Formal Asymmetric Synthesis of a Cholesterol Absorption Inhibitor Bearing a 2-Azaspiro[3.5]nonan-1-one Moiety

Takeshi Kambara and Kiyoshi Tomioka*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

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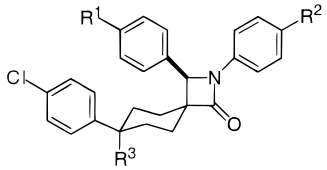
Introduction

Azetidin-2-one has been known as the central motif of the so-called β-lactam antibiotics.[1] The recent discovery of potent cholesterol absorption inhibition (CAI) by a class of azetidinones renewed interest in this class of compounds.[2] Subsequent work by the Schering-Plough group led to the further discovery that conformationally fixed spiro-fused azetidin-2-ones **1** and **2** also displayed potent CAI activity.[3] These efforts have stimulated significant synthetic interest in developing asymmetric processes.[4] The approaches to these types of azetidinones have employed chiral auxiliary- and chiral pool-based chemistry.[5,6] A recently reported brilliant exception for the construction of (*R*)-azetidin-2-one was the catalytic asymmetric aldol strategy followed by amination and cyclization.[7] Clearly, a catalytic and short-step asymmetric condensation process of an enolate with an imine would be much more effective to afford directly the desired azetidin-2-one. We have been engaged in the catalytic asymmetric condensation of a lithium ester enolate with an imine employing an external chiral ligand strategy.[8] We describe herein a short-step, catalytic asymmetric synthesis of substituted 2-azaspiro[3.5]nonan-1-one **8**, the key intermediate for Sch 58053 **1**.[9]



1: Sch 58053

R^1 = OH, R^2 = F, R^3 = OH

2: Sch 54016

R^1 = OMe, R^2 = H, R^3 = H

Results and Discussion

The synthetic strategy was to construct the spiro-fused azetidinone with the desired chiral center via an ester enolate−imine condensation. Our methodology employed for the condensation can be divided into two categories. One uses a ternary complex reagent that is comprised of a lithium ester enolate, a lithium amide, and a chiral ligand **5**,[8,10] and the other uses a binary complex[11] of a lithium ester enolate with the chiral ligands **5** or **10**. We examined both methodologies because such reagents are highly effective and readily available.

Our initial attempt at the asymmetric condensation of 4-fluoroaniline imine of 4-benzyloxybenzaldehyde **4** with the ternary reagent of lithium ester enolate **3**,[8,10] generated from 2 equiv of 2-methyl-1-(methylethyl)propyl 2-methylpropanoate, 2.6 equiv of dimethyl ether ligand **5**,[12] and 4.4 equiv of LDA in toluene, produced only a trace amount of the desired azetidinone **6**. Since the addition product was observed by TLC, the cyclization was considered to have suffered from an excess of lithium amide or lithium enolate. This problem was solved by addition of 1 equiv of methanol to quench the excess of lithium amide or lithium enolate prior to warming up for cyclization. Thus, after the reaction of the ternary complex of **3** with **4** was conducted at −60 °C for 8 h, methanol was added. The reaction mixture was allowed to warm to 10 °C over 2 h to afford **6** in 84% yield. The selectivity was determined to be 90% ee by a chiral stationary-phase HPLC.[13]

Encouraged by the high enantioselectivity, we then examined the condensation reaction of a lithium ester enolate **7** bearing the requisite protected 4-oxocyclohexyl moiety. The reaction of **7a** with **4** was conducted under the ternary complex reagent conditions, **7a**−**5**−lithium

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(13) The absolute configuration of **6** has not yet been determined.

