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# MODIFIED 3-HYDROXYPIPECOLIC ACID DERIVATIVES AS AN ORGANOCATALYST†

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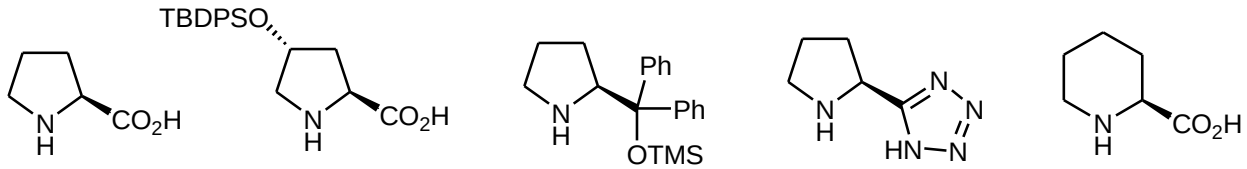
**Abstract** – Novel 3-hydroxypipecolic acid derivatives were synthesized from glycine by using the method we developed previously. Among the 3-hydroxypipecolic acid derivatives obtained, a 2,3-*trans*-3-*O*-TBDPS-4,5-didehydro derivative showed the most promising result as an asymmetric catalyst in the Mannich reaction of ethyl 4-(methoxyphenylimino)acetate and *n*-hexylaldehyde.

## INTRODUCTION

The field of asymmetric organocatalysis has made rapid progress because of a strong demand for development of economical and environment-friendly catalysts.[1] Proline **1**, one of the earliest organocatalysts developed, has been recognized as a powerful asymmetric catalyst that is able to catalyze various reactions including aldol,[1d,2] Mannich,[1d,3] Michael addition,[1d,4] and Diels-Alder[1d,5] reactions. Much interest has been shown in the search for new catalysts based on a proline skeleton, and many proline derivatives, *e.g.*, **2**, **3**, and **4** as shown in Chart 1, have been reported.[6-8]




**1** **2** **3** **4** **5**

**Chart 1**

†This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

In contrast to the extensive studies on proline derivatives, there have been few reports on organocatalysis application of pipecolic acid **5**, a naturally occurring homologue of proline.[9] A study by Barbas revealed that pipecolic acid could act as an effective asymmetric organocatalyst for the Mannich reaction.[9b] We have studied the synthesis of various hydroxylated piperidine and pyrrolidine derivatives that may act as glycosidase inhibitors as transition state analogues (azasugars).[10] Thus, the results of the study by Barbas prompted us to synthesize pipecolic acid derivatives and evaluate their organocatalytic functionality.

## RESULTS AND DISCUSSION

As an initial organocatalyst candidate, we selected 3-hydroxy-4,5-didehydropipecolic acid **6** in which the double bond and hydroxyl moieties could potentially be used for further manipulations of the molecule. This would be an advantage for synthesizing various derivatives and effective for searching for a novel organocatalyst. To prove our concept, we envisioned the synthesis of pipecolic acid derivatives **7-10** from the common intermediate for **6** (Chart 2).

