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Asymmetric Synthesis and Catalytic Activity of 3-Methyl-β-proline in Enantioselective *anti*-Mannich-type Reactions

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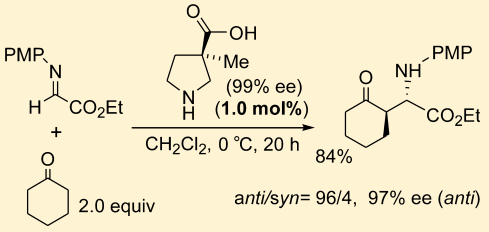
Supporting Information

ABSTRACT: Enantiomerically pure 3-methyl-β-proline was synthesized using an asymmetric phase-transfer-catalyzed alkylation of a cyanopropanoate to establish the all-carbon stereogenic center. The catalytic activity of 3-methyl-β-proline in the Mannich-type reaction between a glyoxylate imine and ketones/aldehydes was subsequently investigated. The catalyst was designed and found to be more soluble in nonpolar organic solvents relative to the unsubstituted β-proline catalyst, and as a result allowed for added flexibility during optimization efforts. This work culminated in the development of a highly *anti*-diastereo- and enantioselective process employing low catalyst loading.



INTRODUCTION

Mannich reactions that provide access to β-amino carbonyl compounds are important C−C bond-forming reactions between an enolizable carbonyl compound and an imine.[1] The stereochemical course (e.g., diastereo- and enantioselectivity) of Mannich-type reactions has been extensively studied. Recently, a lot of direct catalytic asymmetric Mannich-type reactions have been disclosed.[2] With both metal-based catalysis[3] and organocatalysis,[4] *syn*-selective products are typically obtained. In 2002, the first organocatalytic *anti*-selective Mannich-type reaction employing aldehyde donors was reported by Barbas et al.,[4c] and then β-proline catalyst was reported to provide products with high *anti*-diastereo- and enantioselectivities in the Mannich-type reactions employing ketones and hindered aldehydes.[4k,l] This method, however, requires the use of polar solvents and relatively high catalyst loading. In response to the limitations of these methods, complementary pyrrolidine-based catalysts have been developed.[5] As a part of our ongoing studies on the asymmetric synthesis of all-carbon quaternary stereocenters,[6] we were drawn to the synthesis of 3-substituted β-prolines. Furthermore, the substituent at the 3-position of β-prolines was considered to potentially alter the reactive conformation of the pyrrolidine ring as well as affect the spatial arrangement of carboxyl group. As a result of these effects, the stereochemical course of the Mannich-type reaction using these catalysts may be unique. In addition, the substituent would increase the lipophilicity of the amino acid and provide for a more organic-soluble catalyst. This could help to change the transition-state conformation in a beneficial way and reduce the catalyst loading. In this Article, we report the asymmetric synthesis of 3-methyl-β-proline and its application to the *anti*-diastereoselective catalytic asymmetric direct Mannich-type reaction.

RESULTS AND DISCUSSION

β-Amino acids have received much attention due to their unique characteristics,[7,8] which include enhancing proteolytic stability and the tendency to form stable secondary structures of peptides. Thus, β-prolines as well as other acyclic β-amino acids have become sought-after synthetic targets.[9] Despite the fact that several syntheses of β-proline,[8b,10] and a few syntheses of substituted β-prolines,[4k,11] have been reported, there were no general methods disclosed for the synthesis of 3-substituted-β-prolines.[12] Therefore, we targeted our initial efforts on discovering a general route toward 3-substituted-β-prolines. The results of these studies are depicted in Scheme 1. Racemic 3-methyl-β-proline was derived from *tert*-butyl 2-cyanopropanoate (**1**) by first alkylation with ethyl iodoacetate under phase-transfer-catalyzed conditions to provide the cyanodiester **2** in 97% yield. The chemoselective nitrile reduction ($NaBH_4$, $CoCl_2$)[13] of **2** occurred with spontaneous ring closure to afford lactam **3**. Conversion of **3** into the corresponding thiolactam **4** with Lawesson's reagent, subsequent reduction of the thiolactam (Raney-Ni), and *N*-protection with *Z*-chloride provided the *N*-protected β-proline **5**. Removal of the *t*-butyl group upon treatment with TFA and subsequent deprotection of the Cbz group (Pd/C, H_2) gave 3-methyl-β-proline (**7**) in 45% yield over seven steps. The catalytic activity in the Mannich-type reaction of cyclohexanone was first explored with racemic 3-methyl-β-proline (**7**) (Table 1). The previously reported conditions for Mannich-type reactions using the unsubstituted β-proline catalyst[4l] were initially investigated to explore the feasibility of the substituted catalyst in the racemic sense (Table 1, entry 1). An excellent *anti*-selectivity was obtained in the reaction using 10 equiv of cyclohexanone; however, reducing the amount of the substrate caused a slight