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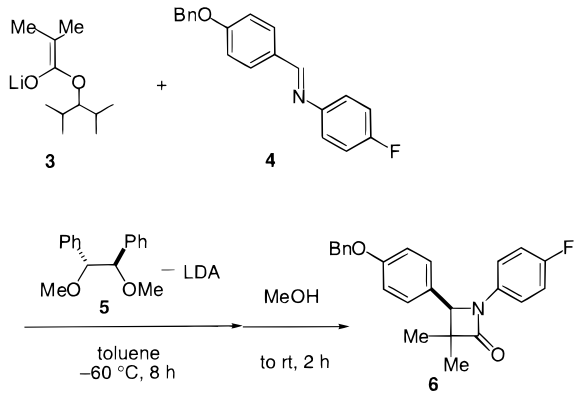
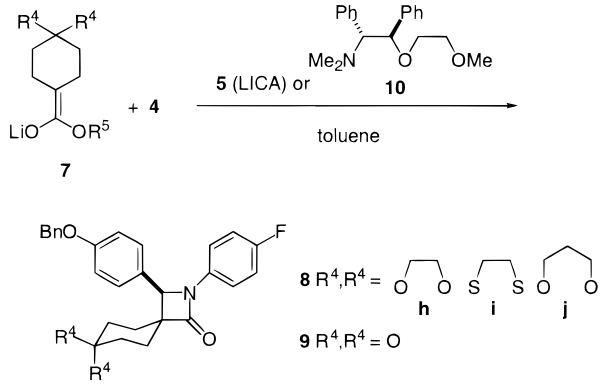


cyclohexylisopropylamide (LICA),[14] to afford (+)-**8h** in 74% yield and 62% ee (Table 1, entry 1). Although the selectivity was unexpectedly low, enantioenrichment was possible by recrystallization from ethanol to afford **8h** in over 98% ee and 40% overall yield. Unmasking of the ketal group in **8h** in aqueous acetic acid at 90 °C gave ketone (+)-(*R*)-**9** in 97% yield. Since the two-step and high-yield conversion of (*R*)-**9** to **1** has been already reported,[7] the present asymmetric synthesis constitutes the shortest-step formal synthesis of optically active **1**.



Although the enantioselective formal total synthesis of **1** was completed with the development delineated above, further efforts were continued to improve the efficiency of the condensation reaction. Thus, the reaction of a ternary complex of **7b**, generated from the ethyl ester, gave **8h** in 47% ee (entry 2). The corresponding binary complex of **7b**, generated from 2 equiv of the ester, 2.2 equiv of LICA, and 2.6 equiv of **5**, gave only 38% ee. Then, we changed the ethylenedioxy ketal protection to the ethylenedithio group. The reaction of the ternary complex of **7c** gave **8i** in a much poorer selectivity of 53% ee (entry 4). The ternary and binary complexes of the corresponding ethyl ester enolate **7d** also were not good enolate reagents, giving 37% ee and 27% ee (entries 5 and 6). Good selectivity was attained using the ternary complex of **7e** having a trimethlenedioxy protection to afford **8j** in 71% ee (entry 7). The reactions using **7f** were not satisfactory, giving **8j** in 52% ee and 36% ee (entries 8 and 9). The absolute configurations of (+)-**8i**,**j** were also determined by converting to (+)-(*R*)-**9**.

Although the results obtained above using a chiral diether ligand **5** were unsatisfactory, we were able to establish the highly enantioselective condensation of **7g** using a tridentate chiral aminodiether **10**.[11a] The reaction of the binary complex of **7g** was mediated by a stoichiometric amount of **10** at −40 °C for 1 h to give (+)-**8h** in 90% ee and quantitative yield (entry 10).[15] The catalytic asymmetric reaction was also realized using 20 mol % of **10** at −40 °C for 4 h to give **8h** in 81% ee and 86% yield. It is also important to note that the ligand **10** was recoverable quantitatively for reuse.

In summary, employing an enolate−imine condensation process, we have invented a catalytic enantioselective and direct synthesis of spiro-fused azetidin-2-one (+)-**8h**, the established intermediate for cholesterol absorption inhibitor, Sch 58053 **1**. We believe that the developed methodology is applicable to a catalytic asymmetric construction of a variety of substituted 2-azaspiro[3.5]-nonan-1-ones of pharmaceutical potency.

Experimental Section[16]

4-(2-Aza-2-(4-fluorophenyl)vinyl)-1-benzyloxybenzene (4). A mixture of 4-benzyloxybenzaldehyde (21.2 g, 100 mmol) and 4-fluoroaniline (11.1 g, 100 mmol) was stirred at 100 °C for 1 h. Recrystallization of a brown solid from EtOH afforded **4** as colorless plates (25.4 g, 84%) of mp 132−133 °C. IR (Nujol): 1600, 1500 cm^{-1}. MS *m*/*z*: 305 (M^+). Anal. Calcd for $C_{20}H_{16}FNO_2$: C, 78.67; H, 5.28; N, 4.59. Found: C, 78.58; H, 5.48; N, 4.48.