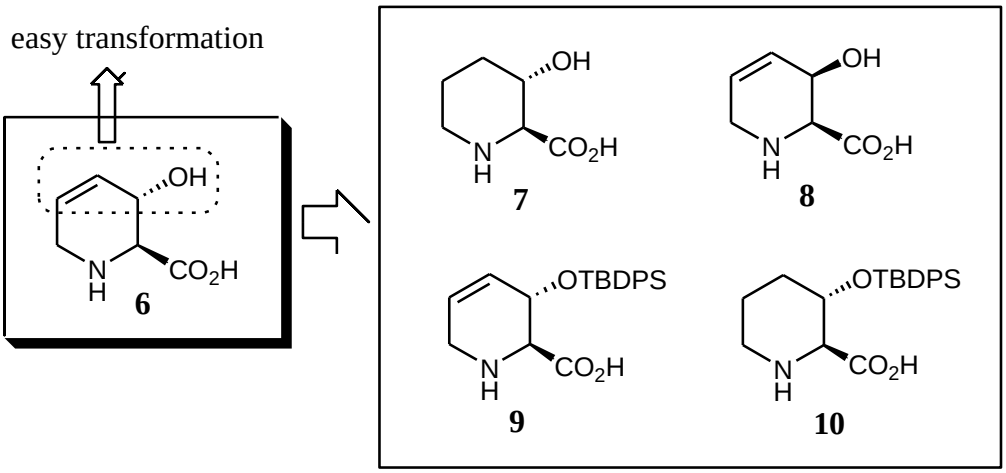
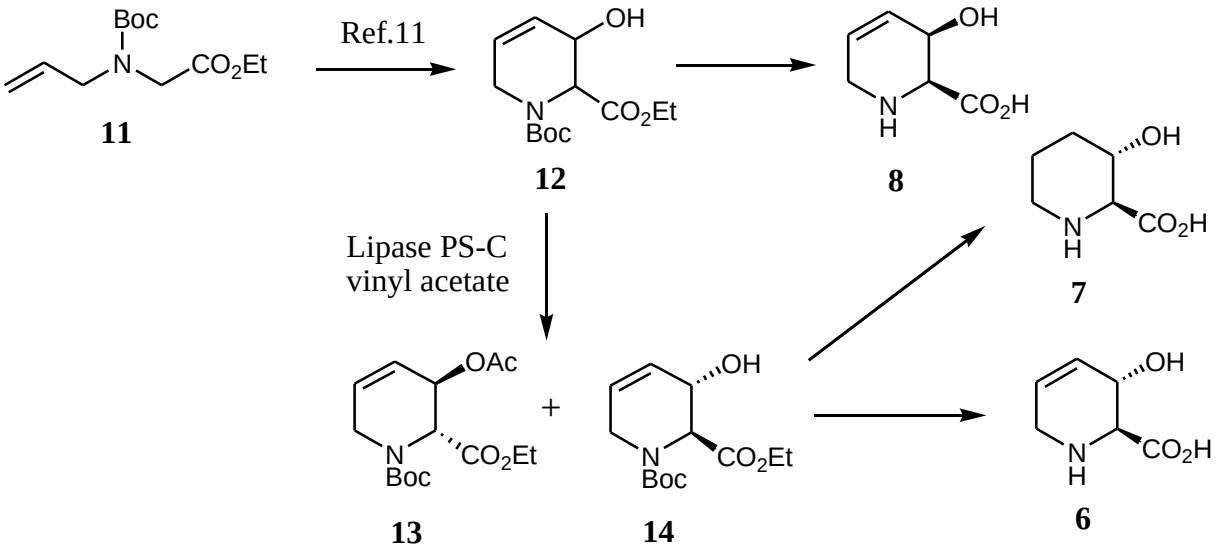


