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Kinetic Resolution of Racemic α-tert-Alkyl-α-hydroxy Esters by Enantiomer-Selective Carbamoylation

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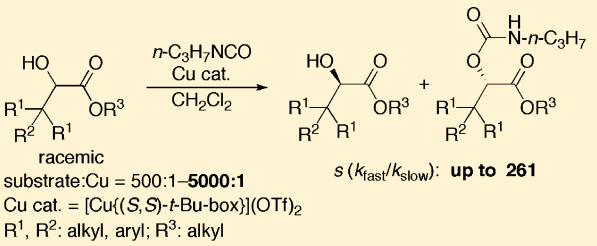
Supporting Information

ABSTRACT: Kinetic resolution of sterically hindered racemic α-tert-alkyl-α-hydroxy esters is performed by enantiomer-selective carbamoylation with the t-Bu-Box−Cu(II) catalyst (Box = bis(oxazoline)). The reaction with 0.5 equiv of n-C_3H_7NCO is carried out with a substrate-to-catalyst molar ratio of 500−5000 at −20 to 25 °C. The high enantiomer-discrimination ability of the catalyst achieves an excellent stereoselectivity factor ($s = k_{fast}/k_{slow}$) of 261 in the best case. A catalytic cycle for this reaction is proposed.



Optically active α-hydroxy esters have been widely used as the intermediates and the chiral auxiliaries for the synthesis of biologically useful compounds.[1,2] Kinetic resolution of these racemic alcohols is one of the most reliable and generally employable methods to obtain the chiral compounds in an enantiomerically pure form (in principle), although the chemical yield is 50% at most.[2b,3,4] Many useful asymmetric reactions including enzymatic transformations have been developed for this purpose. To our knowledge, however, no efficient procedures applicable to the α-tert-alkyl-α-hydroxy esters have been reported, primarily because of the marked steric hindrance around the hydroxy group.[5] Figure 1

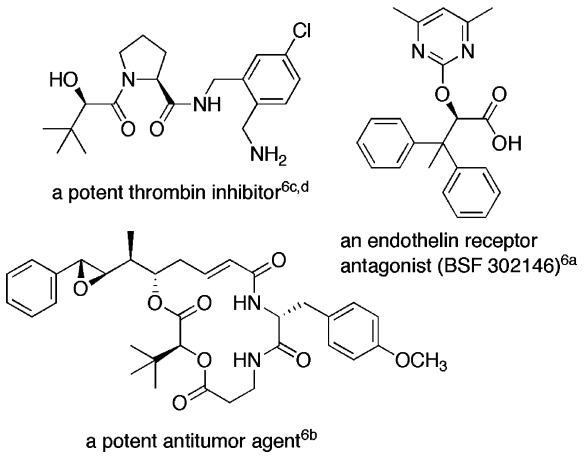


Figure 1. Bioactive molecules with structures derived from α-tert-alkyl-α-hydroxy esters.

shows examples of bioactive molecules that have structures derived from chiral α-tert-alkyl-α-hydroxy esters.[6] Thus, development of an efficient resolution method of this class of compounds is required from the scientific and practical viewpoints.[7]

We recently reported the kinetic resolution of α-hydroxy γ-lactones with the enantiomer-selective carbamoylation catalyzed by the chiral bis(oxazoline) (Box)−Cu(II) complexes.[8−10] The racemic α-hydroxy γ-lactones smoothly reacted with 0.5 equiv of isocyanates (RNCO) to give the carbamate and the unreacted substrate in high ee for both compounds. The reaction was conducted with a substrate-to-catalyst molar ratio (S/C) of 2000−3000, and the stereoselectivity factor s (k_{fast}/k_{slow})[11] reached 209 in the best case.[8] Thus, we expected that the high catalytic activity and enantioselectivity of the Box−Cu(II) complex enables efficient kinetic resolution of bulky α-tert-alkyl-α-hydroxy esters with the enantiomer-selective carbamoylation.

Racemic methyl 2-hydroxy-3,3-dimethylbutanoate [(±)-**1a**] was selected as a substrate to optimize the reaction conditions (Table 1). When (±)-**1a** (5.0 mmol, 0.5 M) and 0.5 equiv of n-C_3H_7NCO were mixed with [Cu{(*S*,*S*)-*t*-Bu-box}](OTf)$_2$ (TfO$^-$ = trifluoromethanesulfonate) [(*S*,*S*)-**3**][8,12] (10 μmol, S/C = 500) in CH_2Cl_2 at 25 °C, the conversion reached 50.2% in 1 h to give the unreacted (*R*)-**1a** in 95.1% ee and the carbamate (*S*)-**2a** in 94.4% ee (entry 1). A sufficiently high s value of 130 was obtained. The enantiomer selectivity was decreased with the increase of the substrate concentration (entries 1−3). An increase of reaction temperature during the carbamoylation under the higher substrate-concentration conditions due to the heat of the reactions is considered to be the main reason for the decrease in enantiomer selectivity. It is noteworthy that the carbamoylation proceeded smoothly at an S/C of 5000 with maintenance of a high level of

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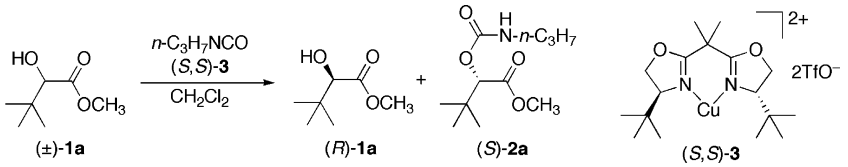
Table 1. Carbamoylation of Racemic Methyl 2-Hydroxy-3,3-dimethylbutanoate [(±)-1a] with Chiral Cu(II) Catalyst 3[a]



entry	temp (°C)	$[\mathbf{1a}]_0$ (M)[b]	S/C[c]	time (h)	ee_{1a} (%)[d]	ee_{2a} (%)[d]	convn (%)[e]	s[f]
1	25	0.5	500	1	95.1	94.4	50.2	130
2	25	0.8	500	1	93.8	93.9	50.0	112
3	25	3.4	500	1	92.3	91.3	50.3	73
4	25	0.5	1000	1	96.6	93.7	50.7	126
5	25	0.5	2000	1	94.8	93.3	50.4	106
6	25	0.5	5000	2	94.4	93.3	50.3	104
7	0	0.5	500	1	80.5	96.8	45.4	153
8	0	0.8	500	1	82.1	96.7	45.9	153
9	0	3.4	500	1	95.4	95.6	50.0[g]	170
10	0	neat[h]	500	1	95.8	93.2	50.7	111
11	0	3.4	1000	2	96.0	94.8	50.3	148
12	0	3.4	2000	3	92.6	94.6	49.4	121
13	−20	3.4	500	3	96.4	96.6	49.9	234
14	−20	3.4	1000	6	93.6	95.7	49.4	160

