz, CH_2), 3.87 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 4.84 (m, 1 H, CH), 6.80–6.95 (m, 3-H).

Kinetic Resolution of 2-Halo-1-arylethanols 2; Typical Procedure. 2-Chloro-1-phenylethanol (**2a**, 2.00 g, 12.8 mmol) was dissolved in dry diisopropyl ether (64 mL). Dry lipase Amano P (6.4 g) and isopropenyl acetate (**1b**, 2.56 g, 25.5 mmol) were added successively to the solution and the mixture was stirred at room temperature with monitoring the conversion by HPLC (hexane/AcOEt, 10:1). The reaction ceased at 52% conversion (17 h). The enzyme was removed by filtration and the filtrate was evaporated to give a colorless oil. The ester **3a** and the unreacted alcohol **2a** were separated by column chromatography on silica gel (hexane/AcOEt, 20:1–15:1) to give optically active **3a** (1.23 g, 52% yield) and **2a** (0.88 g, 44% yield). Compounds (*R*)-**2a–e** and (*S*)-**3a–g** were enzymatically resolved by this procedure. Satisfactory combustion analyses (±0.3% of calcd values) for carbon and hydrogen were obtained for all products.

(*R*)-2-Chloro-1-phenylethanol (2a): $[\alpha]^{25}_D$ −51.5° (*c* 2.0, cyclohexane) [lit.[10] $[\alpha]^{25}_D$ +53.3° (*c* 2, cyclohexane) for optically pure *S* isomer], 97% ee; MS (70 eV), *m/e* (relative intensity) 156 (M^+, 2.7).

(*R*)-2-Bromo-1-(2-naphthyl)ethanol (2b): $[\alpha]^{25}_D$ −38.8° (*c* 2.54, $CHCl_3$). The ee was determined by ^1H NMR analysis of the corresponding MTPA ester and found to be 80%.

(*R*)-2-Bromo-1-(4-bromophenyl)ethanol (2c): $[\alpha]^{25}_D$ −31.0° (*c* 2.85, $CHCl_3$). The ee was calculated to be 94% by HPLC analysis of the corresponding MTPA ester.

(*R*)-2-Bromo-1-(4-methoxyphenyl)ethanol (2d): $[\alpha]^{25}_D$ −37.7° (*c* 1.0, $CHCl_3$); MS (70 eV), *m/e* (relative intensity), 230 (M^+, 8) and 232 ($[M + 2]^+$, 8). The ee was calculated from ^{19}F NMR analysis of the corresponding MTPA ester (δ 4.27 and 4.35 with CF_3CO_2H as internal standard), 87% ee.

(−)-2-Chloro-1-(3,4-dimethoxyphenyl)ethanol (2e): $[\alpha]^{25}_D$ −43.1° (*c* 1.04, $CHCl_3$). The ee was calculated to be 87% by ^1H NMR analysis of the corresponding MTPA ester.

(*S*)-2-Chloro-1-phenylethyl acetate (3a) was prepared from racemic **2a** and **1b**: $[\alpha]^{25}_D$ + 73.2° (*c* 2.02, acetone) [lit.[10] $[\alpha]^{25}_D$ −80.0° (*c* 2, acetone) for optically pure *R* isomer], 92% ee; ^1H NMR (200 MHz) δ 2.14 (s, 3 H, OAc), 3.71 (dd, 1 H, J_1 = 4.8, J_2 = 11.6 Hz, CH_2), 3.80 (dd, 1 H, J_1 = 7.7, J_2 = 11.6 Hz, CH_2), 5.96 (dd, 1 H, J_1 = 4.8, J_2 = 7.7 Hz, CH), 7.22–7.47 (m, 5-H).

(*S*)-2-Bromo-1-(2-naphthyl)ethyl acetate (3b) was prepared from racemic **2b** and **1b**: $[\alpha]^{25}_D$ +70.0° (*c* 3.0, $CHCl_3$); ^1H NMR (200 MHz) δ 2.17 (s, 3 H, OAc), 3.66 (dd, 1 H, J_1 = 5.0, J_2 = 11.0 Hz, CH_2), 3.75 (dd, 1 H, J_1 = 7.8, J_2 = 11.0 Hz, CH_2), 6.14 (dd, 1 H, J_1 = 5.0, J_2 = 7.8 Hz, CH), 7.40–7.55 and 7.75–8.00 (m, 7-H). The ee was determined as 95% by HPLC analysis of the corresponding 1-(2-naphthyl)ethanol prepared by $LiAlH_4$ reduction of **3b** (vide infra).

