  Bull. Chem. Soc. Jpn., 55, 3277—3282 (1982)

The Enantioselective Michael Addition of Thiols to Cycloalkenones by Using (2*S*, 4*S*)-2-Anilinomethyl-1-ethyl-4-hydroxypyrrolidine as Chiral Catalyst

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(Received May 24, 1982)

Catalytic asymmetric addition of thiols to 2-cycloalkenone was studied by using the chiral amino alcohols, derived from L-hydroxyproline or (*S*)-proline, as base catalysts. Detailed investigation was carried out on the effects of the structure of the catalyst, the reaction medium, the temperature, and the concentration on the enantioselectivity. Good optical yields (47—88%) were achieved by the reaction of arenethiols and 2-cyclohexen-1-one in toluene at −5 °C, by using the catalyst (2*S*, 4*S*)-2-anilinomethyl-1-ethyl-4-hydroxypyrrolidine.

Considerable attention has been focused on the asymmetric synthesis in the past decade, and a remarkable progress has made it one of the powerful tools in the preparation of chiral natural products.[1] Most of the fruitful cases to date are classified as "stoichiometric asymmetric synthesis," that is, a stoichiometric amount of chiral source is effectively used with the aid of the electronic and steric factors to obtain the desired chiral compound in high optical purity. However, from the synthetic point of view it suffers a fatal and inevitable disadvantage, namely, the separation of the chiral source from the reaction products. In this sense the development of "catalytic asymmetric synthesis" is very attractive and highly desirable in synthetic organic chemistry.

Concerning the catalytic asymmetric synthesis, there have been reported only limited successful examples, and most of them belong to the following two classes of reactions: i) The chiral transition-metal complex catalyzed reactions including the fruitful asymmetric hydrogenations—in this field, a rapid progress has been made recently; Sharpless' V catalyzed oxidation,[2a] Kumada's Ni catalyzed cross-coupling reaction,[2b] Otsuka's aymmetric isomerization,[2c] and so on. ii) The chiral base catalyzed reaction——although this type of reactions has been known for years, successful cases are rare; Wynberg has successfully employed cinchona alkaloids as chiral catalysts in the asymmetric Michael addition of thiols or β-keto esters,[3a,3b] and Cram reported the highly stereoselective Michael addition of β-keto esters using chiral crown ethers complexed to potassium base.[3c]

Recently we reported several types of successful asymmetric reactions based on the chiral pyrrolidine derivatives,[4] and this prompted us to undertake the exploration of the catalytic asymmetric synthesis using optically active pyrrolidine derivatives as chiral catalysts. It was found that (2*S*,4*S*)-2-anilinomethyl-1-ethyl-4-hydroxypyrrolidine (**5a**) is a quite efficient catalyst for the asymmetric addition of arenethiols to 2-cyclohexen-1-one and the optical yield as high as 88% was realized under the specified conditions as briefly reported in the previous communication.[5] Herein, we describe the results of the detailed investigation on the effects of the structure of the catalyst, the reaction medium, the temperature, and the concentration on the enantioselectivity.

Results

Chiral Catalysts. Chiral catalysts employed in the present study are derived from natural amino acids, L-hydroxyproline and (*S*)-proline. (2*S*,4*S*)-1-Benzyloxycarbonyl-4-hydroxyproline (Z-allohydroxyproline)[6] was treated with Ac_2O–pyridine to give the acetate **1**, which was condensed with several kinds of amines to afford the corresponding amides **2a**—**e**, respectively. Hydrogenation of **2a**—**e** on 10% Pd–C in MeOH gave the amines **3a**—**e**, which were successively acylated (**4a**—**f**), and reduced ($LiAlH_4$–THF) to give the chiral catalysts **5a**—**f**. The chiral catalysts **5g** and **5h** were also prepared by the similar procedure starting from (2*S*,4*R*)-1-benzyloxycarbonyl-4-hydroxyproline[6] (**1g**) and (*S*)-1-benzyloxycarbonylprolinanilide (**2h**).[4] The catalyst **5i** was prepared by the reduction of the

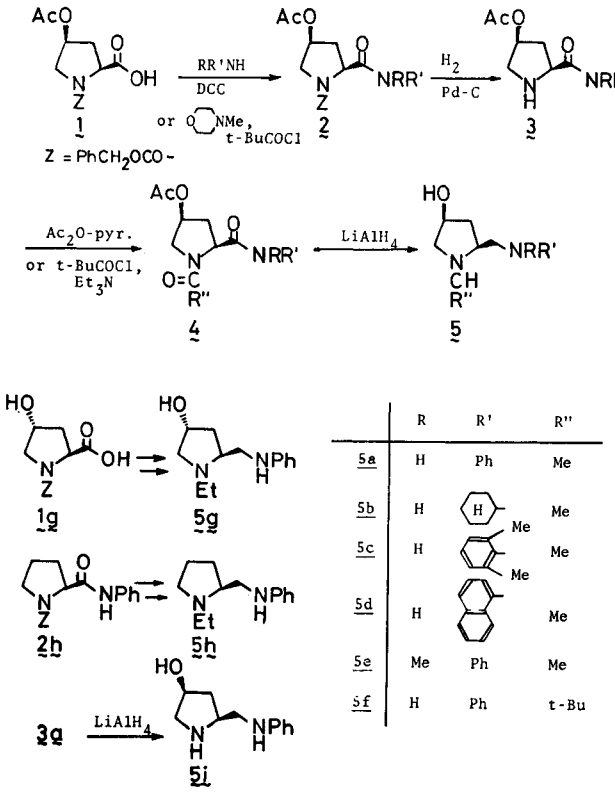
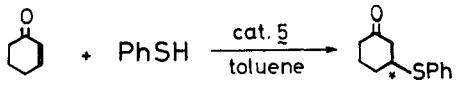


Fig. 1. Preparation of the catalysts.