2-Methyl-1-(methylethyl)propyl 2-Methylpropanoate (the Ester Corresponding to 3). A mixture of isobutyric acid (60 g, 0.68 mol), 2,4-dimethylpentan-3-ol (237 g, 2.04 mol), and *p*-toluenesulfonic acid monohydrate (1.22 g, 6.8 mmol) in toluene (60 mL) was stirred under reflux (with Dean−Stark trap) for 2 d and quenched with saturated $NaHCO_3$. The organic layer was washed with brine and then dried over Na_2SO_4. Concentration followed by distillation (bp 75 °C/15 mmHg) gave the ester as a colorless oil (68 g, 53%). IR (neat): 1730 cm^{-1}. MS *m*/*z*: 186 (M^+). Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.65; H, 11.85.

2-Methyl-1-(methylethyl)propyl 4-Oxocyclohexanecarboxylate. A mixture of 4-oxocyclohexanecarboxylic acid[17] (3.55 g, 25 mmol), 2-methyl-1-(methylethyl)propanol (3.02 g, 26 mmol), DCC (6.19 g, 30 mmol), and 4-(dimethylamino)pyridine (0.92 g, 8 mmol) in $CHCl_3$ (25 mL) was stirred at room temperature for 0.5 h. After filtration, the filtrate was concentrated to give an oil. Chromatography (EtOAc/hexane = 3/1, then ether) gave the ester (4.98 g, 83%) as a colorless oil. IR (film): 1720 cm^{-1}. MS *m*/*z*: 240 (M^+). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.98; H, 10.08.

1-Ethylpropyl 4-Oxocyclohexanecarboxylate. By the same procedure for the above ester, the ester was obtained in 83% yield as a colorless oil of bp 150 °C (2.5 mmHg). IR (film): 1720 cm^{-1}. MS *m*/*z*: 212 (M^+). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.74; H, 9.76.

2-Methyl-1-(methylethyl)propyl 1,4-Dioxaspiro[4.5]decane-8-carboxylate (the Ketal Corresponding to 7a). According to the reported procedure for ethyl 1,4-dioxaspiro[4.5]-decane-8-carboxylate,[7] the ketal was obtained in 98% yield as an oil of bp 160 °C (0.9 mmHg). IR (film): 1725 cm^{-1}. MS *m*/*z*: 284 (M^+). Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.34; H, 9.83.

2-Methyl-1-(methylethyl)propyl 1,4-Dithiaspiro[4.5]decane-8-carboxylate (the Thioketal Corresponding to 7c). By the same procedure for the ethyl ester below, the ketone (120 mg, 0.5 mmol) was converted into the ketal (97%) as an oil of

(14) Use of LDA did not exceed the selectivity obtained by use of LICA.

(15) The ternary complex of **10** did not afford satisfactory selectivity.

(16) Purification was carried out using silica gel column chromatography unless otherwise noted.

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Table 1. Asymmetric Condensation of 7 with 4 Mediated by 5 and 10 Giving 8[a]

entry	7	R^4	R^5	ligand	LICA/equiv[b]	*T*/°C (time/h)	8	yield/%	ee/%
1	**a**	$O(CH_2)_2O$	*i*-Pr_2CH	**5**	1.2	−60 (15), 0 (0.5)[c]	**h**	74	62
2	**b**	$O(CH_2)_2O$	Et	**5**	1.2	−60 (15)	**h**	37	47
3	**b**	$O(CH_2)_2O$	Et	**5**	0	−70 to 0 (2)	**h**	99	38
4	**c**	$S(CH_2)_2S$	*i*-Pr_2CH	**5**	1.2	−20 (2)	**i**	61	53
5	**d**	$S(CH_2)_2S$	Et	**5**	1.2	−60 (20)	**i**	47	37
6	**d**	$S(CH_2)_2S$	Et	**5**	0	−15 (2)	**i**	70	27
7	**e**	$O(CH_2)_3O$	*i*-Pr_2CH	**5**	1.2	−40 (2), 0 (0.5)[c]	**j**	75	71
8	**f**	$O(CH_2)_3O$	Et	**5**	1.2	−60 (20)	**j**	71	52
9	**f**	$O(CH_2)_3O$	Et	**5**	0	−15 (2)	**j**	98	36
10	**g**	$O(CH_2)_2O$	Et_2CH	**10**	0	−40 (1)	**h**	99	90