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Scheme 1. Synthesis of 3-Methyl-β-proline

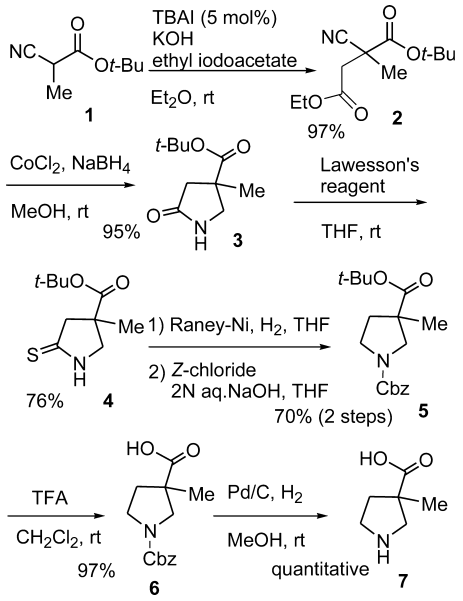
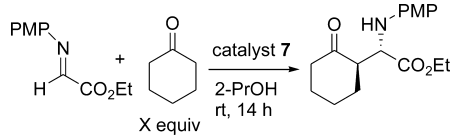


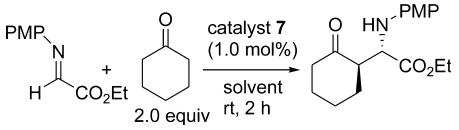
Table 1. Mannich-type Reaction of Cyclohexanone Catalyzed by 7



entry	catalyst (mol %)	X (equiv)	yield (%)	dr[a] (anti/syn)
1	10	10	80	>99/1
2	10	2	91	94/6
3	5	2	99	95/5
4	1	2	quant	95/5
5	0.5	2	89	93/7

[a]Determined by ^{1}H NMR of the crude reaction mixture.

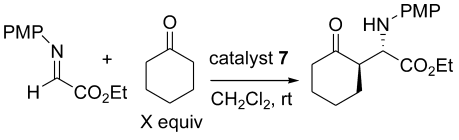
Table 2. Solvent Effects on the Mannich-type Reaction of Cyclohexanone



entry	solvent	yield (%)	dr[a] (anti/syn)
1	2-PrOH	87	94/6
2	DMSO	10	57/43
3	AcOEt	53	67/33
4	THF	56	52/48
5	CH_3CN	86	95/5
6	CH_2Cl_2	85	98/2
7	$CHCl_3$	54	95/5
8	toluene	35	86/14

[a]Determined by ^{1}H NMR of the crude reaction mixture.