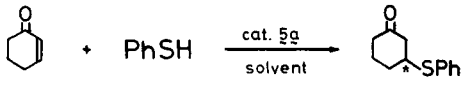
Table 1. Effects of the structure of the catalysts in the asymmetric addition of benzenethiol to 2-cyclohexen-1-one



Entry	Catalyst	Yield/%	$[\alpha]_{577}^{21}$/°	Opt.yield/%[a]
1	**5a**	86	+48.7	67
2	**5b**	90	+24.6	34
3	**5c**	67	+50.1	69
4	**5d**	90	+52.5	72
5	**5e**	81	+41.6	57
6	**5f**	24	+19.0	26
7	**5g**	84	+ 7.1	10
8	**5h**	68	+ 0.9	3
9	**5i**	89	+15.4	21

a) Optical yields were calculated based on the reported value in Ref. 3a.

Table 2. Effects of the reaction medium



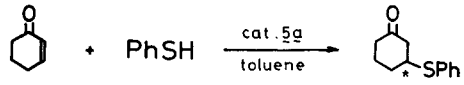
Entry	Solvent	Yield/%	Opt.yield/%
1	Petroleum ether	94	14
2	Cyclohexane	79	30
3	CH_2Cl_2	76	49
4	CCl_4	88	64
5	Benzene	87	65
6	Toluene	86	67
7	EtOH	91	0.1

amine **3a** with $LiAlH_4$ (Fig. 1).

The Structure of the Catalysts. Of the chiral bases **5a**—**i** thus prepared, the suitable structure of the catalyst for the asymmetric Michael addition of benzenethiol to 2-cyclohexen-1-one was pursued. The general reactions were carried out according to the following procedure: In the presence of 0.04 mmol of the catalyst (**5a**—**i**), 2-cyclohexen-1-one (5 mmol) in toluene (5 ml) and benzenethiol (4 mmol) in toluene (5 ml) were admixed and kept standing for 2 d. After the usual work-up (see Experimental section), the optical rotation of the resulting 3-phenylthio-1-cyclohexanone was measured in benzene at 21 °C.

The results are summarized in Table 1. The most noteworthy point is the pivotal role of the hydroxyl group in the enantioselection (entry 1, 7, 8). Obviously, the β-oriented hydroxyl group of the catalyst **5a** directs the stereochemical course of the present reaction, and either the absence or the difference of the orientation of the hydroxyl group of the pyrrolidine ring causes great diminution of the enantioselectivity. While the optical yields were fairly good in cases of the catalysts bearing an aromatic ring (**5a**, **5c**, **5d**), substantial decrease of the e.e. was observed when the catalyst (**5b**) lacked an aromatic ring. When the catalysts **5e**, **5i**, in which both of the amino groups are tertiary and secondary, respectively, were employed, the optical yields were reduced as compared with the case of the catalyst **5a** (entry 1, 5, 9). The poor chemical yield found for the entry 6 is attributable to the decrease of the basicity of the amine **5f** by virtue of the bulky substituent. Thus, it was noted that a slight change in the structure of the catalyst causes a great change in the optical yield in the present reaction and good results are obtained when the catalysts **5a**, **5c**, or **5d** were employed.

Table 3. Effects of the reaction temperature



Entry	Temperature/°C	Yield/%	Opt.yield/%
1	50	88	58
2	25	86	67
3	−5	90	70
4	−20	72	69

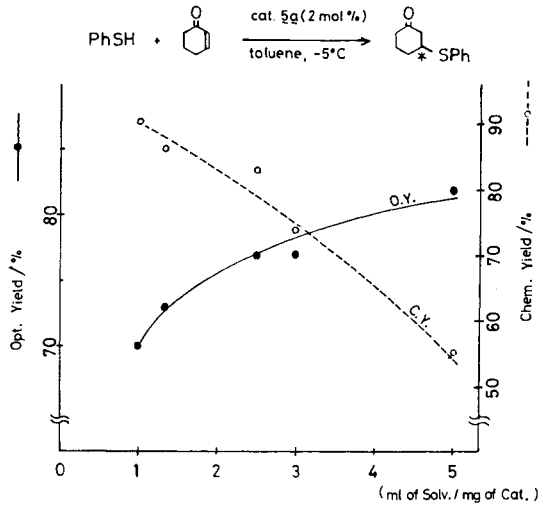


Fig. 2. Effect of the concentration.

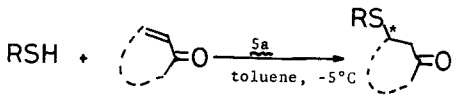
Effect of the Reaction Medium. Next, we examined the effect of the reaction medium on the asymmetric induction. The addition of benzenethiol to 2-cyclohexen-1-one was performed in several kinds of solvents using **5a** as the chiral catalyst (Table 2).

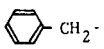
It is noted that the optical yields were strongly dependent on the nature of the solvent used. Better results were obtained in nonpolar aromatic solvents (entry 5, 6) or carbon tetrachloride than the solvent like hydrocarbon or dichloromethane. In the case of ethanol, almost no enantioselection was observed.

Effect of the Reaction Temperature. In order to examine the influence of the reaction temperature on the optical yield, the aforementioned reaction was carried out in toluene at various temperatures ranging over −20 °C to 50 °C, and the results are shown in Table 3.

Although a slight decrease of the optical yield at a higher temperature (entry 1) was observed, the effect of the temperature is as a whole not so remarkable in

Table 4. Asymmetric Michael addition of various thiols to 2-cycloalkenones



Entry	R	Enone	Yield/%	Opt.yield/%
1			83	77
2			75	73
3			84	47
4			75	83
5			74	88
6			22	1
7			85	11
8			64	38
9			74	42

the present reaction.

Effect of Concentration. As the concentration of the reactants is considered to be a significant reaction parameter, the reaction was carried out at various concentration. With the molar ratio of each substrate held constant, the volume of the solvent employed was gradually increased. Figure 2 shows the chemical and optical yields dependence on the concentration.