[a] The reaction was conducted using 2 equiv of **7** and 2.6 equiv of **5** or **10**. [b] The equivalency to **7**. [c] Methanol (1 equiv) was added before warming to 0 °C for cyclization.

bp 220 °C (2.5 mmHg). IR (film): 1725 cm^{-1}. MS *m*/*z*: 316 (M^+). Anal. Calcd for $C_{16}H_{28}O_2S_2$: C, 60.71; H, 8.92. Found: C, 60.66; H, 8.87.

Ethyl 1,4-Dithiaspiro[4.5]decane-8-carboxylate (the Thioketal Corresponding to 7d). A mixture of ethyl 4-oxocyclohexanecarboxylate[17c] (851 mg, 5 mmol), ethanedithiol (629 mg, 7.5 mmol), and boron trifluoride diethyl etherate (5 mmol) in CH_2Cl_2 (5 mL) was stirred for 15 min at 0 °C. Concentration followed by chromatography (EtOAc/hexane = 1/9) gave the thioketal (1.16 g, 94%) as a colorless oil of bp 200 °C (6 mmHg). IR (film): 1730 cm^{-1}. MS *m*/*z*: 246 (M^+). Anal. Calcd for $C_{11}H_{18}O_2S_2$: C, 53.62; H, 7.36. Found: C, 53.36; H, 7.45.

2-Methyl-1-(methylethyl)propyl 7,11-Dioxaspiro[5.5]undecane-3-carboxylate (the Ketal Corresponding to 7e). By the same procedure for the ketal corresponding to **7a**, the ketone was converted into the ketal (1.73 g, 97%) as an oil of bp 200 °C (1.5 mmHg). IR (film): 1725 cm^{-1}. MS *m*/*z*: 298 (M^+). Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.52; H, 10.29.

Ethyl 7,11-Dioxaspiro[5.5]undecane-3-carboxylate (the Ketal Corresponding to 7f). By the same procedure for the ketal corresponding to **7e**, the ketal was obtained in 96% yield as an oil of bp 190 °C (3 mmHg). IR (film): 1725 cm^{-1}. MS *m*/*z*: 228 (M^+). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.39; H, 9.01.

1-Ethylpropyl 1,4-Dioxaspiro[4.5]decane-8-carboxylate (the Ketal Corresponding to 7g). By the same procedure for the ketal corresponding to **7a**, the ketal was obtained in 98% yield. IR (film): 1725 cm^{-1}. MS *m*/*z*: 256 (M^+). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.31; H, 9.22.

(+)-1-(4-Fluorophenyl)-3,3-dimethyl-4-(4-benzyloxyphenyl)azetidin-2-one (6). A solution of 2-methyl-1-(methylethyl)propyl 2-methylpropanoate (372 mg, 2.0 mmol) and **5** (630 mg, 2.6 mmol) in toluene (3 mL) was added to a solution of LDA (4.4 mmol) in toluene (4 mL) at −78 °C. After the mixture was stirred for 20 min at −78 °C, a solution of imine **4** (239 mg, 0.78 mmol) in toluene (6 mL) was added to the solution. After the mixture was stirred at −60 °C for 8 h, MeOH (0.04 mL, 1 mmol) was added. The mixture was stirred at 0 °C for 15 min and then quenched with saturated NH_4Cl. The mixture was extracted with EtOAc. The combined organic layers were washed with brine and then dried over $MgSO_4$. Concentration followed by chromatography (EtOAc/hexane = 1/5) gave **6** (245 mg, 84%) as a solid of $[\alpha]^{25}_D$ +75.1 (*c* 1.40, $CHCl_3$). Ee was determined to be 90% by HPLC (Daicel Chiralcel OD-H, hexane−*i*-PrOH (50:1), 0.5 mL/min, 250 nm, 31 min (95.1%): 36 min (4.9%)). The ligand **5** was recovered quantitatively. IR (Nujol): 1740 cm^{-1}. MS *m*/*z*: 375 (M^+). Anal. Calcd for $C_{24}H_{22}FNO_2$: C, 76.78; H, 5.91; N, 3.73. Found: C, 76.48; H, 5.88; N, 3.67.