Table 3. Mannich-type Reaction of Cyclohexanone in CH_2Cl_2 Using Catalyst 7



entry	catalyst (mol %)	X (equiv)	time (h)	yield (%)	dr[a] (anti/syn)
1	5	2	2	75	91/9
2	3	2	2	81	97/3
3	2	2	2	86	98/2
4	1	2	2	85	98/2
5	0.5	2	2	81	97/3
6	0.1	2	40	77	95/5
7	1	10	2	92	97/3
8	1	5	2	90	97/3
9	1	1	2	53	96/4
10[b]	1	2	20	93	98/2

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]The reaction was carried out at 0 °C.

decrease in the diastereoselectivity (Table 1, entry 2). We were encouraged by the result that moderately high *anti*-selectivities were obtained even with low catalyst loading (Table 1, entries 4 and 5). Because **7** was found to be more soluble in nonpolar organic solvents, relative to the unsubstituted *β*-proline, it was possible to screen additional solvents to optimize the transformation (Table 2). It bears mentioning that the increased solubility in less polar organic solvents is a consequence of the increase in lipophilicity of the substituted *β*-proline derivatives, and was an element of the initial catalyst design, offering added flexibility in the optimization process. When the reaction was carried out with 1.0 mol % **7** at room temperature in CH_2Cl_2 for 2 h, a high yield and *anti*-diastereoselectivity was obtained (Table 2, entry 6). Notably, the catalyst was completely soluble in this case. Reactions conducted in DMSO or THF afforded almost no diastereoselectivity (Table 2, entries 2 and 4). Further optimization of the reaction conditions using CH_2Cl_2 as a solvent was next studied (Table 3), and **7** was found to catalyze the reaction with very low catalyst loading. Even using 0.1 mol % of **7**, high *anti*-diastereoselectivity was obtained (Table 3, entry 6). By conducting the reaction at 0 °C with 1.0 mol % catalyst, a high yield (93%) and diastereoselectivity (up to anti/syn = 98/2) was achieved (Table 3, entry 10). When the unsubstituted *β*-proline catalyst was used under the same conditions as in entry 4, the catalyst solubility was an issue.[14] As a result, the chemical yield suffered (25%), and the anti/syn diastereoselectivity was reduced to 96/4. Because catalyst **7** was found to be effective in providing high diastereoselectivity with low catalyst loading, we next investigated the synthesis of enantiomerically pure **7**. In Scheme 2, the asymmetric synthesis of **7** is shown. Construction of the all-carbon quaternary stereocenter was carried out using (*R*,*R*)-3,5-bistrifluoromethylphenyl-NAS bromide as a chiral phase-transfer catalyst in the alkylation of **1** with ethyl iodoacetate.[6b] Using this methodology, **2** was obtained in good enantiopurity (86% ee) and was converted to **6** following the same synthetic sequence as that of racemic **7**. In addition, it was found that the enantio purity of **6** could be further enriched to 99% ee with a single recrystallization of the diastereomeric (*S*)-1-phenylethylamine salts.[15] Catalytic hydrogenation of **6** removed the Cbz group and provided the enantiomerically pure 3-methyl-*β*-proline (**7**). With the optically active catalyst in hand, the enantioselectivity of the Mannich-type reaction was investigated and directly compared to the results obtained with the unsubstituted *β*-proline (**8**) using typical ketones and aldehydes (Table 4). With aldehyde substrates, even 0.5 mol % of **7** afforded products with high

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Scheme 2. Enantioselective Synthesis of 3-Methyl-β-proline

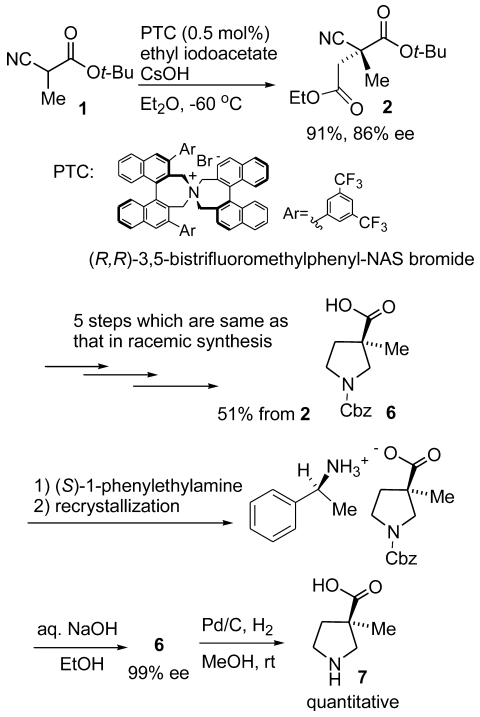
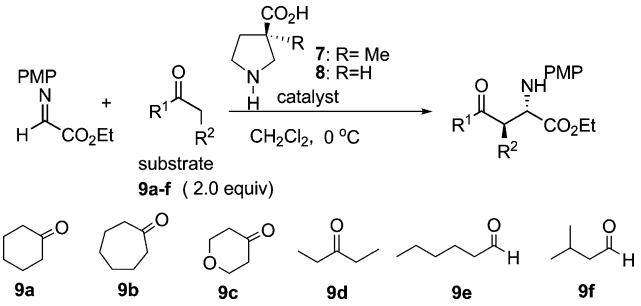