[a]Unless otherwise stated, reactions were conducted using (±)-**1a** (1−5 mmol) and 0.5 equiv of n-C_3H_7NCO in CH_2Cl_2 containing (*S,S*)-**3**. [b]Initial concentration of **1a**. [c]Substrate-to-catalyst molar ratio. [d]Determined by chiral GC analysis. [e]Convn = $ee_{1a}/(ee_{1a} + ee_{2a})$. [f]$s = \ln[(1 - \text{convn})(1 - ee_{1a})]/\ln[(1 - \text{convn})(1 + ee_{1a})]$. [g]Isolated yields of (*R*)-**1a** and (*S*)-**2a** are 45% and 50%, respectively. [h]Reaction without solvent.

enantioselectivity (s > 100), although superior enantiomer discrimination was available in the reactions under lower S/C conditions (entries 4−6). The reaction at 0 °C with an initial substrate concentration of 0.5 M showed enantioselectivity higher than that observed at 25 °C (s value, 153 vs 130) (entries 1 and 7). Interestingly, the higher substrate-concentration condition of 3.4 M resulted in even better enantiomer discrimination, although the reason for this result was not clear (entries 7−9). The carbamoylation without solvent still afforded very high enantioselectivity (s = 111) (entry 10). This feature has benefit for application to practical and green synthesis. The kinetic resolution ($[\mathbf{1a}]_0$ = 3.4 M) at 0 °C with an S/C of 1000 or 2000 still exhibited a high level of enantioselectivity and reactivity (entries 11 and 12). A remarkably high enantiomer selectivity (s = 234 at S/C = 500, s = 160 at S/C = 1000) was obtained in the reaction at −20 °C (entries 13 and 14).

The kinetic resolution of a series of α-*tert*-alkyl-α-hydroxy esters **1** by using enantiomer-selective carbamoylation with the Cu(II) catalyst (*S,S*)-**3** (S/C = 500) at 0 °C was examined. The results are summarized in Table 2. The initial substrate concentration ($[\mathbf{1}]_0$) was set at 2.9−3.4 M, except for the hardly soluble compounds **1g**, **1h**, and **1i** in CH_2Cl_2. 2-Hydroxy-3,3-dimethylbutanoates with a methyl, ethyl, isopropyl, or *tert*-butyl ester moiety, (±)-**1a**−**1d**, smoothly reacted with 0.5 equiv of n-C_3H_7NCO in 1 h to give the *R*-enriched substrates (*R*)-**1a**−**1d** and the corresponding *S* carbamates (*S*)-**2a**−**2d** in high ee (entries 1−4). The s values in the range of 153−195 suggest that the size of the ester group (CO_2R^3) is not a decisive factor for the enantiomer selection. A high s value of 182 was obtained in the carbamoylation of the substrate with an even bulkier α-[dimethyl(phenyl)]methyl group (±)-**1e**, although it took a longer period to reach 50% conversion (entry 5). The α-*tert*-alkyl structure of the substrates is crucial to achieve high enantioselectivity. Thus, the s values of the reactions with the α-isopropyl- and α-(diphenyl)methyl-substituted hydroxy esters, (±)-**1f** and -**1g**, were only 12 and 29, respectively (entries 6 and 7). In contrast, much higher enantioselectivity (s = 261) was observed in the reaction of the α-[methyl(diphenyl)]methyl substrate (±)-**1h** (entry 8). The kinetic resolution using 50 mmol (13.5 g) of (±)-**1h** and a 0.6 equiv of n-C_3H_7NCO was conducted to obtain enantiomerically pure (*R*)-**1h** (entry 9). The *R* alcohol in >99.9% ee (6.3 g) was obtained at 53% conversion (see the Experimental Section). (*R*)-**1h** is known to be readily converted to the enantiomer of an endothelin receptor antagonist BSF302146 (see Figure 1).[6a] The s value of 21 for the α-[methoxy(diphenyl)]methyl substrate (±)-**1i** was much lower than that in the reaction of (±)-**1h** (s = 261), although the bulkiness of both α-substituents is similar (entries 8 and 10). The β-methoxy function of **1i** may coordinatively interact with the Cu(II) center of the catalyst **3**, resulting in the insufficient enantiomer discrimination. The α-hydroxy ester with a 1-methylcyclohexyl group at the α position (±)-**1j** was also kinetically resolved with high enantioselectivity (entry 11).

A proposed mechanism for the carbamoylation of α-hydroxy esters catalyzed by Box−Cu(II) complexes is shown in Scheme 1.[8] [Cu(Box)](OTf)$_2$ (**A**) liberates the counteranion, TfO^-, to become the solvated cationic species $[Cu(Box)S_n]^{2+}$ (**B**) in the reaction mixture. The weakly binding molecules (S) are replaced by an α-hydroxy ester (HE) to form a chelation complex **C**. The species **C** reacts with RNCO to afford the carbamate (CAR)−Cu(II) complex **D**. The mode of carbamoylation at the stage of **C** to **D** is not clear yet. Catalytic species **B** and/or **C** are regenerated with release of the carbamate. The three cationic species, **B**, **C**, and **D**, could be in equilibrium. The HE−Cu(II) species **C** with a rigid five-membered chelate structure is more stable than the solvated complex **B** and the CAR−Cu(II) complex **D** with a seven-membered chelate structure, so that this reaction proceeds without serious product inhibition and achieves a high turnover number. The carbamoylation is one of the addition reactions