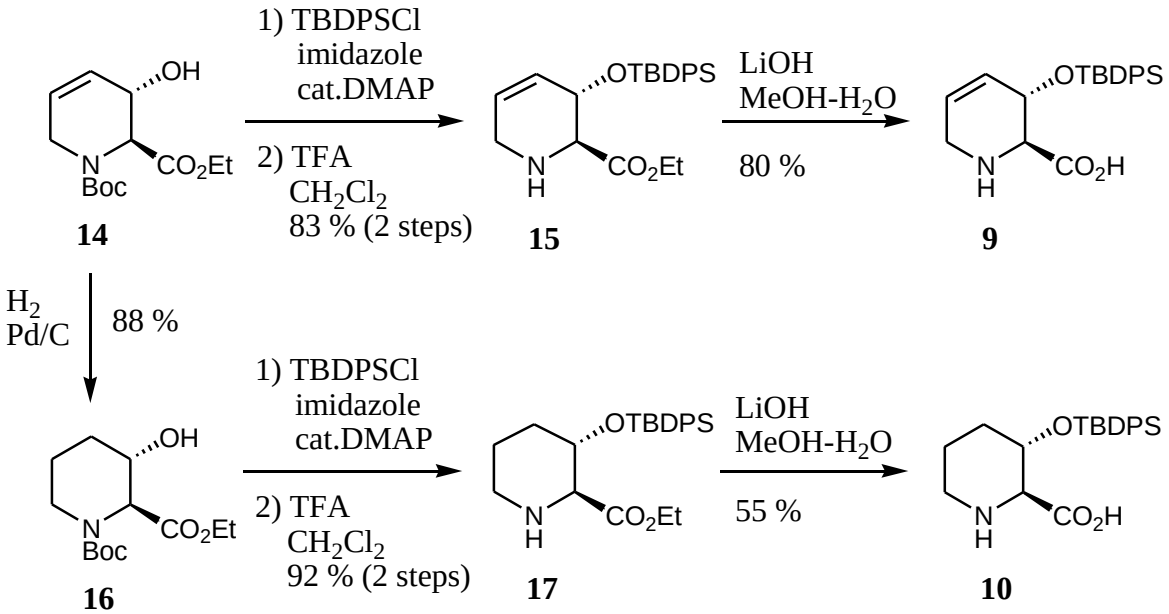

**Chart 2**

Recently, we have achieved the synthesis of all stereoisomers of 3-hydroxypipecolic acids from *N*-allylglycine derivative **11**, obtained easily from glycine, as shown in Scheme 1.[11] By this method, pipecolic acid derivatives **6**, **7**, and **8** were synthesized. The synthesis includes a step for lipase-catalyzed kinetic resolution of racemic **12**, which has the virtue of enabling both of the enantiomers of pipecolic acid derivatives to be prepared in the same way. This will be a great advantage for catalyst preparation since either of the desirable enantiomers of the catalyst will be obtainable by this method.




**Scheme 1**

The chiral building block **14** obtained from lipase resolution[11] [99% ee: determined by chiral HPLC after converting to the corresponding *N*-tosyl derivative (data not shown)] was also used for synthesizing 3-*O*-TBDPS derivatives, which were selected as organocatalyst candidates designed on the basis of 3-hydroxyproline derivative **2**. Compound **14** was silylated at the 3-hydroxyl group, and subsequent deprotection of the Boc group gave a tetrahydropyridine derivative **15** in 83% yield. Hydrolysis of **15** by LiOH gave a 2,3-*trans*-3-*O*-TBDPS-4,5-didehydro derivative **9** in good yield (Scheme 2). Similarly, a 2,3-*trans*-3-*O*-TBDPS derivative **10** was synthesized from **16** obtained by catalytic hydrogenation of **14**.[11]



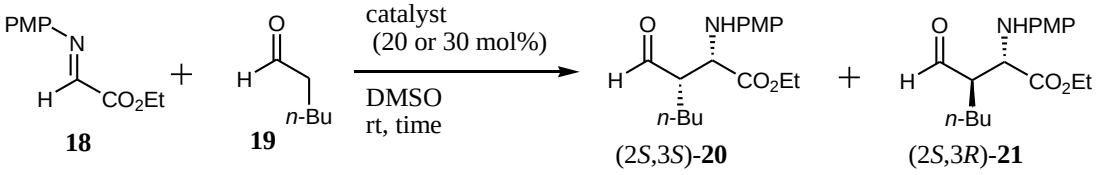

**Scheme 2**

The pipecolic acid derivatives **6-10** thus obtained were examined for their organocatalytic functionality. First, we tested an asymmetric Mannich reaction between ethyl 4-(methoxyphenylimino)acetate **18** and

*n*-hexylaldehyde **19** in DMSO[9b] using **6**, **7**, and **8** and compared their abilities with those of pipecolic acid **5**. After an appropriate reaction time, the resulting Mannich reaction products were isolated by silica gel column chromatography and their optical purities were determined by chiral HPLC analysis.[12] The results are summarized in Table 1.

The reaction using 4,5-didehydro-2,3-*trans*-3-hydroxypipecolic acid **6** gave Mannich products (2*S*,3*S*)-*syn*-**20** and its *anti*-isomer (2*S*,3*R*)-**21** in moderate yields with high ees (entry 1), which were slightly lower than those of parental pipecolic acid (entry 4). The reaction using 2,3-*cis*-isomer **8** gave results similar to those of the reaction using **6**, with slight improvement of *syn*-selectivity of diastereomer formation (entry 3). The reaction of 2,3-*trans*-3-hydroxypipecolic acid **7** gave results comparable to those of the reaction using pipecolic acids, but the reaction yield was slightly diminished (entry 2).

**Table 1. Asymmetric Mannich Reaction Catalyzed by Pipecolic Acid Derivatives 6-8**



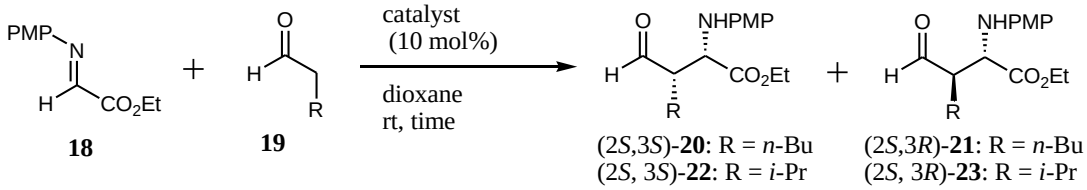

| entry | catalyst | time (h) | yield[a] (%) | dr[b] *syn* / *anti* | ee (%)[c] *syn* (*anti*) |
|---|---|---|---|---|---|
| 1 | **6** (30 mol%) | 11 | >66 | 1.7 / 1.0 | 88 (88) |
| 2 | **7** (30 mol%) | 16 | 63 | 1.4 / 1.0 | 93 (96) |
| 3 | **8** (20 mol%) | 9 | 66 | 2.0 / 1.0 | 79 (94) |
| 4 | **5** (30 mol%) | 12 | 83 | 1.5 / 1.0 | >99 (>99) |

[a]Isolated yield, [b]Ratios of diastereomers were determined based on $^1$H NMR, [c]Enantiomeric excess of the products were determined by HPLC analysis (see Experimental section).