Table 4. *anti*-Selective Mannich-type Reaction



entry	substrate	catalyst	catalyst (mol %)	time (h)	yield (%)	dr[a] (anti/syn)	anti ee[b] (%)
1	**9a**	**7**	1.0	20	84	96/4	97
2	**9a**	**8**	1.0	20	20	85/15	81
3[c]	**9b**	**7**	5.0	72	53	79/2[d]	71
4[c]	**9b**	**8**	5.0	72	35	91/9[d]	62
5	**9c**	**7**	1.0	44	92	98/2	90
6	**9c**	**8**	1.0	44	42	90/10	73
7[c]	**9d**	**7**	10	78	76	48/52[d]	72
8[c]	**9d**	**8**	10	78	21	80/20[d]	88
9	**9e**	**7**	0.5	20	99	98/2	92
10	**9e**	**8**	0.5	20	85	95/5	82
11	**9f**	**7**	0.5	20	92	95/5	93
12	**9f**	**8**	0.5	20	56	92/8	66

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Determined by chiral HPLC analysis. [c]The reaction was carried out at rt. [d]Determined by HPLC analysis of isolated product.

diastereo- and enantioselectivities in high yields. When the less reactive cyclohexanone substrate was subjected to the reaction conditions, a considerable difference in the yield between using catalyst **7** or **8** was observed, with **7** dramatically outperforming the unsubstituted catalyst **8**. Cycloheptanone and pentan-3-one required increasing the catalyst loading to 5.0−10 mol % of **7** to provide a favorable yield. The use of acyclic pentan-3-one resulted in a decrease in diastereoselectivity. It was also found that an increase in the yield and enantioselectivity was generally observed with the substituted β-proline catalyst relative to the unsubstituted catalyst **8**.

■ CONCLUSION

We have developed a general asymmetric synthetic route toward the synthesis of chiral 3-substituted β-prolines bearing an all-carbon quaternary stereogenic center. Furthermore, the now accessible chiral 3-substituted β-prolines were demonstrated to be effective and differential catalysts for use in Mannich-type reactions of ketones/aldehydes with ethyl glyoxylate imines. It was found that **7** was more soluble in nonpolar organic solvents as compared to the unsubstituted β-proline **8**. The catalyst **7** effected Mannich-type reactions with low catalyst loadings achieving high *anti*-diastereo- and enantioselectivities. These results suggest that improvement in the solubility of amino acid catalysts in nonpolar organic solvents could lead to the development of more effective asymmetric organocatalysts. Additional investigations are under way directed at applying **7** as a catalyst in other asymmetric transformations.

■ EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial suppliers and used without further purification. Commercially available dehydrated solvents were used for all reactions. Column chromatography was performed using silica gel (spherical, neutral, 100−200 μm) or NH silica gel (100−200 mesh). NMR spectra were recorded on 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) spectrometers. HRMS were obtained by the FAB technique with a double sector mass spectrometer. HPLC analysis was conducted on an HPLC system equipped with chiral stationary-phase columns (0.46 cm × 25 cm).