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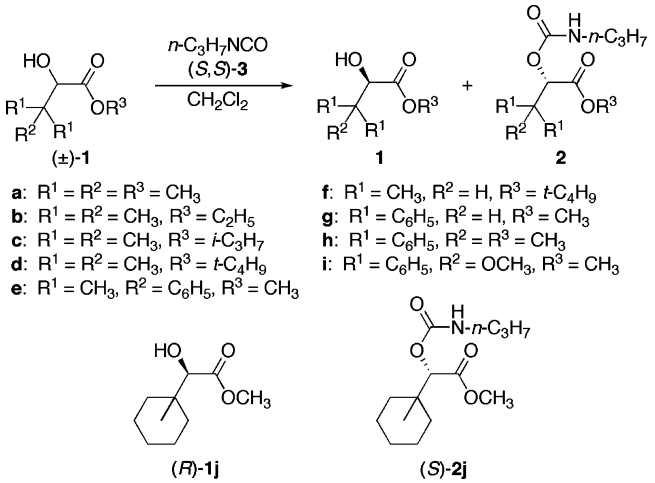
Table 2. Carbamoylation of Racemic α-Hydroxy Esters (±)-1 with Chiral Cu(II) Catalyst 3[a]



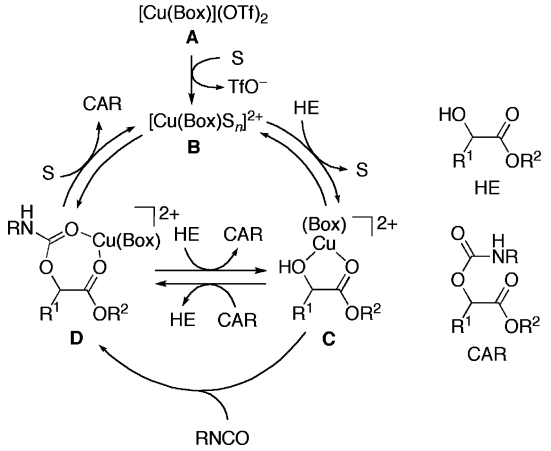
entry	1	$[1]_0$ (M)[b]	time (h)	ee_1 (%)[c]	ee_2 (%)[c]	convn (%)[d]	yield of 1/2 (%)[e]	s[f]
1	**1a**	3.4	1	95.4 (*R*)	95.6 (*S*)	50.0	45/50	170
2	**1b**	3.2	1	96.8 (*R*)	94.7 (*S*)	50.5	48/46	153
3	**1c**	2.9	1	96.0 (*R*)	95.3 (*S*)	50.2	42/49	164
4	**1d**	2.9	1	97.2 (*R*)	95.7 (*S*)	50.4	47/45	195
5	**1e**	3.4	3	97.2 (*R*)	95.4 (*S*)	50.5	43/50	182
6	**1f**	3.0	1	71.8	69.1	51.0	45/46	12
7	**1g**	1.9[g]	2	82.7	83.7	49.7	45/43	29
8	**1h**	0.8	12	96.6 (*R*)	96.9 (*S*)	49.9	48/50	261
9	**1h**[h]	0.8	6	>99.9 (*R*)	89.5 (*S*)	52.8	47/ –	nd[i]
10	**1i**	1.7	3	51.4	85.5	37.5	53/32	21
11	**1j**	3.4	3	94.6 (*R*)	95.1 (*S*)	49.9	50/45	146

[a]Unless otherwise stated, reactions were conducted using (±)-**1** (1–5 mmol) and 0.5 equiv of *n*-C_3H_7NCO at 0 °C in CH_2Cl_2 containing (*S*,*S*)-**3**. S/C = 500. [b]Initial concentration of **1**. [c]Determined by chiral GC analysis. Absolute configurations of **1** and **2** are indicated in the parentheses. [d]Convn = $ee_1/(ee_1 + ee_2)$. [e]Isolated yield. [f]$s = \ln[(1 - \text{convn})(1 - ee_1)]/\ln[(1 - \text{convn})(1 + ee_1)]$. [g]The approximate number is shown, because **1g** is a solid substrate. [h]Reaction using 50 mmol of **1h** and 0.6 equiv of *n*-C_3H_7NCO. [i]This value is not available, because the ee_1 value is almost 1.

but not a substitution reaction. Therefore, there is no leaving anion that inhibits the catalytic performance of Cu(II) cationic species.

In conclusion, the *t*-Bu-Box–Cu(II)-catalyzed carbamoylation precisely discriminates two enantiomers of α-*tert*-alkyl-α-hydroxy esters to give the unreacted hydroxy esters and the carbamates in high ee. The reaction was carried out with an S/C in the range of 500–5000 under a high concentration of substrates (ca. 3 M or without solvent). A remarkably high *s* value (k_{fast}/k_{slow}) of 261 is observed in the best case. A series of such sterically hindered chiral α-hydroxy esters, which are difficult compounds to prepare by other methods, is obtained through the enantiomer-selective reaction. The performance of a multigram-scale reaction demonstrates the facility for scale up of this process. A plausible catalytic cycle for this reaction is also described.

Scheme 1. Proposed Mechanism for the Cu(II)-Catalyzed Carbamoylation of α-Hydroxy Esters[a]



[a]HE = α-hydroxy ester, CAR = carbamate, S = solvent or weakly coordinated compounds.

EXPERIMENTAL SECTION

General Remarks. Racemic hydroxy esters **1a–1g** and **1j** were prepared via cyanosilylation of the corresponding aldehydes followed by hydrolysis of the nitrile moiety and esterification with *N*,*N*′-diisopropyl-*O*-alkylisourea reagents.[13] (±)-**1h** and **1i** were prepared in accordance with the literature.[14] (*S*)-2,2-Isopropylidene-bis(4-*tert*-butyl-2-oxazoline) was purchased from a commercial source and used without further purification. Racemic carbamates **2a–2i** were prepared as described in the literature.[15] *n*-Propyl isocyanate and anhydrous $Cu(OTf)_2$ were purchased from a commercial source. Anhydrous THF and CH_2Cl_2 were purchased from a commercial source and used without further purification. For preparative column chromatography and thin layer chromatography, commercially available silica gel (100–210 mm) and precoated TLC (silica gel, 1.0 mm) were used, respectively. NMR spectra were recorded on two types of spectrometer: 270 MHz for ^1H NMR, 67.8 MHz for ^{13}C NMR; and 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR. The

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chemical shifts were reported downfield from TMS (δ = 0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. High-pressure liquid chromatography (HPLC) analysis, gas chromatography (GC) analysis, IR spectra, optical rotations, and melting points (mps) were measured on standard commercial equipments.