(*S*)-2-Bromo-1-(4-bromophenyl)ethyl acetate (3c) was prepared from racemic **2c** and **1b**: $[\alpha]^{25}_D$ +56.6° (*c* 3.4, $CHCl_3$); ^1H NMR (200 MHz) δ 2.14 (s, 3 H, OAc), 3.54 (dd, 1 H, J_1 = 5.4, J_2 = 10.8 Hz, CH_2), 3.62 (dd, 1 H, J_1 = 7.4, J_2 = 10.8 Hz, CH_2), 5.91 (dd, 1 H, J_1 = 5.4, J_2 = 7.4 Hz, CH), 7.18–7.25 and 7.45–7.55 (m, 4-H); MS (70 eV), *m/e* (relative intensity), 320 (M^+, 1.2) and 322 $[M + 2]^+$, 2). The ee was found to be 95% by ^1H NMR in the presence of chiral shift reagent Eu(hfc)$_3$ [ca. 5 mg of Eu(hfc)$_3$ for 10 mg of **3c** in 700 μL of $CDCl_3$, δ 2.68 and 2.73, OAc].

(*S*)-2-Bromo-1-(4-methoxyphenyl)ethyl acetate (3d) was prepared from racemic **2d** and **1b**: $[\alpha]^{25}_D$ +73.4° (*c* 1.03, $CHCl_3$); ^1H NMR (200 MHz) δ 2.11 (s, 3 H, OAc), 3.54 (dd, 1 H, J_1 = 5.0, J_2 = 10.8 Hz, CH_2), 3.65 (dd, 1 H, J_1 = 8.2, J_2 = 10.8 Hz, CH_2), 3.80 (s, 3 H, OMe), 5.92 (dd, 1 H, J_1 = 5.0, J_2 = 8.2 Hz, CH), 7.84–7.92 and 7.23–7.35 (m, 4-H); MS (70 eV), *m/e* (relative intensity), 272 (M^+, 7) and 274 ($[M + 2]^+$, 7). The ee was determined as 93% [^1H NMR, Eu(hfc)$_3$].

(+)-2-Chloro-1-(3,4-dimethoxyphenyl)ethyl acetate (3e) was prepared from racemic **2e** and **1b**: $[\alpha]^{25}_D$ +83.2° (*c* 1.02, $CHCl_3$); ^1H NMR (200 MHz) δ 2.12 (s, 3 H, OAc), 3.68 (dd, 1 H, J_1 = 4.8 J_2 = 11.6 Hz, CH_2), 3.79 (dd, 1 H, J_1 = 7.9, J_2 = 11.6 Hz, CH_2), 3.87 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 5.89 (dd, 1 H, J_1 = 4.8, J_2 = 7.9, CH), 6.80–6.96 (m, 3-H). The ee was calculated to be 97% [^1H NMR, Eu(hfc)$_3$].

(*S*)-2-Chloro-1-phenylethyl butyrate (3f) was prepared from racemic **2a** and vinyl butyrate (**1c**): $[\alpha]^{25}_D$ +66.2° (*c* 1.02, acetone) [lit.[10] $[\alpha]^{25}_D$ −68.6° (*c* 1, acetone) for optically pure *R* isomer], 97% ee; ^1H NMR (200 MHz) δ 0.94 (t, 3 H, J = 7.4 Hz, CH_3), 1.68 (sextet, 2 H, J = 7.4 Hz, CH_2CH_3), 2.38 (2 t, 2 H, J = 7.4 Hz, $COCH_2$), 3.71 (dd, 1 H, J_1 = 4.9, J_2 = 11.6 Hz, CH_2), 3.79 (dd, 1 H, J_1 = 7.6, J_2 = 11.6 Hz, CH_2), 5.97 (dd, 1 H, J_1 = 4.9, J_2 = 7.6 Hz, CH), 7.30–7.40 (m, 5-H).