Synthesis of Racemic 3-Methyl-β-proline (7). *1-tert-Butyl 4-Ethyl 2-Cyano-2-methylbutanedioate (**2**).* To a solution of *tert*-butyl 2-cyanopropanoate (329 mg, 2.12 mmol) in Et_2O (13 mL) were added ethyl iodoacetate (544 mg, 2.54 mmol), TBAI (39 mg, 0.106 mmol), and powdered KOH (593 mg, 10.59 mmol). The solution was stirred at rt for 18 h under Ar atmosphere, and then water was added. After being neutralized with diluted HCl, AcOEt (30 mL) was added. The organic layer was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 4/1) to give **2** (494 mg, 2.05 mmol) in 97% yield as a colorless oil: R_f = 0.42 (1:4, hexane/AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, t, J = 7.2 Hz), 1.52 (9H, s), 1.62 (3H, s), 2.77 (1H, d, J = 16.8 Hz), 2.98 (1H, d, J = 17.2 Hz), 4.19 (2H, q, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 23.5, 27.5, 41.1, 41.4, 61.3, 84.0, 119.5, 167.3, 168.6; IR (film) ν 2983, 2360, 1739, 1458, 1371, 1157, 1030, 843 cm^{-1}; HRMS (FAB) m/z: calcd for $C_{12}H_{20}NO_4$ $[M + H]^+$ 242.1392, found 242.1367.

*tert-Butyl 3-Methyl-5-oxopyrrolidine-3-carboxylate (**3**).* A mixture of $NaBH_4$ (1.33 g, 35.3 mmol) and $CoCl_2$ (917 mg, 7.06 mmol) was added to a solution of **2** (852 mg, 3.53 mmol) in dry MeOH (50 mL) at 0 °C, and the solution was stirred at rt for 24 h under Ar atmosphere. After 10% aqueous Rochelle salt (10 mL) was added, the mixture was stirred for 3 h and filtered. MeOH in the filtrate was evaporated, and the resulting solution was extracted with AcOEt (15 mL × 4). The combined organic layer was washed with H_2O and brine, and dried over $MgSO_4$. After filtration, the solvent was evaporated to give **3** (664 mg, 3.34 mmol) in 95% yield as a colorless solid: mp 77−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, s), 1.46 (9H, s), 2.17 (1H, d, J = 17.2 Hz), 2.84 (1H, d, J = 17.2 Hz), 3.14 (1H, d, J = 10.0 Hz), 3.74 (1H, d, J = 10.0 Hz), 6.00 (1H, brs); ^{13}C

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NMR (100 MHz, $CDCl_3$) δ 24.5, 27.8, 41.1, 46.0, 51.4, 81.4, 174.1, 176.5; IR (KBr) ν 3234, 2929, 1722, 1668, 1254, 1165 779 cm^{-1}. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.63; H, 8.77; N, 7.09.

*tert-Butyl 3-Methyl-5-thioxopyrrolidine-3-carboxylate (**4**).* To a solution of **3** (2.00 g, 10.1 mmol) in THF (75 mL) was added Lawesson's reagent (4.17 g, 10.3 mmol). The solution was stirred at rt for 17 h under Ar atmosphere. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on NH-silica gel (hexane/AcOEt = 2/1) to give **4** (1.63 g, 7.56 mmol) in 76% yield as a colorless solid: mp 80−81 °C; R_f = 0.42 (2:1, hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, s), 1.46 (9H, s), 2.78 (1H, d, J = 18.4 Hz), 3.32 (1H, d, J = 18.0 Hz), 3.39 (1H, d, J = 11.2 Hz), 4.05 (1H, d, J = 11.2 Hz), 7.70 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 27.8, 48.7, 51.9, 58.1, 81.9, 174.0, 203.8; IR (KBr) ν 3136, 2968, 1726, 1554, 1369, 1151, 1090, 845, 795 cm^{-1}. Anal. Calcd for $C_{10}H_{17}NO_2S$: C, 55.78; H, 7.96; N, 6.51. Found: C, 55.97; H, 8.07; N, 6.51.