Typical Procedure for Enantiomer-Selective Carbamoylation of Racemic Methyl 2-Hydroxy-3,3-dimethylbutanoate [(±)-1a]. [Cu{(*S*,*S*)-*t*-Bu-box}](OTf)$_2$ [(*S*,*S*)-**3**] was prepared by the method described in a previous report.[8] Freshly distilled (±)-**1a** (731 mg, 5.00 mmol) was placed in an oven-dried 20-mL Schlenk flask equipped with a Teflon-coated magnetic stirring bar, a serum-rubber cap, and a rubber balloon filled with argon. The 20 mM CH_2Cl_2 solution of (*S*,*S*)-**3** (0.50 mL, 10 μmol) was added to this flask through a syringe filter unit (pore size of 450 nm) to remove turbidity. The resulting solution was stirred for 10 min at 0 °C. To this solution was added *n*-C_3H_7NCO (0.23 mL, 2.5 mmol), and the reaction mixture was stirred at 0 °C for 1 h. Methanol (1 mL) was added to the mixture, and it was concentrated under reduced pressure. The residue was passed through a silica gel pad eluted with ethyl acetate to remove metal components, affording a mixture of recovered (*R*)-**1a** and the carbamate (*S*)-**2a**. The ee values of **1a** and **2a**, ee_{1a} and ee_{2a}, respectively, were determined by GC analysis. The conversion was estimated by the following equation: convn = $ee_{1a}/(ee_{1a} + ee_{2a})$.[11] The estimated conversion value agreed well with that determined by GC analysis using tetralin as an internal standard. The stereoselectivity factor ($s = k_{fast}/k_{slow}$) was calculated by the following equation: $s = \ln[(1 - convn)(1 - ee_{1a})]/\ln[(1 - convn)(1 + ee_{1a})]$.[11]

*(R)-Methyl 2-Hydroxy-3,3-dimethylbutanoate [(R)-**1a**].* 45% yield (333 mg, colorless oil); R_f = 0.21 (eluent, *n*-hexane/ethyl acetate = 8:1); $[\alpha]^{23}_D$ −35.5 (*c* 0.96, $CHCl_3$) (lit.[14] $[\alpha]^{22}_D$ +40.4 (*c* 3.22, $CHCl_3$), 97% ee (*S*)); IR (KBr) 3516, 2958, 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 2.74 (d, 1H, *J* = 8.0 Hz), 3.79 (s, 3H), 3.82 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.7, 35.1, 51.9, 78.4, 174.7; HRMS (ESI): *m*/*z* calcd 169.0841, [M + Na$^+$], obsd 169.0838; Chiral GC analysis: column, CP-Chirasil-Dex (0.32 mm × 25 m); carrier gas, helium (72 kPa); column temp, 80 °C; retention time (t_R) of (*R*)-**1a**: 8.8 min, t_R of (*S*)-**1a**: 10.2 min; 95% ee.

*(S)-Methyl 3,3-Dimethyl-2-propylaminocarbonyloxybutanoate [(S)-**2a**].* 50% yield (577 mg, colorless oil); R_f = 0.07 (eluent, *n*-hexane/ethyl acetate = 8:1); $[\alpha]^{23}_D$ +13.8 (*c* 1.03, $CHCl_3$); IR (KBr) 3376, 2964, 2876, 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J* = 6.0 Hz), 1.01 (s, 9H), 1.54 (sext, 2H, *J* = 6.0 Hz), 3.15 (q, 2H, *J* = 6.0 Hz), 4.61 (s, 1H), 4.89 (br s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.0, 22.9, 26.0, 33.5, 42.6, 51.4, 79.8, 155.8, 170.5; Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12, H, 9.15, N, 6.06, Found: C, 56.84, H, 9.12, N, 6.01; HRMS (ESI): *m*/*z* calcd 254.1368 [M + Na$^+$], obsd 254.1371; Chiral GC analysis: column, CP-Chirasil-Dex; carrier gas, helium (72 kPa); initial column temp, 80 °C (11 min) to 140 °C (8.5 min) at a rate of 10 °C min^{-1}; t_R of (*S*)-**2a**: 23.8 min, t_R of (*R*)-**2a**: 24.7 min; 96% ee.

*(R)-Ethyl 2-Hydroxy-3,3-dimethylbutanoate [(R)-**1b**].* 48% yield (389 mg, colorless oil); R_f = 0.39 (eluent, *n*-hexane/ethyl acetate = 6:1); $[\alpha]^{27}_D$ −25.3 (*c* 1.05, $CHCl_3$) (lit.[6d] $[\alpha]^{25}_{365}$ = −84 (*c* 1, CH_3OH), >95% ee (*R*)); IR (KBr) 3513, 2959, 1727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.32 (t, 3H, *J* = 7.2 Hz), 2.78 (d, 1H, *J* = 7.6 Hz), 3.79 (d, 1H, *J* = 7.6 Hz), 4.19−4.33 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.2, 25.7, 35.2, 61.2, 78.3, 174.3; HRMS (ESI): *m*/*z* calcd 183.0992 [M + Na$^+$], obsd 183.0995; Chiral GC analysis: column, CP-Chirasil-Dex; carrier gas, helium (72 kPa); column temp, 80 °C (11 min) to 110 °C at a rate of 10 °C min^{-1}; t_R of (*R*)-**1b**: 12.9 min, t_R of (*S*)-**1b**: 13.3 min; 97% ee.