Because of the low solubility of compounds **6-8**, the reaction solvents to be used for Mannich reaction were limited to polar solvents like DMSO. On the other hand, compounds **9** and **10** in which a TBDPS group was installed at the 3-hydroxyl group may have a more lipophilic character than that of compounds **6-8** and could be used in less polar solvents. Thus, we tested the asymmetric Mannich reaction using **9** and **10** in 1,4-dioxane, which is often used for proline-catalyzed reaction. Although these compounds themselves could not dissolve in dioxane, the reaction mixture became clear after addition of *n*-hexylaldehyde **19**. As a result, both **9** and **10** showed improved results in comparison with those of **6-8** (Table 2, entries 1 and 3). The use of 10 mol% 2,3-*trans*-3-*O*-TBDPS-4,5-didehydro derivative **9** as a catalyst gave a result comparable to that of 30 ml% pipecolic acid **5**. In addition, **9** also showed a

promising result with high ee when used in the reaction between ethyl 4-(methoxyphenylimino)acetate and isopentylaldehyde (Table 2, entry 2). It is noteworthy that a new pipecolic acid-based catalyst that could be used in a less polar solvent was obtained by the simple modification of **6** as we initially planned.

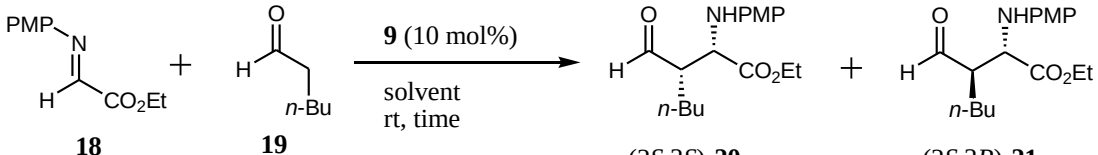
**Table 2. Asymmetric Mannich Reaction Catalyzed by Pipecolic Acid Derivatives 9 and 10 Bearing a 3-*O*-TBDPS Group**




| entry | R | catalyst | time (h) | yield (%)[a] | dr[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| | | | | | *syn* / *anti* | *syn* (*anti*) |
| 1 | *n*-Bu | **9** | 16 | 66 | 1.3 / 1.0 | 95 (98) |
| 2 | *i*-Pr | **9** | 86 | 71 | 2.0 / 1.0 | 99 (96) |
| 3 | *n*-Bu | **10** | 21 | 75 | 1.8 / 1.0 | 96 (88) |

[a]Isolated yield, [b]Ratios of diastereomers were determined based on $^1$H NMR, [c]Enantiomeric excess of the products were determined by HPLC analysis (see Experimental section).

**Table 3. Effect of the Solvent on Asymmetric Mannich Reaction Using 9**




| entry | solvent | time (h) | yield (%)[a] | dr[b] | ee (%)[c] |
|---|---|---|---|---|---|
| | | | | *syn* / *anti* | *syn* (*anti*) |
| 1 | DMSO | 29 | 77 | 1.7 / 1.0 | 97 (97) |
| 2 | THF | 24 | 69 | 1.7 / 1.0 | 98 (97) |
| 3 | $CH_2Cl_2$ | 12 | 75 | 1.3 / 1.0 | 98 (95) |
| 4 | $CH_3CN$ | 13 | 74 | 1.0 / 1.0 | 97 (96) |
| 5 | DMF | 36 | 64 | 1.7 / 1.0 | 97 (97) |
| 6 | hexane | 9 | 35 | 1.7 / 1.0 | >36 (44) |
| 7 | dioxane : $H_2O$ = 9 : 1 | 9 | 62 | 2.5 / 1.0 | 79 (79) |

[a]Isolated yield, [b]Ratios of diastereomers were determined based on $^1$H NMR, [c]Enantiomeric excess of the products were determined by HPLC analysis (see Experimental section).