(+)-(*R*)-2-Aza-2-(4-fluorophenyl)-8,11-dioxa-3-(4-(benzyloxy)phenyl)dispiro[3.2.4.2]tridecan-1-one (Table 1, Entry 1, (+)-(*R*)-8h). A solution of the ester corresponding to **7a** (284 mg, 1.0 mmol) and **5** (315 mg, 1.3 mmol) in toluene (3 mL) was added to a solution of LICA (2.2 mmol) in toluene (15 mL) at −78 °C. After being stirred for 20 min at −78 °C, a solution of **4** (153 mg, 0.5 mmol) in toluene (7 mL) was added. After the mixture was stirred at −60 °C for 20 h, absolute MeOH (0.5 mmol) was added. The mixture was stirred at 0 °C for 15 min and then quenched with saturated NH_4Cl. The mixture was extracted with EtOAc. The organic layers were washed with brine and then dried over Na_2SO_4. Concentration followed by chromatography (EtOAc/hexane = 1/1) gave **8h** (176 mg, 74%) as a pale yellow solid of mp 69−72 °C and $[\alpha]^{25}_D$ +24.5 (*c* 1.00, $CHCl_3$). Ee was determined to be 62% by HPLC (Daicel Chiralpak AS, hexane−*i*-PrOH (2:1), 0.5 mL/min, 250 nm, 13 min (19%): 19 min (81%)). IR (Nujol): 1740 cm^{-1}. MS *m*/*z*: 473 (M^+). Anal. Calcd for $C_{29}H_{28}FNO_4$: C, 73.56;, H, 5.96; N, 2.96. Found: C, 73.41; H, 5.99;, N, 2.96. The ligand **5** was recovered quantitatively.

Enantioenrichment by Recrystallization of (+)-8h. Recrystallization of **8h** (69.4 mg, 0.15 mmol, 62% ee) from EtOH (0.8 mL) gave back **8h** (37.4 mg, 54%) of mp 66−67 °C and $[\alpha]^{25}_D$ +39.3 (*c* 1.20, $CHCl_3$). Ee was determined to be over 98%.

(+)-(*R*)-2-(4-Fluorophenyl)-3-(4-benzyloxy)phenyl)-2-azaspiro[3.5]nonane-1,7-dione ((+)-(*R*)-9). A solution of (+)-**8h** (31.4 mg, 0.07 mmol, 98% ee) in 30% AcOH (3 mL) was stirred for 36 h at 90 °C. The mixture was diluted with AcOEt, washed with saturated $NaHCO_3$ and brine, and then dried over Na_2SO_4. Concentration followed by chromatography (ether/hexane = 2/3) gave (+)-(*R*)-**9** (27.5 mg, 97%) as a white powder of mp 62−67 °C and $[\alpha]^{22.6}_D$ +40.5 (*c* 0.56, EtOH). Ee was determined to be 98% by HPLC (Daicel Chiralpak AS, hexane−*i*-PrOH (1:2), 0.5 mL/min, 250 nm, 21 min (1.05%): 36 min (99.0%)). IR (Nujol): 1740, 1725 cm^{-1}. MS *m*/*z*: 429 (M^+). Anal. Calcd for $C_{27}H_{24}FNO_3$: C, 75.51; H, 5.63; N, 4.42. Found: C, 75.32; H, 5.78; N, 3.26. NMR data were identical with those reported.[7]

Table 1,Entry 3. The binary complex of **7b** (the ester: 429 mg, 2.0 mmol) and **5** (630 mg, 2.6 mmol) in toluene (3 mL) gave **8h** (469 mg, 99%, 38% ee) as a colorless solid of mp 55−60 °C and $[\alpha]^{25}_D$ +15.6 (*c* 1.17, $CHCl_3$).