*(S)-Methyl 3,3-Dimethyl-2-propylaminocarbonyloxybutanoate [(S)-**2b**].* 46% yield (572 mg, colorless oil); R_f = 0.17 (eluent, *n*-hexane/ethyl acetate = 6:1); $[\alpha]^{28}_D$ +9.25 (*c* 1.02, $CHCl_3$); IR (KBr) 3377, 2965, 2875, 1731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* = 7.4 Hz), 1.02 (s, 9H), 1.28 (t, 3H, *J* = 7.2 Hz), 1.49−1.59 (m, 2H), 3.15 (q, 2H, *J* = 6.6 Hz), 4.15−4.28 (m, 2H), 4.59 (s, 1H), 4.88 (br s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.0, 14.0, 23.0, 26.1, 33.5, 42.6, 60.6, 79.9, 155.9, 170.0; Anal. Calcd for $C_{12}H_{23}NO_4$: C, 58.75, H, 9.45, N, 5.71. Found: C, 58.98, H, 9.67, N, 5.64; HRMS (ESI): *m*/*z* calcd 268.1519 [M + Na$^+$], obsd 268.1518; Chiral GC analysis: column, CP-Chirasil-Dex; carrier gas, helium (72 kPa); initial column temp, 80 °C (11 min) to 150 °C (8.5 min) at a rate of 10 °C min^{-1}; t_R of (*S*)-**2b**: 23.7 min, t_R of (*R*)-**2b**: 24.2 min; 95% ee.

*(R)-Isopropyl 2-Hydroxy-3,3-dimethylbutanoate [(R)-**1c**].* 42% yield (337 mg, colorless oil); R_f = 0.36 (eluent, *n*-hexane/ethyl acetate = 6:1); $[\alpha]^{22}_D$ −24.4 (*c* 1.04, $CHCl_3$); IR (KBr) 3515, 2981, 1721 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.30 (d, 6H, *J* = 6.3 Hz), 2.81 (d, 1H, *J* = 7.4 Hz), 3.75 (d, 1H, *J* = 7.4 Hz), 5.13 (hept, 1H, *J* = 6.3 Hz); ^{13}C NMR (67.7 MHz, $CDCl_3$) δ 21.6, 21.7, 25.7, 35.1, 69.0, 78.2, 173.7; HRMS (ESI): *m*/*z* calcd 197.1148 [M + Na$^+$], obsd 197.1151; Chiral GC analysis: column, CP-Chirasil-Dex; carrier gas, helium (58 kPa); column temp 80 °C (16 min) to 100 °C at a rate of 10 °C min^{-1}; t_R of (*S*)-**1c**: 16.9 min, t_R of (*R*)-**1c**: 17.2 min; 96% ee.

*(S)-Isopropyl 3,3-Dimethyl-2-propylaminocarbonyloxybutanoate [(S)-**2c**].* 49% yield (587 mg, colorless oil), R_f = 0.17 (eluent, *n*-hexane/ethyl acetate = 6:1); $[\alpha]^{23}_D$ +8.31 (*c* 1.08, $CHCl_3$); IR (KBr) 3383, 2966, 2876, 1732 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J* = 7.6 Hz), 1.02 (s, 9H), 1.25 (d, 3H, *J* = 6.2 Hz),1.28 (d, 3H, *J* = 6.2 Hz), 1.47−1.57 (m, 2H), 3.15 (q, 2H, *J* = 6.8 Hz), 4.54 (s, 1H), 4.87 (br s, 1H), 5.09 (hept, 1H, *J* = 6.2 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.1, 21.6, 21.7, 23.0, 26.2, 33.6, 42.7, 68.3, 80.0, 155.9, 169.4; Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.21, H, 9.72, N, 5.40. Found: C, 60.13, H, 10.03, N, 5.43; HRMS (ESI): *m*/*z* calcd 282.1676 [M + Na$^+$], obsd 282.1673; Chiral GC analysis: column, CP-Chirasil-Dex; carrier gas, helium (72 kPa); initial column temp, 80 °C (16 min) to 150 °C (11 min) at a rate of 10 °C min^{-1}; t_R of (*S*)-**2c**: 30.6 min, t_R of (*R*)-**2c** 31.5 min; 95% ee.

*(R)-tert-Butyl 2-Hydroxy-3,3-dimethylbutanoate [(R)-**1d**].* 47% yield (93 mg, colorless oil); R_f = 0.34 (eluent, *n*-hexane/ethyl acetate = 10:1); $[\alpha]^{23}_D$ −19.7 (*c* 0.93, $CHCl_3$); IR (KBr) 3510, 2979, 1719, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.50 (s, 9H), 2.86 (d, 1H, *J* = 8.0 Hz), 3.67 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.9, 28.0, 35.3, 78.4, 82.4, 173.9; HRMS (ESI): *m*/*z* calcd 211.1305 [M + Na$^+$], obsd 211.1308; Chiral GC analysis: column, CP-Chirasil-Dex; carrier gas, helium (72 kPa); column temp, 100 °C; t_R of (*S*)-**1d**: 6.9 min, t_R of (*R*)-**1d**: 7.2 min; 97% ee.

*(S)-tert-Butyl 3,3-Dimethyl-2-propylaminocarbonyloxybutanoate [(S)-**2d**].* 45% yield (131 mg, colorless oil), R_f = 0.13 (eluent, *n*-hexane/ethyl acetate =10:1); $[\alpha]^{23}_D$ +7.31 (*c* 1.31, $CHCl_3$); IR (KBr) 3394, 2967, 2875, 1728, 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* = 7.4 Hz), 1.01 (s, 9H), 1.45−1.63 (m, 11H), 3.15 (q, 2H, *J* = 6.4 Hz), 4.47 (s, 1H), 4.86 (br s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.1, 23.1, 26.3, 28.0, 33.6, 42.7, 80.2, 81.4, 156.0, 169.1; Anal. Calcd for $C_{14}H_{27}NO_4$: C, 61.51, H, 9.96, N, 5.12, Found: C, 61.10, H, 10.01, N, 5.10; HRMS (ESI): *m*/*z* calcd 296.1832 [M + Na$^+$], obsd 296.1827; Chiral GC analysis: column, CP-Chirasil-Dex; carrier gas, helium (72 kPa); column temp, 100 °C (10 min) to 150 °C (7 min) at a rate of 10 °C min^{-1}; t_R of (*S*)-**2d**: 20.8 min, t_R of (*R*)-**2d**: 21.3 min; 96% ee.