*tert-Butyl N-Cbz-3-methylpyrrolidine-3-carboxylate (**5**).* In a 100 mL two-necked flask, Raney nickel slurry in water (3 mL) was placed under Ar atmosphere, then washed two times with H_2O (5 mL × 2), two times with MeOH (5 mL × 2), and two times with THF (5 mL × 2), respectively, by decantation. After THF (10 mL) was added, compound **4** (215 mg, 1.0 mmol) in THF (20 mL) was added. The solution was stirred under an H_2 atmosphere for 2 h at rt. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated to half volume. To the solution was added *Z*-chloride (1.02 g, 6.0 mmol). The solution was made weakly basic (pH 8−10) with 20% aqueous NaOH solution, and stirred at rt for 16 h. After being neutralized with aqueous HCl, the solution was extracted with CH_2Cl_2 (20 mL × 4). The combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvent was evaporated, and the residue was purified by column chromatography on NH-silica gel (hexane/AcOEt = 10/1) to give **5** (223 mg, 0.698 mmol) in 70% yield as a pale yellow oil: R_f = 0.30 (10:1, hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) 5:4 mixture of conformational isomers: δ 1.29 (3H × 5/9, s), 1.30 (3H × 4/9, s), 1.43 (9H, s), 1.70−1.76 (1H, m), 2.27−2.32 (1H, m), 3.18 (1H × 5/9, d, J = 10.8 Hz), 3.25 (1H × 4/9, d, J = 10.8 Hz), 3.46−3.52 (2H, m), 3.81 (1H, d, J = 11.2 Hz), 5.13 (2H, s), 7.33−7.36 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 27.8, 35.7 (35.0), 45.2 (44.9), 49.5 (48.5), 55.2 (54.7), 66.7, 81.0, 127.82, 127.85, 127.91, 128.4, 136.9, 174.5; IR (film) ν 2976, 1707, 1419, 1363, 1138, 848, 698 cm^{-1}; HRMS (FAB) m/z: calcd for $C_{18}H_{26}NO_4$ $[M + H]^+$ 320.1862, found 320.1882.

*N-Cbz-3-methylpyrrolidine-3-carboxylic Acid (**6**).* To a solution of **5** (160 mg, 0.50 mmol) in CH_2Cl_2 (3.0 mL) was added TFA (370 μL, 5.0 mmol), and the solution was stirred for 17 h at rt. After the solvent was evaporated, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1/2) to give **6** (127 mg, 0.48 mmol) in 97% yield as a pale yellow solid; mp 113−115 °C; R_f = 0.39 (1:2, hexane/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) 5:4 mixture of conformational isomers: δ 1.36 (3H × 5/9, s), 1.37 (3H × 4/9, s), 1.76−1.84 (1H, m), 2.32−2.40 (1H, m), 3.24 (1H × 5/9, d, J = 10.8 Hz), 3.29 (1H × 4/9, d, J = 11.2 Hz), 3.47−3.55 (2H, m), 3.87 (1H × 5/9, d, J = 10.8 Hz), 3.90 (1H × 4/9, d, J = 10.4 Hz), 5.11 (2H, s), 7.28−7.35 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.11 (22.06), 34.9 (35.7), 45.2 (44.9), 48.7 (47.8), 54.6 (55.1), 67.01 (66.97), 127.9, 128.0, 128.5, 136.6 (136.7), 154.9, 181.0; IR (KBr) ν 3089, 2978, 1730, 1660, 1435, 1369, 1213, 1115, 732, 669 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.94; H, 6.56; N, 5.32.

*3-Methyl-β-proline (**7**).* To the solution of **6** (76 mg, 0.29 mmol) in dry MeOH (5.0 mL) was added 10% Pd/C (31 mg, 10 mol %), and the solution was stirred under H_2 atmosphere for 1 h at rt. The reaction mixture was filtered through a pad of Celite, and the filtrate was evaporated to give **7** (37 mg, 0.29 mmol) in quantitative yield as a colorless solid: ^{1}H NMR (400 MHz, CD_3OD) δ 1.35 (3H, s), 1.78 (1H, dt, J = 12.8, 8.8 Hz), 2.40 (1H, dt, J = 13.2, 6.0 Hz), 2.83 (1H, d, J = 11.2 Hz), 3.32−3.34 (2H, m), 3.70 (1H, d, J = 11.2 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 22.8, 37.1, 46.0, 51.7, 55.5, 181.8; IR (KBr) ν 3423, 2966, 1630, 1571, 1400, 1255, 806, 789 cm^{-1}; HRMS (FAB) m/z: calcd for $C_6H_{12}NO_2$ $[M + H]^+$ 130.0868, found 130.0878.