An increase in the optical yield was observed under higher dilution condition at the expense of the reaction rate, and the concentration of 2 or 3 (ml toluene/mg catalyst) appears to strike the proper balance, producing the optically active adduct without suffering a significant decrease in the chemical yield.

Reaction with Various Thiols and Enones. Under the optimized conditions, the Michael additions of several other thiols to conjugated cycloalkenones were performed (Table 4).

The additions of aromatic thiols to 2-cyclohexen-1-one gave satisfactory results. Among them, the addition of *p-t*-butylbenzenethiol furnished the adduct in 88% optical purity where the *R* enantiomer was predominantly formed.[3a] On the other hand the alkanethiol (entry 6) gave a poor result, and this may be attributable to the difference of the pK_a values of the thiols. The addition of *p-t*-butylbenzenethiol to the other cycloalkenones gave the adducts in moderate optical yields.

Discussion

From the correlation between the structure of the catalyst and the enantioselectivity described above, we can now elucidate the mechanism of the enantioselection, briefly described in our previous paper.[5] Concerning this point, Wynberg *et al.* proposed a mechanism mainly based on the kinetic measurement and the structures of the substrates in their pioneering work on the cinchona alkaloid catalyzed asymmetric thiol addition.[3a] In our case, various sterically modified analogs of the base catalyst are readily available, and the elucidation of the mechanism depends mainly on the effects of the structure of the catalyst on the optical yields. From the experimental results, three notable points must be taken into consideration, namely, i) the role of the hydroxyl group of the catalyst, ii) the role of the aromatic ring, and iii) the absolute configuration of the predominantly formed enantiomer (*R*). With these in mind, and from the CPK model inspection, we propose the following mechanistic pathway (Fig. 3).

At the first stage of the reaction, the ammonium thiolate complex is formed, where the ammonium counterpart has a 5-5 fused rigid structure[4,5] by virtue of a hydrogen bonding as illustrated in **A**. This rigid structure is supposed to be a crucial factor in the enantioselection, because the enantioselectivity decreased when the substituent of the amine became more bulky, where the above structure is no longer a preferred one. Moreover, in a solvent like toluene, the thiolate anion is stabilized by π-π interaction, and the freedom of its location is further limited by the interaction with the aromatic ring of the catalyst. At the next stage, the approach of the cyclohexenone to the complex **A** takes place with a hydrogen-bond interaction between the carbonyl group and the hydroxyl group of the catalyst. In a protic solvent like ethanol, this interaction must be cancelled to result in no enantioselection. Finally, the attack of the thiolate anion to the enone occurs, where two pathways **B** and **C** are possible. In case of the pathway **C**, the steric congestion of the anilino

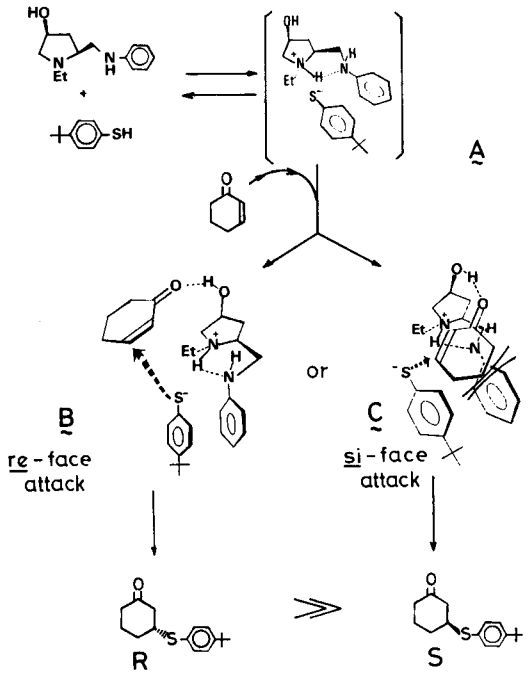


Fig. 3. Mechanism of the enantioselection.

group and the cyclohexenone ring may prevent the complex **A** and the enone from reaching the transition state, thus the preferential attack on the *re*-face of 2-cyclohexen-1-one, through the pathway **B**, takes place resulting in the predominant formation of the *R* enantiomer.

In conclusion, it is noted that the chiral amino alcohol **5a** is a highly efficient catalyst in the asymmetric Michael addition of aromatic thiols to 2-cyclohexen-1-one, and higher optical yields are realized in comparison with the earlier methods.

Experimental

General. Melting and boiling points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 spectrometer with Me_4Si as an internal standard. IR spectra were taken on a Hitachi 260-30 spectrophotometer. MS data were obtained on a JEOL JMS-D 300 mass spectrometer at 70 eV. Optical rotations were measured on a JASCO DIP-181 polarimeter. All the solvents used were purified according to the standard procedure and stocked over molecular sieves 4A.

Materials. L-Hydroxyproline was kindly supplied from Ajinomoto Co., Inc., and was used without further purification. All the other reagents were commercially obtained and purified by distillation or recrystallization before use.

Preparation of (2S, 4S)-4-acetoxy-1-benzyloxycarbonylproline (1) To a suspension of (2*S*, 4*S*)-1-benzyloxycarbonyl-4-hydroxyproline[6] (10.8 g, 40.8 mmol) in CH_2Cl_2 (50 ml) was added acetic anhydride (6.50 g, 63.7 mmol), pyridine (13 ml) and catalytic amount of DMAP, and the resulting solution was stirred for 6 h at room temperature. The solvent was evaporated *in vacuo*, diluted with AcOEt, and washed with 2 mol dm^{-3} HCl saturated with NaCl. The organic layer was extracted with 4% aqueous $NaHCO_3$ solution, and the alkaline solution was washed with AcOEt, acidified with 6 mol dm^{-3} HCl and back-extracted with AcOEt (×3). The combined organic layer was washed with brine, dried over Na_2SO_4. Concentration under reduced pressure gave **1** as white crystals (9.39 g, 75%): mp 107—108 °C; $[\alpha]_D^{27}$ −58.7° (*c* 1.03, $CHCl_3$); IR (KBr disk) 1740, 1700, 1680, 1580, 1500, 770, and 700 cm^{-1}; NMR ($CDCl_3$) δ=1.9 (2H, s), 2.2—2.5 (2H, m), 3.6—3.7 (2H, m), 4.3—4.7 (1H, m), 5.1 (3H, s), and 10.5 (1H, s). Found: C, 58.76; H, 5.49; N, 4.47%. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.57; N, 4.56%.