*(R)-Methyl 2-Hydroxy-3-methyl-3-phenylbutanoate [(R)-**1e**].* 43% yield (90.4 mg, colorless oil); R_f = 0.39 (eluent, *n*-hexane/ethyl acetate = 4:1); $[\alpha]^{24}_D$ −43.2 (*c* 0.550, $CHCl_3$); IR (KBr) 3507, 2971, 2881, 1732 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.46 (s, 3H), 2.70 (d, 1H, *J* = 7.3 Hz), 3.60 (s, 3H), 4.22 (d, 1H, *J* = 7.3 Hz), 7.23−7.37 (m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 24.5, 24.6, 42.3, 51.9, 78.6, 126.3, 126.4, 128.0, 144.8, 173.9; Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21, H, 7.74, Found: C, 68.93, H, 7.78; HRMS (ESI): *m*/*z* calcd 231.0990 [M + Na$^+$], obsd 231.0992; Chiral HPLC analysis: column, CHIRALPAK AS-H (0.46 cm × 25 cm); eluent, *n*-hexane/2-propanol = 90:10; flow, 0.5 mL min^{-1}; column temp, 40 °C; detection, UV 254 nm; t_R of (*R*)-**1e**: 11.5 min, t_R of (*S*)-**1e**: 9.3 min; 97% ee.

*(S)-Methyl 3-Methyl-3-phenyl-2-propylaminocarbonyloxybutanoate [(S)-**2e**].* 50% yield (150 mg, colorless oil); R_f = 0.25 (eluent, *n*-hexane/ethyl acetate = 4:1); $[\alpha]^{24}_D$ +40.4 (*c* 0.93, $CHCl_3$); IR (KBr) 3372, 2967, 2876, 1729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 7.6 Hz), 1.42 (s, 3H), 1.45−1.50 (m, 5H), 3.09 (q, 2H,

J = 6.8 Hz), 3.56 (s, 3H), 4.78 (br s, 1H), 5.09 (s, 1H), 7.21−7.38 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 22.9, 24.5, 24.8, 40.5, 42.6, 51.5, 79.5, 126.1, 126.4, 127.9, 144.9, 155.5, 170.1; HRMS (ESI): m/z calcd 316.1519 [M + Na^+], obsd 316.1515; Chiral HPLC analysis: column, CHIRALPAK AS-H; eluent, n-hexane/2-propanol = 90:10; flow, 0.5 mL min^{-1}; column temp, 40 °C; detection, UV 254 nm; t_R of (*R*)-**2e**: 8.8 min, t_R of (*S*)-**2e**: 10.0 min; 95% ee.

*(−)-tert-Butyl 2-Hydroxy-3-methylbutanoate [(−)-**1f**].* 45% (94 mg, colorless oil); R_f = 0.53 (eluent, n-hexane/ethyl acetate = 6:1); $[\alpha]^{25}_D$ −4.4 (c 0.31, $CHCl_3$); IR (KBr) 3515, 2964, 2876, 1721 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.86 (d, 3H, J = 4.5 Hz), 1.02 (d, 3H, J = 6.9 Hz), 1.49 (s, 3H), 2.01−2.08 (m, 1H), 2.75 (d, 1H, J = 5.9 Hz), 3.92 (dd, 1H, J = 3.3 Hz, 5.9 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 15.7, 18.7, 27.9, 32.0, 74.8, 82.0, 174.1; HRMS (ESI): m/z calcd 197.1148 [M + Na^+], obsd 197.1152; Chiral GC analysis: column, CP-Chirasil-Dex; carrier gas, herium (72 kPa); column temp, 100 °C; t_R of major **1f**: 6.3 min, t_R of minor **1f**: 5.8 min; 72% ee.

*(+)-tert-Butyl 3-Methyl-2-propylaminocarbonyloxybutanoate [(+)-**2f**].* 46% (142 mg, colorless oil); R_f = 0.35 (eluent, n-hexane/ethyl acetate = 6:1); $[\alpha]^{26}_D$ +1.6 (c 1.28, $CHCl_3$); IR (KBr) 3389, 2967, 2876, 1728, 1519 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.91−1.00 (m, 9H), 1.47 (s, 9H), 1.51−1.57 (m, 2H), 2.13−2.21 (m, 1H), 3.16 (q, 2H, J = 6.7 Hz), 4.72 (d, 1H, J = 4.3 Hz), 4.86 (br s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.2, 17.1, 18.7, 23.1, 28.0, 30.2, 42.7, 76.9, 81.5, 156.0, 169.7; HRMS (EI): m/z calcd 260.1862 [M + H^+], obsd 260.1871; Chiral HPLC analysis: column CHIRALPAK AD-H (0.46 cm × 25 cm), eluent, n-hexane/2-propanol = 97:3, flow, 1.0 mL min^{-1}, column temp, 40 °C; detection, UV 230 nm; t_R of major **2f**: 7.5 min, t_R of minor **2f**: 6.8 min; 69% ee.

*(+)-Methyl 2-Hydroxy-3,3-diphenylpropanoate [(+)-**1g**].* 45% yield (115 mg, colorless solid); R_f = 0.17 (eluent, n-hexane/ethyl acetate = 6:1); $[\alpha]^{24}_D$ +27.2 (c 0.74, $CHCl_3$); Mp 62−64 °C; IR (KBr) 3487, 3028, 2950, 2923, 1737 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.77 (d, 1H, J = 6.5 Hz), 3.70 (s, 3H), 4.49 (d, 1H, J = 3.8 Hz), 4.94 (dd, 1H, J = 3.8 Hz, 6.5 Hz), 7.20−7.43 (m, 10H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 52.5, 54.2, 73.4, 126.5, 126.7, 127.1, 128.36, 128.38, 128.5, 129.3, 138.9, 141.2, 174.1; Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98, H, 6.29. Found: C, 74.93, H, 6.47; HRMS (ESI): m/z calcd 279.0992 [M + Na^+], obsd 279.0988; Chiral HPLC analysis: column, CHIRALCEL OD-H (0.46 cm × 25 cm); eluent, n-hexane/2-propanol = 90:10; flow, 0.5 mL min^{-1}; column temp, 40 °C; detection, UV 254 nm; t_R of minor **1g**: 15.9 min, t_R of major **1g**: 17.5 min; 83% ee.