(*S*)-2-Chloro-1-phenylethyl octanoate (3g) was prepared from racemic **2a** and vinyl octanoate (**1d**): $[\alpha]^{25}_D$ +47.9° (*c* 1.01, acetone) [lit.[10] $[\alpha]^{25}_D$ −46.3° (*c* 1, acetone) for *R* isomer], 96% ee

(calculated from HPLC analysis of the corresponding 1-phenylethanol); ^{1}H NMR (200 MHz) δ 0.86 (m, 3 H, CH_3), 1.12–1.40 (m, 8 H, $(CH_2)_4$), 1.64 (m, 2 H, $COCH_2CH_2$), 2.39 (2 t, 2 H, J = 7.4 Hz, $COCH_2$), 3.71 (dd, 1 H, J_1 = 4.8, J_2 = 11.6 Hz, CH_2), 3.79 (dd, 1 H, J_1 = 7.6, J_2 = 11.6 Hz, CH_2), 5.96 (dd, 1 H, J_1 = 4.8, J_2 = 7.6 Hz, CH), 7.30–7.40 (m, 5-H).

Stereochemical Correlation. $LiAlH_4$ Reduction of 3; Typical Procedure. Ester **3b** [100 mg, 0.34 mmol, $[\alpha]^{25}_D$ +70.0° (*c* 3.0, $CHCl_3$)] was reduced with $LiAlH_4$ (25.8 mg, 0.68 mmol) at 0 °C in dry THF (5 mL) for 3 h. The usual workup and chromatographic purification gave (+)-1-(2-naphthyl)ethanol (25.7 mg, 44%): $[\alpha]^{25}_D$ +33.7° (*c* 1.29, EtOH) [lit.[15] $[\alpha]^{25}_D$ +41.3° (*c* 5.07, EtOH) for *R* isomer]; ^{1}H NMR (200 MHz) δ 1.58 (d, 3 H, J = 6.4 Hz, Me), 1.92 (br s, 1 H, OH), 5.07 (q, 1 H, J = 6.4 Hz, CH), 7.23–7.53 and 7.75–7.88 (m, 7-H). The ee was calculated to be 95% by HPLC (CHIRALCEL OB, hexane/propan-2-ol, 9:1, 0.3 mL/min, detected at 280 nm, t_R 43.2 (*S*) and 47.7 (*R*) min, α = 1.15).

(*R*)-(+)-1-Phenylethanol was prepared from ester **3c** [$[\alpha]^{25}_D$ +56.6° (*c* 3.4, $CHCl_3$)] by $LiAlH_4$ reduction (DME, reflux 12 h): $[\alpha]^{25}_D$ +51.4° (*c* 1.56, $CHCl_3$) [lit.[12b] $[\alpha]^{25}_D$ −50.2° (*c* 5.11, $CHCl_3$) for *S* isomer (93% ee)]; ^{1}H NMR (200 MHz) δ 1.50 (d, 3 H, J = 6.4 Hz, Me), 1.84 (s, 1 H, OH), 4.89 (q, 1 H, J = 6.4 Hz, CH), 7.20–7.45 (m, 5-H). The ee was determined as 96% by HPLC (CHIRALCEL OB, hexane/propan-2-ol, 9:1, 0.5 mL/min, detected at 254 nm, t_R 14.9 (*S*) and 18.3 (*R*) min, α = 1.50).

(*R*)-(+)-1-(4-Methoxyphenyl)ethanol was prepared from ester **3d** [$[\alpha]^{25}_D$ +73.4° (*c* 1.0, $CHCl_3$)] by $LiAlH_4$ reduction (THF, 0 °C, 3 h): $[\alpha]^{25}_D$ +31.1° (*c* 2.54, EtOH) [Lit.[16] $[\alpha]^{20}_D$ +19.4° (EtOH) for partially resolved *R* isomer]; ^{1}H NMR (200 MHz) δ 1.47 (d, 3 H, J = 6.5 Hz, Me), 1.83 (br s, 1 H, OH), 3.79 (s, 3 H, OMe), 4.84 (q, 1 H, J = 6.5 Hz, CH), 6.82–6.90 and 7.26–7.35 (m, 4-H).

Acknowledgment. We gratefully acknowledge a Grant-in-Aid from the Ministry of Education of Japan for Scientific Research on Priority Areas, Advanced Molecular Conversion.