(2S,4S)-2-Phenylcarbamoyl-1-benzyloxycarbonyl-4-pyrrolidinyl Acetate (2a). To a THF (40 ml) solution of the acetate **1** (9.10 g, 29.6 mmol) and *N*-methylmorpholine (3.00 g, 29.6 mmol) was slowly added a THF (5 ml) solution of pivaloyl chloride (3.31 g, 29.6 mmol) at −45 °C, and the mixture was gradually warmed to −15 °C during 30 min, stirred for further 30 min at the temperature, and cooled to −45 °C again. A THF (5 ml) solution of aniline (2.77 g, 29.7 mmol) was slowly added to this mixture, and the temperature was gradually raised to room temperature and kept for 4 h. Solvent was removed under reduced pressure, and the residue was taken up in AcOEt, washed successively with brine, ice-cold 1 mol dm^{-3} HCl, brine, ice-cold 4% $NaHCO_3$ solution, and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified on a silica-gel column (AcOEt–hexane 3 : 2) to give white crystals in 75% (8.44 g) yield: mp 87—93 °C; $[\alpha]_D^{27}$ −65.4° (*c* 1.01, $CHCl_3$); IR (KBr disk) 3350, 1720, 1680, 1590, 1490, 750, and 690 cm^{-1}; NMR ($CDCl_3$) δ=1.9 (3H, s), 2.0—2.7 (2H, m), 3.4—3.7 (2H, m), 4.3—4.6 (1H, dd, J_1=3 Hz, J_2=9 Hz), 5.1 (3H, s), 6.9—7.5 (5H, m), and 7.2 (5H, m). Found: C, 66.16; H, 5.80; N, 7.30%. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; H, 7.33%.

(2S,4S)-1-Benzyloxycarbonyl-2-cyclohexylcarbamoyl-4-pyrrolidinyl Acetate (2b). A CH_2Cl_2 solution (2 ml) of the acetate **1** (152 mg, 0.50 mmol) was added at 0 °C to a solution of dicyclohexylcarbodiimide (107 mg, 0.52 mmol) in CH_2Cl_2 (1 ml) and the mixture was stirred for 20 min. Then a CH_2Cl_2 (1 ml) solution of cyclohexylamine (54 mg, 0.55 mmol) was added dropwise to the mixture, and the resulting mixture was stirred for 4 h, while gradually warmed up to room temperature, and stirred overnight. The reaction mixture was concentrated and the residue was suspended with AcOEt and filtered off. The filtrate was washed successively with 10% citric acid solution (5 ml×3), brine (5 ml×1), ice-cold 4% $NaHCO_3$ solution (5 ml×3), and brine (5 ml×1), dried over Na_2SO_4 and concentrated to afford crude crystals of the amide **2b** (220 mg), The crystals were further purified with SiO_2 TLC (AcOEt–hexane) to give white crystals in 95% (192 mg) yield. Mp 85—87 °C; $[\alpha]_D^{21}$ −37.6° (*c* 0.95, CH_2Cl_2); IR (KBr disk) 3330, 1740, 1700, 1660, and 730 cm^{-1}; NMR ($CDCl_3$) δ=0.7—2.1 (10H, m), 1.9 (3H, s), 2.1—2.9 (2H, m), 3.2—4.0 (3H, m), 4.4 (1H, dd, J_1=8 Hz, J_2=3 Hz), 5.1 (2H, s), 5.1—5.3 (1H, m), 6.0—6.4 (1H, broad), 7.5 (5H, s). Found: C, 65.19; H, 7.18; N, 7.47%. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.27; N, 7.21%.

(2S,4S)-1-Benzyloxycarbonyl-2-(2,6-xylylcarbamoyl)-4-pyrrolidinyl Acetate (2c): Yield 76%; mp 123—125 °C; $[\alpha]_D^{24}$ −54.9° (*c* 1.01, CH_2Cl_2); IR (KBr disk) 3260, 1740, 1710, 770, and 700 cm^{-1}; NMR ($CDCl_3$) δ=2.0 (3H, s), 2.2 (6H, s), 2.1—2.9 (2H, m), 3.5—4.1 (2H, m), 4.6 (1H, dd, J_1=9 Hz, J_2=3 Hz), 5.2 (2H, s), 5.1—5.4 (1H, m), 7.0 (3H, s), 7.3 (5H, s), and 7.8—8.3 (1H, broad). Found: C, 67.32; H, 6.52; N, 7.06%. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.39; N, 6.83%.

(2S,4S)-1-Benzyloxycarbonyl-2-(1-naphthylcarbamoyl)-4-pyrrolidinyl Acetate (2d): Yield 94%; $[\alpha]_D^{21}$ −26.1° (*c* 1.00, CH_2Cl_2); IR (KBr disk) 3300, 1740, 1700, 800, 780 and 700 cm^{-1}; NMR ($CDCl_3$) δ=1.9 (3H, s), 2.1—3.0 (2H, m), 3.8 (2H, d, J=6 Hz), 4.7 (1H, dd, J_1=9 Hz, J_2=2 Hz), 5.3 (2H, s), 5.2—5.4 (1H, m), 7.2—8.0 (12H, m), and 8.8—9.2 (1H, broad); MS, Found: *m/e* 432.1660. Calcd for $C_{25}H_{24}N_2O_5$: M, 432.1683.