Table 1, entry 4: 2-aza-2-(4-fluorophenyl)-3-(4-(benzyloxy)phenyl)-8,11-dithiadispiro[3.2.4.2]tridecan-1-one (8i). By the same procedure as for **8h** (entry 1), **8i** was obtained in 61% yield as a pale yellow solid of mp 92−97 °C and $[\alpha]^{25}_D$ +7.3 (*c* 1.02, $CHCl_3$). Ee was determined by HPLC to be 53% (Daicel Chiralpak AS, hexane−*i*-PrOH (2:1), 0.5 mL/min, 250 nm, 16 min (23.6%): 29 min (76.4%)). IR (Nujol): 1735 cm^{-1}. MS *m*/*z*: 505 (M^+). Anal. Calcd for $C_{29}H_{28}FNO_2S_2$: C, 68.88; H, 5.58; N, 2.77. Found: C, 68.61; H, 5.63; N, 2.68.

Table 1, entry 7: 2-aza-2-(4-fluorophenyl)-8,12-dioxa-3-(4-(benzyloxy)phenyl)dispiro[3.2.5.2]tetradecan-1-one (8j). By the same procedure as for **8h** (entry 1), **8j** (182 mg, 75%) was obtained as a pale yellow solid of $[\alpha]^{25}_D$ +26.0 (*c* 1.00, $CHCl_3$). Ee was determined to be 71% by HPLC (Daicel Chiralpak AS, hexane−*i*-PrOH (2:1), 0.5 mL/min, 250 nm, 14 min (14.3%): 22 min (85.7%)). IR (Nujol): 1735 cm^{-1}. MS *m*/*z*: 487 (M^+). Anal. Calcd for $C_{30}H_{30}FNO_4$: C, 73.90; H, 6.20; N, 2.87. Found: C, 73.66; H, 6.32; N, 2.90.

Dethioketalization of 8i. To a solution of (+)-**8i** (40.5 mg, 0.08 mmol, 27% ee) in 75% MeCN was added cerium ammonium nitrate (350 mg, 0.64 mmol). The pale orange suspension was stirred for 0.5 h at room temperature and quenched with saturated $NaHCO_3$. The mixture was extracted with EtOAc. The organic layers were washed with brine and then dried over Na_2SO_4. Concentration followed by chromatography (EtOAc/hexane = 2/1) gave (+)-**9** (22.2 mg, 65%, 27% ee) as a powder of mp 52−56 °C and $[\alpha]^{22.6}_D$ +9.3 (*c* 0.65, EtOH).

Deketalization of 8j. By the same procedure for hydrolysis of **8a**, (+)-**8j** (73.1 mg, 0.15 mmol, 36% ee) was converted to (+)-**9**

(59.2 mg, 92%, 37% ee) as a powder of mp 62−67 °C and $[\alpha]^{22.6}_D$ +14.5 (*c* 0.57, EtOH).

Stoichiometric Asymmetric Reaction Using 10 (Table 1, entry 10). A solution of the ester corresponding to **7g** (384 mg, 1.5 mmol) and aminodiether **10** (569 mg, 1.95 mmol) in toluene (6 mL) was added to a solution of LDA (1.65 mmol) in toluene (5 mL) at −78 °C. After the mixture was stirred for 1 h, a solution of **4** (230 mg, 0.75 mmol) in toluene (6 mL) was added. After the mixture was stirred at −45 °C for 1 h, 5% AcOH (15 mL) was added and the mixture was extracted with EtOAc. The organic layers were washed with 5% AcOH and brine and then dried over Na_2SO_4. Concentration followed by chromatography (ether/hexane = 1/5, then ether) gave (+)-**8h** (357 mg, 99%, 90% ee) as a powder of mp 65−67 °C and $[\alpha]^{25}_D$ +38.0 (*c* 1.06, $CHCl_3$). The chiral ligand **10** was recovered quantitatively from the acidic layer.

Catalytic Asymmetric Reaction Using 20 Mol % of 10. By the same procedure above (entry 10) using 20 mol % of **10** (44 mg, 0.15 mmol), **4** (230 mg, 0.75 mmol) was converted into (+)-**8h** (306 mg, 86%, 81% ee) as a powder of mp 66−70 °C and $[\alpha]^{25}_D$ +34.5 (*c* 1.08, $CHCl_3$).

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Supporting Information Available: ^1H and ^{13}C NMR peak assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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