Registry No. **1a**, 108-05-4; **1b**, 108-22-5; **1c**, 123-20-6; **1d**, 818-44-0; (±)-**2a**, 105228-01-1; (−)-**2a**, 56751-12-3; (±)-**2b**, 117465-33-5; (−)-**2b**, 85554-14-9; (±)-**2c**, 117465-34-6; (−)-**2c**, 96855-38-8; (±)-**2d**, 117340-79-1; (−)-**2d**, 117465-37-9; (±)-**2e**, 117340-80-4; (−)-**2e**, 117465-38-0; **3a**, 103665-43-6; **3b**, 117340-81-5; **3c**, 117340-82-6; **3d**, 117340-83-7; **3e**, 117340-84-8; **3f**, 117465-35-7; **3g**, 117465-36-8; 2-bromo-1-(4-bromophenyl)ethanone, 99-73-0; 2-bromo-1-(4-methoxyphenyl)ethanone, 2632-13-5; 2-bromo-1-(2-naphthalenyl)ethanone, 613-54-7; chloromethyl 3,4-dihydroxyphenyl ketone, 99-40-1; chloromethyl 3,4-dimethoxyphenyl ketone, 20601-92-7; chloromethyl phenyl ketone, 532-27-4; lipase amano p, 9001-62-1; (*R*)-(+)-1-(4-methoxyphenyl)ethanol, 1517-70-0; (+)-1-(2-naphthyl)ethanol, 52193-85-8; (*R*)-(+)-1-phenylethanol, 1517-69-7.

(*S*)-Proline Benzyl Ester as Chiral Auxiliary in Lewis Acid Catalyzed Asymmetric Diels–Alder Reactions

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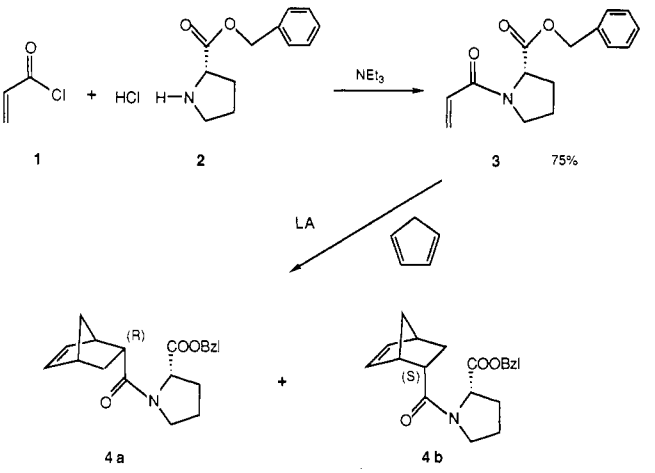
Received July 20, 1988

Asymmetric Diels–Alder reactions in which the cycloadducts are formed in high yields and with excellent diastereoselectivities have been carried out with chiral dienophilic esters,[1,5] α,β-unsaturated acyloxazolidinones[2] and -sultams.[3] In most cases reported the observed selectivities were explained exclusively by steric shielding. However, several authors recently have demonstrated that chelation with Lewis acids allows for an efficient differentiation of the diastereotopic faces of chiral acrylates.[2-5] This holds true especially for the acrylic acid ester of (*R*)-pantolactone.[5] The purpose of this paper is to describe that by using (*S*)-proline benzyl ester as chiral auxiliary high diastereoselectivities are obtained in Lewis acid catalyzed Diels–Alder reactions.

N-Acryloyl-(*S*)-proline benzyl ester (**3**) is easily prepared from acrylic acid chloride and proline benzyl ester hydrochloride.[6] It reacts with cyclopentadiene in the presence of Lewis acids in dichloromethane as solvent in good yields to provide the Diels–Alder adducts (Scheme I, Table I).

Depending on the catalyst used, either the 5*R* product **4a** or the 5*S* product **4b** is formed in excess. The best stereoselection is achieved at −10 °C in the presence of $TiCl_4$ (**4a**:**4b** = 97:3); however, at this temperature the yield

Scheme I



LA = Lewis Acid (see Table I)

Table I. Results of the Lewis Acid Catalyzed Diels–Alder Reactions between Cyclopentadiene and *N*-Acryloyl-(*S*)-proline Benzyl Ester

entry	temp, °C	Lewis acid	equiv of Lewis acid	yield, %	ratio **4a**:**4b**	endo/exo ratio
1	−10	$TiCl_4$	1	53	97:3	94:6
2	0	$TiCl_4$	1	85	96.5:3.5	92:8
3	10	$TiCl_4$	1	95	94:6	92:8
4	20	$TiCl_4$	1	95	96:4	90:10
5	30	$TiCl_4$	1	95	95:5	90:10
6	0	$TiCl_4$	0.75	83	96.3:3.7	93:7
7	0	$SnCl_4$	1	79	77:23	90:10
8	0	$ZnCl_2$	1	92	20:80	91:9
9	0	BF_3	1	80	16:84	91:9
10	0	$EtAlCl_2$	1	96	10:90	92:8

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