(2S,4S)-1-Benzyloxycarbonyl-2-(methylphenylcarbamoyl)-4-pyrrolidinyl Acetate (2e): Yield 58%; $[\alpha]_D^{22}$ +81° (*c* 1.5, CH_2Cl_2); IR (neat) 3300, 1700, 1590, 1495, 770 and 700 cm^{-1}; NMR ($CDCl_3$) δ=2.0 (3H, s), 1.8—2.6 (2H, m), 3.1 (1.5H. s), 3.2 (1.5H, s), 3.4—4.5 (3H, m), 4.6—5.0 (1H, m), 5.0 (2H, s), and 6.9—7.3 (5H, m); MS, Found: *m/e* 396.1690. Calcd for $C_{22}H_{24}N_2O_5$: M, 396.1685.

(2S,4R)-1-Benzyloxycarbonyl-4-hydroxyprolinanilide(2g): Yield 47%; mp 146—147 °C; $[\alpha]_D^{26}$ −50° (*c* 1, MeOH); IR (KBr disk) 1700, 1685 cm^{-1}; NMR ($CDCl_3$–CD_3OD) δ=2.0—2.4 (2H, m), 2.95 (2H, s), 3.6 (2H, d, J=3 Hz), 4.35—4.55 (2H, m), 5.05 (2H, s), and 6.9—7.3 (10H, m). Found: C, 66.86; H, 5.81; N, 8.25%. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23%.

(2S,4S)-2-Phenylcarbamoyl-4-pyrrolidinyl Acetate (3a). The anilide **2a** (8.23 g, 21.7 mmol) and 10% Pd–C (800 mg) were stirred vigorously in MeOH (60 ml) under a H_2 atmosphere overnight. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated to give **3a** in quantitative (5.33 g) yield: mp 64—72 °C; $[\alpha]_D^{22}$ −13.4° (*c* 1.06, EtOH); IR (KBr disk) 3350, 1720, 1660, 750, and 690 cm^{-1}; NMR ($CDCl_3$) δ=1.8 (3H, s), 2.3 (2H, dd, J_1=6 Hz, J_2=3 Hz), 2.6 (1H, broad), 3.0—3.4 (2H, m), 3.9 (1H, t, J=6 Hz), 5.1—5.3 (1H, m), 6.9—7.7 (5H,m), and 9.5—9.8 (1H, broad); Found C, 62.92; H, 6.65; N, 11.19%. Calcd for $C_{13}H_1N_2O_3$: C, 62.89; H, 6.50; N, 11.28%.

Similar treatment of **2b—e**, **2g**, and **2h** to that described

above gave the corresponding amines **3b—e**, **3g**, and **3h**, respectively. The yields and physical data are shown below.

*(2S,4S)-2-Cyclohexylcarbamoyl-4-pyrrolidinyl Acetate (**3b**)*: Yield 100%; mp 122—123 °C (cyclohexane); $[\alpha]_D^{20}$ −11.4° (*c* 1.01, CH_2Cl_2); IR (KBr disk); 3300, 3200, 1730, and 1640 cm^{-1}; NMR ($CDCl_3$) δ=1.0—2.4 (13H, m), 1.95 (3H, s), 2.8—3.9 (4H, m), 5.0—5.3 (1H, m), and 7.2—7.5 (1H, m). Found: C, 61.18; H, 8.72; N, 10.91%. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.02%.

*(2S,4S)-(2,6-Xylylcarbamoyl)-4-pyrrolidinyl Acetate (**3c**)*: Yield 100%; $[\alpha]_D^{23}$ −38.3° (*c* 1.05, CH_2Cl_2); IR (KBr disk) 3330, 3225, 1720, 1640, and 785 cm^{-1}; NMR ($CDCl_3$) δ=2.0 (3H, s), 2.2 (6H, s), 2.3—2.5 (2H, m), 3.0—3.5 (3H, m), 3.8—4.0 (1H, dd, J_1=9 Hz, J_2=6 Hz), 5.1—5.4 (1H, m), 7.1 (3H, s), and 9.0—9.2 (1H, broad); MS, Found: *m/e* 276.1483. Calcd for $C_{15}H_{20}N_2O_3$: M, 276.1473.

*(2S,4S)-2-(1-Naphthylcarbamoyl)-4-pyrrolidinyl Acetate (**3d**)*: Yield 100%; $[\alpha]_D^{21}$ +87° (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) 3300, 1735, 1680, and 800 cm^{-1}; NMR ($CDCl_3$) δ=1.80 (3H, s), 2.1—2.6 (3H, m), 3.1—3.4 (2H, broad), 3.9—4.1 (1H, m), 5.1—5.4 (1H, m), and 7.1—8.3 (7H, m); MS, Found: *m/e* 298.1320. Calcd for $C_{17}H_{18}N_2O_3$: M, 298.1317.

*(2S, 4S)-2-(Methylphenylcarbamoyl)-4-pyrrolidinyl Acetate (**3e**)*: Yield 95%; $[\alpha]_D^{23}$ −82.5° (*c* 1.0, CH_2Cl_2); IR (KBr disk) 3310, 1730, 1650, 1590, 1490, 780 cm^{-1}; NMR ($CDCl_3$) δ=1.7—2.2 (2H, m), 2.0 (3H, s), 2.5—3.9 (2H, m), 3.2 (3H, s), 4.3—4.6 (1H, broad), 4.8—5.1 (1H, m), and 7.0—7.5 (5H, m). Found: C, 63.69; H, 7.10; N, 10.29%. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68%.

*(2S,4R)-4-Hydroxyprolinanilide (**3g**)*: Yield 100%; mp 149—150 °C (H_2O); $[\alpha]_D^{24}$ −38.5° (*c* 1, MeOH); IR (KBr disk) 3270, 1650, 1600, and 1500 cm^{-1}; NMR (CD_3OD) δ=1.7—2.2 (2H, m), 2.95 (2H, d, J=3 Hz), 3.95 (1H, t, J=8 Hz), 4.30 (1H, m), 4.65 (2H, s), and 6.8—7.5 (5H, m). Found: C, 63.32; H, 6.99; N, 13.28%. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58%.