Synthesis of (*R*)-3-Methyl-β-proline (7). *(R)-1-tert-Butyl 4-Ethyl 2-Cyano-2-methylbutanedioate (**2**).*[6b] To a solution of *tert*-butyl 2-cyanopropanoate (1.55 g, 10.0 mmol) in Et_2O (60 mL) at −60 °C were added ethyl iodoacetate (2.57 g, 12.0 mmol), (*R*,*R*)-3,5-bistrifluoromethylphenyl-NAS bromide (54.0 mg, 0.05 mmol), and CsOH (6.35 g, 42.4 mmol). The solution was stirred at −60 °C for 1 d under Ar atmosphere, and then washed with water (10 mL) and brine (10 mL), and dried over $MgSO_4$. After the solvent was concentrated under reduced pressure, the resulting residue was purified by column chromatography on silica gel (hexane/AcOEt = 4/1) to give **2** (2.20 g, 9.13 mmol) in 91% yield with 86% ee as a colorless oil. $[\alpha]^{25}_D$ = +15.8 (*c* 2.0, $CHCl_3$, ee = 86%). The ee was determined by HPLC analysis (Daicel CHIRALCEL OJ-H, 2-propanol/hexane = 1:75, 1.0 mL/min retention time: 9.1 min (major enantiomer) and 11.6 min (minor enantiomer).

*Optical Resolution of Compound **6**.* Compound **6** (200 mg, 0.76 mmol), which was prepared from **2** (86% ee) following the same synthetic sequence as that of racemic **6**, and (*S*)-(−)-1-phenylethylamine (92 mg, 0.76 mmol) were dissolved in warm benzene (1.0 mL). After being cooled to room temperature, the precipitate was filtered and recrystallized from EtOH/hexane to yield crystals (114 mg, 0.30 mol). The crystals were dissolved in EtOH (1.0 mL), and a solution of NaOH (12 mg, 0.30 mol) in H_2O (1.0 mL) was added. After the solution was stirred for 2 h, H_2O (2.0 mL) was added, and extracted with AcOEt (8 mL × 3). The aqueous layer was acidified with diluted HCl and extracted with AcOEt (10 mL × 3). The latter combined organic layer was washed with H_2O (2.0 mL) and brine (1.0 mL), and dried over $MgSO_4$. The solvent was concentrated under reduced pressure to give **6** (78 mg, 0.30 mol) with 99% ee. $[\alpha]^{27}_D$ = −28.3 (*c* 0.21, $CHCl_3$, ee = 99%). The ee was determined by HPLC analysis (Daicel CHIRALCEL AD-H, EtOH/hexane = 1:8, 1.0 mL/min, retention time: 14.1 min (major enantiomer) and 17.3 min (minor enantiomer)).

*(R)-3-Methyl-β-proline (**7**).* Compound **6** (99% ee) was hydrogenated in the same manner as that for the hydrogenation of the racemate **6**, and (*R*)-3-methyl-β-proline (**7**) was obtained in quantitative yield as a colorless solid: mp 216 °C (decomp); $[\alpha]^{31}_D$ = −26.4 (*c* 0.20, MeOH, ee = 99%). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80%; H, 8.58%; N, 10.84%. Found: C, 55.32%; H, 8.54%; N, 10.54%.