*(−)-Methyl 3,3-Diphenyl-2-propylaminocarbonyloxypropanoate [(−)-**2g**].* 43% yield (144 mg, colorless wax); R_f = 0.10 (eluent, n-hexane/ethyl acetate = 6:1); $[\alpha]^{24}_D$ +77.3 (c 1.21, $CHCl_3$); IR (KBr) 3374, 3066, 3028, 2963, 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76−0.79 (br m, 3H), 0.86 (t, 3H, J = 7.4 Hz), 1.32 (br m, 2H), 1.47 (sext, 2H, J = 7.4 Hz), 2.96−3.01 (br m, 2H), 3.09 (q, 2H, J = 7.4 Hz), 3.49 (s, 3H), 3.51 (s, 3H), 4.55 (d, 1H, J = 7.4 Hz), 4.63−4.64 (m, 1H), 4.78 (br s, 1H), 5.72 (d, 1H, J = 7.4 Hz), 7.20−7.31 (m, 10H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 11.1, 23.0, 42.8, 52.0, 52.5, 74.6, 126.9, 127.0 (two signals), 128.4, 128.7, 139.5, 139.6, 155.3, 170.7; Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36, H, 6.79, N, 4.10. Found: C, 70.33, H, 6.88, N, 4.10; HRMS (ESI): m/z calcd 364.1519 [M + Na^+], obsd 364.1515; Chiral HPLC analysis: column, CHIRALCEL OD-H; eluent, n-hexane/2-propanol = 90:10; flow, 0.5 mL min^{-1}; column temp, 40 °C; detection, UV 254 nm; t_R of minor **2g**: 8.8 min, t_R of major **2g**: 10.0 min; 84% ee.

*(R)-Methyl 2-Hydroxy-3,3-diphenylbutanoate [(R)-**1h**].*[6a] 48% yield (650 mg, colorless solid); R_f = 0.35 (eluent, n-hexane/ethyl acetate = 4:1); $[\alpha]^{23}_D$ −92.3 (c 0.97, $CHCl_3$); Mp 33 °C; IR (KBr) 3504, 3088, 3056, 3028, 2950, 1732 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.77 (s, 3H), 2.97 (d, 1H, J = 8.1 Hz), 3.45 (s, 3H), 5.00 (d, 1H, J = 8.1 Hz), 7.17−7.36 (m, 10H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 24.3, 51.5, 52.0, 76.2, 126.1, 126.4, 127.81, 127.82, 128.0, 145.0, 146.2, 173.8; Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53, H, 6.71. Found: C, 75.48, H, 6.83; HRMS (ESI): m/z calcd 293.1148 [M + Na^+], obsd 293.1150; Chiral HPLC analysis: column, CHIRALPAK IA (0.46 cm × 25 cm); eluent, n-hexane/2-propanol = 90:10; flow, 0.5 mL min^{-1}; column temp, 40 °C; detection, UV 254 nm; t_R of (*S*)-**1h**: 13.3 min, t_R of (*R*)-**1h**: 15.0 min; 97% ee.

*(S)-Methyl 3,3-Diphenyl-2-propylaminocarbonyloxybutanoate [(S)-**2h**].* 50% yield (893 mg, colorless solid); R_f = 0.21 (eluent, n-hexane/ethyl acetate =4:1); $[\alpha]^{24}_D$ +206 (c 0.99, $CHCl_3$); Mp 99−101 °C; IR (KBr) 3401, 3088, 3061, 3028, 2963, 2878, 1729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79−0.82 (br m, 3H), 0.90 (t, 3H, J = 8.0 Hz), 1.34−1.41 (br m, 2H), 1.46−1.57 (m, 2H), 1.88 (s, 3H), 2.99−3.02 (br m, 2H), 3.08−3.21 (m, 2H), 3.31 (s, 3H), 4.63 (br s, 1H), 4.86 (br s, 1H), 5.71 (s, 1H), 7.11−7.32 (m, 10H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.0, 22.9, 23.5, 42.7, 49.1, 51.5, 77.2, 126.3, 126.4, 127.5, 127.7, 127.8, 127.9, 145.1, 145.4, 155.4, 170.0; Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96, H, 7.09, N, 3.94. Found: C, 70.64, H, 7.15, N, 3.91; HRMS (ESI): m/z calcd 378.1676 [M + Na^+], obsd 378.1676; Chiral HPLC analysis: column, CHIRALPAK IA; eluent, n-hexane/2-propanol = 90:10; flow, 0.5 mL min^{-1}; column temp, 40 °C; detection, UV 254 nm; t_R of (*S*)-**2h**: 11.3 min, t_R of (*R*)-**2h**: 13.8 min; 97% ee.

*(−)-Methyl 2-Hydroxy-3-methoxy-3,3-diphenylpropanoate [(−)-**1i**].* 53% yield (151 mg, colorless solid); R_f = 0.22 (eluent, n-hexane/ethyl acetate =6:1); $[\alpha]^{23}_D$ −9.00 (c 1.36, $CHCl_3$); Mp 97−100 °C; IR (KBr) 3498, 3059, 3026, 2951, 2833, 1732 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.95 (d, 1H, J = 8.1 Hz), 3.15 (s, 3H), 3.62 (s, 3H), 5.17 (d, 1H, J = 8.1 Hz), 7.28−7.43 (m, 10 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 52.2 (two signals), 73.7, 84.8, 127.4, 127.56, 127.59, 127.7, 128.4, 128.8, 139.8, 140.5, 172.7, Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31, H, 6.34. Found: C, 71.36, H, 6.42; HRMS (ESI): m/z calcd 309.1097 [M + Na^+], obsd 309.1099; Chiral HPLC analysis: column, CHIRALPAK IA; eluent, n-hexane/2-propanol = 90:10; flow, 0.5 mL min^{-1}; column temp, 40 °C; detection, UV 254 nm; t_R of minor **1i**: 11.4 min, t_R of major **1i**: 13.0 min; 51% ee.