*(S)-Prolinanilide (**3h**)*: Yield 100%; mp 76—77 °C; $[\alpha]_D^{27}$ −71.0° (*c* 1.03, EtOH); IR (KBr disk) 3360, 3225, 1665, and 1600 cm^{-1}; NMR ($CDCl_3$) δ=1.1—2.2 (4H, m), 2.3—3.2 (3H, m), 3.5—3.9 (1H, m), 6.7—7.6 (5H, m); Found: C, 69.53; H, 7.58; N, 14.84%. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73%.

*(2S,4S)-1-Acetyl-2-phenylcarbamoyl-4-pyrrolidinyl Acetate (**4a**)*. To a CH_2Cl_2 (5 ml) solution of **3a** was added a pyridine (9 ml) solution of acetic anhydride (1.12 g, 11.0 mmol) and a catalytic amount of 4-(dimethylamino)pyridine, and the solution was kept standing overnight at room temperature. The reaction mixture was diluted CH_2Cl_2, washed successively with 1 mol dm^{-3} HCl, brine, 4% aqueous $NaHCO_3$ solution and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the purification of the residue with basic alumina thin layer chromatography (benzene–MeOH) gave **4a** as white crystals in 90% (2.55 g) yield. Mp 112—113.5 °C; $[\alpha]_D^{25}$ −115° (*c* 1.01, CH_2Cl_2); IR (CH_2Cl_2) 1730, 1680, 1590, 1490, 1220, and 1180 cm^{-1}; NMR ($CDCl_3$) δ=1.8—3.0 (2H, m), 1.8 (0.6H, s), 2.0 (2.4H, s), 2.1 (0.6H, s), 2.2 (2.4H, s), 3.5—3.9 (2H, m), 4.4—4.6 (0.2H, dd, J_1=9 Hz, J_2=3 Hz), 4.7—4.9 (0.8H, dd, J_1=9 Hz, J_2=3 Hz), 5.1—5.4 (1H, m), 6.9—7.7 (5H, m), 8.6—8.8 (0.2H, broad), and 9.3—9.6 (0.8H, broad); Found: C, 61.95; 6.41; N, 9.45%. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65%. The amides **4b—e**, **4g**, and **4h** were obtained according to essentially the same procedures as described above. The amide **4f** was obtained from **3a** by a similar procedure using pivaloyl chloride in place of acetic anhydride.

*(2S,4S)-1-Acetyl-2-cyclohexylcarbamoyl-4-pyrrolidinyl Acetate (**4b**)*: Yield 79%; mp 107—109 °C (acetone–P.E.); IR (neat) 3300, 1740, 1660, and 1640 cm^{-1}; NMR ($CDCl_3$) δ=1.0—2.0 (10H, m), 2.0 (3H, s), 2.1 (3H, s), 2.1—2.9 (2H, m), 3.3—3.9 (4H, m), 4.1—4.6 (1H, m), 5.0—5.3 (1H, m), 6.5—6.8 (1H, broad); Found: C, 60.95; H, 8.10; N, 9.51%. Calcd for $C_{15}H_{24}N_2O_4$: C, 60.79; H, 8.16; N, 9.45%.

*(2S,4S)-1-Acetyl-2-(2,6-xylylcarbamoyl)-4-pyrrolidinyl Acetate (**4c**)*: Yield 75%; mp 169—172 °C (THF–pentane); $[\alpha]_D^{21}$ −85° (*c* 1.1, CH_2Cl_2); IR (KBr disk) 3300, 1730, 1675, 1630, and 780 cm^{-1}; NMR ($CDCl_3$) δ=2.0 (3H, s), 2.1 (3H, s), 2.2 (6H, s), 2.0—3.0 (2H, m), 3.4—4.0 (2H, m), 4.8 (1H, dd, J_1=9 Hz, J_2=3 Hz), 5.1—5.4 (1H, m), 7.0 (3H, s), and 8.5—8.6 (1H, broad); Found: C, 64.16; H, 7.27; N, 8.72%. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80%.

*(2S,4S)-1-Acetyl-2-(1-naphthylcarbamoyl)-4-pyrrolidinyl Acetate (**4d**)*: Yield 66%; mp 237—241 °C (EtOH); IR (KBr disk) 3320, 1730, 1670, 1630, and 800 cm^{-1}; NMR ($CDCl_3$) δ=1.6 (1.2H, s), 2.1 (2.8H, s), 2.2 (3H, s), 3.1—3.3 (1H, m), 3.6—4.0 (3H, m), 4.9—5.1 (1H, m), 5.3—5.5 (1H, m), 7.4—8.2 (7H, m), and 9.8—10.0 (1H, broad); Found: C, 66.87; H, 5.80; N, 8.05%. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23%.

*(2S,4S)-1-Acetyl-2-methylphenylcarbamoyl-4-pyrrolidinyl Acetate (**4e**)*: Yield 91%; $[\alpha]_D^{23}$ +56° (*c* 0.51, EtOH); IR (neat) 1740, 1660, 1640, 780. and 700 cm^{-1}; NMR ($CDCl_3$) δ=1.9—2.5 (2H, m), 2.0 (6H, s), 3.2 (3H, s), 3.6 (1H, dd, J_1=12 Hz, J_2=4 Hz), 3.9 (1H, dd, J_1=12 Hz, J_2=2 Hz), 4.3 (1H, t, J=8 Hz), 4.9 (1H, m), 7.3 (5H, s); MS, Found: *m/e* 304.1422. Calcd for $C_{16}H_{20}N_2O_4$: M, 304.1422.