A Typical Procedure for the Asymmetric Mannich-type Reaction Using *N*-PMP-Protected Glyoxylate Imine. To a solution of *N*-PMP-protected glyoxylate imine (162 mg, 0.78 mmol) in dry CH_2Cl_2 (1.5 mL) were added catalyst **7** (99% ee, 1.0 mg, 1.0 mol %) and cyclohexanone (162 μL, 1.57 mmol) at 0 °C. The solution was stirred for 20 h, and then Et_2O was added (15 mL). The organic layer was washed with H_2O (1.0 mL) and brine (0.5 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give ethyl 2-(*p*-methoxyphenylamino)-2-(2′-oxocyclohexyl) acetate as a mixture of diastereomers. The yield and diastereomeric ratio of the Mannich product were determined by ^{1}H NMR using mesitylene as an internal standard. After column chromatography on silica gel (hexane/AcOEt = 3/1), the enantiomeric excess of the products was determined by chiral-phase HPLC.

Ethyl (2*S*,1′*R*)-2-(*p*-Methoxyphenylamino)-2-(2′-oxocyclohexyl)acetate.[4l,16] ^{1}H and ^{13}C NMR spectrum data were in accordance with those in the literature. HPLC analysis: Daicel Chiralpak IA, hexane/2-PrOH = 92/8, 0.5 mL/min, retention time, 32.7 min (*anti* minor enantiomer) and 42.2 min (*anti* major enantiomer).

Ethyl (2*S*,1′*R*)-2-(*p*-Methoxyphenylamino)-2-(2′-oxocycloheptyl)acetate.[4m] ^{1}H and ^{13}C NMR spectrum data were in accordance with those in the literature. The dr was determined by HPLC analysis of isolated product. HPLC analysis: Daicel Chiralpak AD-H, hexane/2-PrOH = 9/1, 1.0 mL/min, retention time, 21.7 min (*anti* minor enantiomer) and 28.1 min (*anti* major enantiomer).

Ethyl (2*S*,3′*S*)-2-(*p*-Methoxyphenylamino)-2-(4′-oxotetrahydropyran-3′-yl)acetate.[4l] ^{1}H and ^{13}C NMR spectrum data were

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in accordance with those in the literature. HPLC analysis: Daicel Chiralpak IA, hexane/EtOH = 90/10, 1.0 mL/min, retention time, 33.6 min (*anti* minor enantiomer) and 53.0 min (*anti* major enantiomer).

Ethyl (2*S*,3*R*)-2-(*p*-Methoxyphenylamino)-3-methyl-4-oxohexanoate.[4l] ^{1}H and ^{13}C NMR spectrum data were in accordance with those in the literature. The dr was determined by HPLC analysis of isolated product. HPLC analysis: Daicel Chiralpak AS-H, hexane/2-PrOH = 99/1, 1.0 mL/min, retention time, 27.9 min (*anti* major enantiomer) and 49.3 min (*anti* minor enantiomer).

Ethyl (2*S*,3*R*)-3-Formyl-2-(*p*-methoxyphenylamino)-heptanoate.[4k] ^{1}H and ^{13}C NMR spectrum data were in accordance with those in the literature. HPLC analysis: Daicel Chiralpak OJ-H, hexane/EtOH = 9/1, 1.0 mL/min, retention time, 9.9 min (*anti* minor enantiomer) and 12.1 min (*anti* major enantiomer).

Ethyl (2*S*,3*R*)-3-Formyl-2-(*p*-methoxyphenylamino)-4-methylpentanoate.[4k] ^{1}H and ^{13}C NMR spectrum data were in accordance with those in the literature. HPLC analysis: Daicel Chiralpak AD-H, hexane/2-PrOH = 8/2, 1.0 mL/min, retention time, 8.0 min (*anti* minor enantiomer) and 9.1 min (*anti* major enantiomer).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Diastereomeric (*S*)-1-phenylethylamine salts, which were prepared from racemic **6**, could not be recrystallized using the same solvent (EtOH/hexane) as that applied to the salts prepared from optically active **6** (86% ee). Using different solvents (AcOEt/hexane) enabled the recrystallization of the diastereomeric salts; optical purity of **6** after treatment of the crystals with NaOH solution was 27% ee with 21% recovery.

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