*(+)-Methyl 3-Methoxy-3,3-diphenyl-2-propylaminocarbonyloxypropanoate [(+)-**2i**].* 32% yield (119 mg, colorless wax); R_f = 0.08 (eluent, n-hexane/ethyl acetate = 6:1); $[\alpha]^{24}_D$ +90.1 (c 1.10, $CHCl_3$); IR (KBr) 3370, 3060, 2963, 2876, 2840, 1729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75−0.79 (br m, 3H), 0.90 (t, 3H, J = 8.0 Hz), 1.20−1.27 (br m, 2H), 1.47−1.54 (m, 2H), 2.92−2.97 (br m, 2H), 3.08−3.22 (m, 2H), 3.28 (s, 3H), 3.31 (s, 3H), 3.52 (s, 3H), 4.62 (br s, 1H), 4.78 (br s, 1H), 5.99 (s, 1H), 7.28−7.33 (m, 10H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.0, 22.9, 42.8, 51.8, 52.9, 75.6, 83.5, 127.41, 127.47, 127.54, 127.7, 127.9, 128.1, 140.6, 141.2, 155.0, 168.7; HRMS (ESI): m/z calcd 394.1625 [M + Na^+], obsd 394.1627; Chiral HPLC analysis: column, CHIRALCEL OD-H; eluent, n-hexane/2-propanol = 90:10; flow, 0.5 mL min^{-1}; column temp, 40 °C; detection, UV 254 nm; t_R of major **2i**: 13.4 min, t_R of minor **2i**: 16.9 min; 85% ee.

*(R)-Methyl 2-Hydroxy-3,3-pentamethylenebutanoate [(R)-**1j**].* 50% yield (92.1 mg, colorless oil); R_f = 0.37 (eluent, n-hexane/ethyl acetate = 4:1); $[\alpha]^{23}_D$ −27.5 (c 0.48, $CHCl_3$), IR (KBr) 3508, 2927, 2856, 1732 cm^{-1}; ^{1}H NMR (400 MHz,$CDCl_3$) δ 0.88 (s, 3H), 1.30−1.55 (m, 10H), 2.68 (d, 1H, J = 8.0 Hz), 3.79 (s, 3H), 3.96 (d, 1H, J = 8.0 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.4, 21.59, 21.61, 26.1, 33.7, 34.0, 37.9, 52.0, 77.6, 175.0; HRMS(ESI): m/z calcd for $C_{10}H_{18}O_3$: 209.1148 [M + Na^+], obsd 209.1150; Chiral GC analysis: column, CP-Chirasil-Dex; carrier gas, helium (80 kPa); column temp, 80 to 130 °C at a rate of 0.5 °C min^{-1}; t_R of (*R*)-**1j**: 50.9 min, t_R of (*S*)-**1j**: 52.0 min; 95% ee.

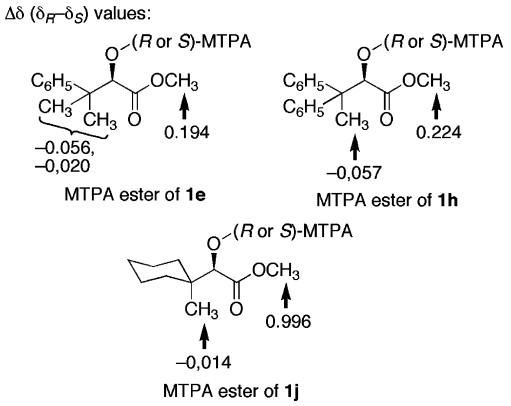
*(S)-Methyl 3,3-Pentamethylene-2-propylaminocarbonyloxybutanoate [(S)-**2j**].* 45% yield (120 mg, colorless oil); R_f = 0.23 (eluent, n-hexane/ethyl acetate = 4:1); $[\alpha]^{23}_D$ +17.2 (c 0.670, $CHCl_3$), IR (KBr) 3386, 3056, 2934, 1719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, 3H, J = 8.0 Hz), 0.97 (s, 3H), 1.26−1.59 (m, 10H), 3.15 (q, 2H, J = 6.8 Hz), 3.74 (s, 3H), 4.78 (s, 1H), 4.86 (br s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.1, 20.1, 21.3, 21.4, 23.0, 25.9, 34.1, 36.3, 42.7, 51.5, 78.9, 156.0, 170.6; HRMS(ESI): m/z calcd for $C_{14}H_{25}NO_4$: 294.1676 [M + Na^+], obsd 294.1674; Chiral GC analysis: column, CP-Chirasil-Dex; carrier gas, helium (80 kPa); initial column temp, 130 °C; t_R of (*S*)-**2j**: 98.1 min, t_R of (*R*)-**2j**: 101.4 min; 95% ee.

Gram-Scale Enantiomer-Selective Carbamoylation of 1h (Table 2, entry 9). Racemic substrate (±)-**1h** (13.5 g, 49.9 mmol) and CH_2Cl_2 (46 mL) were placed in an oven-dried 200-mL three-necked flask equipped with a Teflon-coated magnetic stirring bar,

a serum-rubber cap, and a rubber balloon filled with argon. A 25 mM CH_2Cl_2 solution of (*S*,*S*)-**3** (4.0 mL, 100 μmol) was added to this flask through a syringe filter unit. The resulting solution was stirred for 15 min at 0 °C. To this solution was added *n*-C_3H_7NCO (2.60 g, 30.2 mmol, 0.61 equivalents to **1h**), and the reaction mixture was stirred for 5.5 h at 0 °C. Methanol (10 mL) was added to the mixture, which was then concentrated under reduced pressure to give the crude product (17.1 g) as a green viscous oil. The crude product was purified by column chromatography (eluent, *n*-hexane/ethyl acetate = 8:1 to 2:1) to give (*R*)-**1h** in >99.9% ee (6.27 g, 47% yield); $[\alpha]^{23}_{D}$ −98.2 (*c* 1.13, $CHCl_3$).

Determination of the Absolute Configuration of Products. The absolute configurations of (*R*)-**1c** and -**1d** were determined by comparing their chiral GC behaviors with those of the authentic samples prepared from commercially available (*S*)-2-hydroxy-3,3-dimethylbutanoic acid by esterification according to the method described in the literature.[13c]

The absolute configurations of (*R*)-**1e**, -**1h**, and -**1j** were estimated by ^{1}H NMR analysis after conversion to the (*R*)- and (*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (MTPA) esters.[16] The values of $\Delta\delta$ ($\delta_R-\delta_S$) are listed below.



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of compounds **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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