*(2S, 4S)-2-Phenylcarbamoyl-1-pivaloyl-4-pyrrolidinyl Acetate(**4f**)*: Yield 72%; mp 134—135 °C; $[\alpha]_D^{24}$ −64.3° (*c* 1.02, CH_2Cl_2); IR (KBr disk) 3300,1740, 1700, 1600, 1500, 760, and 700, cm^{-1}; NMR ($CDCl_3$) δ=1.3 (9H, s), 2.0 (3H, s), 2.2—2.7 (2H, m), 3.7 (1H, dd, J_1=12 Hz, J_2=5 Hz), 4.2 (1H, dd, J_1=12 Hz, J_2=6 Hz), 4.8 (1H, dd, J_1=6 Hz, J_2=2 Hz), 5.1—5.3 (1H, m), 6.8—7.5 (5H, m), and 9.1—9.2 (1H, broad); Found: C, 64.89; H, 7.55; N, 8.28%. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43%.

*(2S, 4R)-1-Acetyl-2-phenylcarbamoyl-4-pyrrolidinyl Acetate (**4g**)*: Yield 84%; $[\alpha]_D^{25}$ −43° (*c* 1.0, CH_2Cl_2); IR (neat) 3300, 1740, 1630, 1600, 1500, and 740 cm^{-1}; NMR ($CDCl_3$) δ=1.95 (3H, s), 2.00 (3H, s), 2.0—2.8 (2H, m), 3.4 (1H, dd, J_1=12 Hz, J_2=2 Hz), 3.9 (1H, dd, J_1=12 Hz, J_2=5 Hz), 4.7 (1H, t, J=7 Hz), 5.1—5.4 (1H, m), 6.8—7.6 (5H, m), and 9.5 (1H, broad); MS, Found; *m/e* 290.1236. Calcd for $C_{15}H_{18}N_2O_4$: M, 290.1266.

*(S)-1-Acetylprolinanilide (**4h**)*: Yield 74%; $[\alpha]_D^{26}$ −176° (*c* 1.1, CH_2Cl_2); IR (KBr disk) 3280, 1700, 1630, 1600, 1500, 760, and 700 cm^{-1}; NMR ($CDCl_3$) δ=1.6—2.7 (4H, m), 2.1 (3H, s), 3.3—3.6 (2H, m), 4.7 (1H, dd, J_1=8 Hz, J_2=2 Hz), 6.9—7.6 (5H, m), and 9.5—9.7 (1H, broad); MS, Found: *m/e* 232.1208. Calcd for $C_{13}H_{16}N_2O_2$: M, 232.1210.

*(2S, 4S)-2-Anilinomethyl-1-ethyl-4-hydroxypyrrolidine (**5a**)*. Under an argon atmosphere, the acetate **4a** (500 mg, 1.73 mmol) in THF (30 ml) was added to a suspension of $LiAlH_4$ (520 mg, 13.7 mmol) in THF (5 ml) at 0 °C, and the mixture was refluxed for 18 h, and then quenched by the dropwise addition of saturated Na_2SO_4 solution at 0 °C. After removal of the inorganic material and concentration of the organic layer afforded an oil, which was further purified by basic alumina TLC (benzene–MeOH) and bulb-to-bulb distillation to give a colorless oil in 89% (338 mg) yield. Bp 150—170 °C/2 mmHg† (bath temp); $[\alpha]_D^{23}$ −58.1° (*c* 1.03, EtOH); IR (neat) 3375. 1600, 1500, 750, and 695 cm^{-1}; NMR ($CDCl_3$) δ=1.1 (3H, t, J=8 Hz), 1.5—1.9 (1H, m), 2.1—2.5 (3H, m), 2.5—3.0 (2H, m), 3.0—3.3 (4H, m), 4.1—4.5 (2H, m), and 6.5—7.3 (5H, m); Found: C, 70.90; H, 9.37; N, 12.54%.

† 1 mmHg ≈ 133.322 Pa.

Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72%. Catalysts **5b—i** were also obtained by similar $LiAlH_4$ reductions.

(2S,4S)-2-(Cyclohexylaminomethyl)-1-ethyl-4-hydroxypyrrolidine (5b): Yield 81%; bp 140—155 °C/2 mmHg (bath temp); $[\alpha]_D^{21}$ −21° (*c* 1.7, MeOH); IR (neat) 3300 cm^{-1}; NMR ($CDCl_3$) δ=1.0 (3H, t, 6 Hz), 0.9—3.1 (21H, m), 3.3—4.4 (5H, m); MS, Found: *m/e* 227.2111 (M^++1). Calcd for $C_{13}H_{26}N_2O$: (M^+ +1), 227.2122.

(2S,4S)-1-Ethyl-4-hydroxy-2-(2,6-xylidinomethyl)pyrrolidine(5c): Yield 30%; bp 150—170 °C/0.2 mmHg (bath temp.); $[\alpha]_D^{21}$ −138° (*c* 0.9, CH_2Cl_2); IR (neat) 3350, 1470, and 765 cm^{-1}; NMR ($CDCl_3$) δ=1.2 (3H, t, J=8 Hz), 1.6—3.3 (9H, m), 4.0—4.3 (3H, m), and 6.8—7.0 (3H, m); MS, Found: *m/e* 248.1880. Calcd for $C_{15}H_{24}N_2O$: M, 248.1887.

(2S,4S)-1-Ethyl-4-hydroxy-2-(1-naphthylaminomethyl)pyrrolidine (5d): Yield 53%; $[\alpha]_D^{23}$ +1° (*c* 0.2, CH_2Cl_2); IR (neat) 3370, 1580, and 770 cm^{-1}; NMR ($CDCl_3$) δ=1.0 (3H, t, J=7 Hz), 1.5—3.8 (10H, m), 4.0—4.3 (1H, m), 5.0—5.6 (1H, broad), 6.4 (1H, dd, J_1=6 Hz, J_2=2 Hz), and 7.0—7.9 (6H, m); MS, Found: *m/e* 271.1747 (M^+ +1). Calcd for $C_{17}H_{23}N_2O$: (M^+ +1), 271.1809.

(2S,4S)-1-Ethyl-2-(N-methylanilinomethyl)-4-hydroxypyrrolidine (5e): Yield 82%; bp 150—160 °C/1 mmHg (bath temp); $[\alpha]_D^{23}$ −96° (*c* 0.94, EtOH); IR (neat) 3360, 1600, 1500, 750, and 695 cm^{-1}; NMR ($CDCl_3$) δ=1.1 (3H, t, J=6 Hz), 1.4—3.8 (10H, m), 2.9 (3H, s), 4.0—4.2 (1H, m), and 6.3—7.2 (5H, m); Found: C, 71.07; H, 9.76; N, 11.95%. Calcd for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95%.

(2S,4S)-2-Anilinomethyl-4-hydroxy-1-(2,2-dimethylpropyl)pyrrolidine (5f): Yield 87%; bp 150—160 °C/0.4 mmHg (bath temp); $[\alpha]_D^{22}$ −56° (*c* 1.1, CH_2Cl_2); IR (neat) 3370, 1600, 1500, 750 and 690 cm^{-1}; NMR ($CDCl_3$) δ=0.8 (9H, s), 1.6—3.9 (10H, m), 4.0—4.3 (1H, m), and 6.3—7.1 (5H, m); Found: C, 73.42; H, 10.19; N, 10.90%. Calcd for $C_{16}H_{26}N_2O$: C, 73.24; H, 9.99; N, 10.68%.

(2S,4R)-2-Anilinomethyl-1-ethyl-4-hydroxypyrrolidine (5g): Yield 81%; bp 170—180 °C/5 mmHg (bath temp); $[\alpha]_D^{25}$ −39° (*c* 1.0, CH_2Cl_2); IR (KBr disk) 3380, 1600, 1520, 760, and 700 cm^{-1}; NMR ($CDCl_3$) δ=1.0 (3H, t, J=7 Hz), 1.4—4.4 (12H, m), and 6.3—7.3 (5H, m); MS, Found: *m/e* 220.1569. Calcd for $C_{13}H_{20}N_2O$: M, 220.1564.

(S)-2-Anilinomethyl-1-ethylpyrrolidine (5h): Yield 95%; bp 140—150 °C/3 mmHg (bath temp); $[\alpha]_D^{25}$ −53° (*c* 1.0, CH_2Cl_2); IR (neat) 3375, 1610, 1510, 755, and 700 cm^{-1}; NMR ($CDCl_3$) δ=1.1 (3H, t, J=8 Hz), 1.6—3.4 (11H, m), 3.9—4.4 (1H, broad), and 6.5—7.3 (5H, m); Found: C, 76.63; H, 9.91; N, 13.56%. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71%.

(2S,4S)-2-Anilinomethyl-4-hydroxypyrrolidine (5i): Yield 93%; bp 170—180 °C/0.8 mmHg (bath temp); $[\alpha]_D^{25}$ +23.4° (*c* 1.02, $CHCl_3$); NMR ($CDCl_3$) δ=1.2—1.7 (1H, m), 1.9—2.5 (1H, m), 2.6—3.2 (8H, m), 4.1—4.4 (1H, m), and 6.4—7.2 (5H, m); Found: C, 67.86; H, 8.82; N, 14.10%. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57%.

General Procedure for the Michael Addition. Under an argon atmoshpere, a solution of the thiol (4 mmol) in the solvent (25 ml) and the cycloalkenone (5 mmol) containing the freshly distilled catalyst (0.08 mmol) in the solvent (25 ml) were mixed at the specified temperature and kept standing for two days at the temperature. The reaction mixture was washed successively with 1 mol dm^{-3} HCl (5 ml×3), brine (5 ml×1), 1 mol dm^{-3} NaOH (5 ml×3), brine (5 ml×1) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica-gel TLC (hexane–AcOEt). The adduct thus obtained was further purified by short path distillation using Kugelrohr apparatus.

The authors wish to thank Professor Hans Wynberg, the University of Groningen, for providing us valuable informations. Thanks are due to Mr. Masami Ishibashi for mass spectral measurements. Thanks are also due to the Ajinomoto Co., Inc. for the gift of L-hydroxyproline. The present work was supported by a Grant-in-Aid for Scientific Research No. 443006 from the Ministry of Education, Science and Culture.

References

1) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice Hall Inc., (1971); D.Valentine, Jr., and J. W. Scott, *Synthesis*, **1978**, 329; J. W. ApSimon and R. P. Seguin, *Tetrahedron*, **35**, 2797 (1979).

2) a) K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980); b) T. Hayashi, M. Konishi, T. Hioki, M. Kumada, A. Ratajczad, and H. Niedbala, *Bull. Chem. Soc. Jpn.*, **54**, 3615 (1981); c) S. Otsuka, T. Yamagata, K. Tani, H. Takaya, A. Miyashita, R. Noyori, and S. Akutagawa, 44th National Meeting of the Chemical Society of Japan, Okayama, October 1981.

3) a) H. Hiemstra and H. Wynberg, *J. Am. Chem. Soc.*, **103**, 417 (1981); b) H. Wynberg and B. Greijdanus, *J. Chem. Soc., Chem. Commun.*, **1978**, 427; c) D. J. Cram and G. D. Y. Sogah, *ibid.*, **1981**, 625.

4) M. Asami, H. Ohno, S. Kobayashi, and T. Mukaiyama *Bull. Chem. Soc. Jpn.*, **51**, 1869 (1978); T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, and K. Suzuki, *J. Am. Chem. Soc.*, **101**, 1455 (1979); T. Mukaiyama, Y. Sakito, and M. Asami, *Chem. Lett.*, **1978**, 1253; T. Mukaiyama, *Tetrahedron*, **37**, 4111 (1981).

5) T. Mukaiyama, A. Ikegawa, and K. Suzuki, *Chem. Lett.*, **1981**, 165.

6) A. A. Patchett and W. Witkop, *J. Am. Chem. Soc.*, **79**, 185 (1957).