The 3-*O*-TBDPS derivative **9** was further examined for its usefulness as an asymmetric catalyst for the Mannich reaction in various solvents. The results are summarized in Table 3. The Mannich reaction using **9** in DMSO, THF, $CH_2Cl_2$, $CH_3CN$ and DMF gave **20** and **21** in 64-77% yields with similar ee (entries 1-5). In contrast, the use of hexane as the solvent resulted in decreases in both chemical yield and ee (entry 6). The catalyst **9** could be used in aqueous solvent conditions; however, the reaction gave Mannich products with slight decreases in ee (entry 7). The broad solvent compatibility of **9** including an aqueous solvent would be advantageous for use as an organocatalyst.

In conclusion, we have synthesized five pipecolic acid derivatives **6-10** and examined their ability as asymmetric organocatalysts of the Mannich reaction. Among the compounds obtained, a 2,3-*trans*-3-*O*-TBDPS-4,5-didehydro derivative **9** showed the most promising result. The results suggest that our initial target, 4,5-didehydro-3-hydroxypipecolic acid, is a useful scaffold for the design and development of new organocatalysts.

## EXPERIMENTAL

**General.** Melting points are uncorrected. NMR spectra were recorded at 400 MHz ($^1$H), 100 MHz ($^{13}$C) using $CDCl_3$, $CD_3OD$ and $D_2O$. As an internal standard, tetramethylsilane was used for $CDCl_3$ and $CD_3OD$ and 1,4-dioxane was used for $D_2O$. Mass spectra were obtained by EI or FAB mode. Silica gel for chromatography was Fuji Silysia PSQ 100B. When the reagents sensitive to moisture were used, the reaction was performed under argon atmosphere.

**Ethyl (2*S*,3*S*)-3-(*tert*-butyldiphenylsiloxy)-1,2,3,6-tetrahydropyridine-2-carboxylate (15).** To a solution of **14**[11] (103 mg, 0.38 mmol), imidazole (39 mg, 0.57 mmol), DMAP (cat.) in $CH_2Cl_2$ (10 mL) was added TBDPSCl (118 mg, 0.46 mmol) at rt and the mixture was stirred at the same temperature for 9 h. After insoluble materials were removed by celite filtration, the filtrate was washed with brine and dried over $Na_2SO_4$. After filtration, the filtrate was concentrated and the residue was dissolved in $CH_2Cl_2$ (10 mL). To this solution was added TFA (4.5 mL, 59 mmol) and the mixture was stirred at rt for 11.5 h. After the solvents were removed under reduced pressure, the residue was dissolved in MeOH (15 mL) and the resulting solution was neutralized by $NaHCO_3$. The insoluble materials were removed by filtration, the filtrate was concentrated. The residue was purified by silica gel column chromatography (*n*-hexane : AcOEt = 4 : 1) to give **15** (127 mg, 95 %, 2 steps) as a syrup. $[\alpha]_D^{26}$ +58.2 ° ($CHCl_3$, *c* 1.3); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.22 (3H, t, *J* = 7.2 Hz), 1.84 (1H, brs), 3.26-3.37 (2H, m), 3.53 (1H, d, *J* = 6.3 Hz), 4.02-4.16 (2H, m), 4.49-4.50 (1H, m), 5.55 (1H, dd, *J* = 10.2, 2.4 Hz), 5.67 (1H, d, *J* = 11.6 Hz), 7.35-7.44 (6H, m), 7.66-7.72 (4H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 14.0, 19.2, 26.8 (3C),

43.5, 60.9, 62.3, 67.1, 127.5, 127.6, 128.4 (2C), 128.6 (2C), 129.6 (2C), 129.7 (2C), 133.4, 134.1, 135.8, 135.8, 172.2; IR (neat): 2931.9, 2857.7, 1736.9, 1428.2, 1191.0, 1112.5, 702.8 $cm^{-1}$; EI-MS (m/z): 409 ($M^+$); HRMS Calcd for $C_{24}H_{31}NO_3Si$: 409.2037. Found: 409.2065.

**(2*S*,3*S*)-3-(*tert*-Butyldiphenylsiloxy)-1,2,3,6-tetrahydropyridine-2-carboxylic acid [(2*S*,3*S*)-3-(*tert*-Butyldiphenylsiloxy)-4,5-didehydropipecolic acid, 9].** To a solution of **15** (103 mg, 0.25 mmol) in MeOH (2.7 mL) and $H_2O$ (0.9 mL) was added LiOH (28 mg, 1.18 mmol) at rt and the mixture was stirred at the same temperature for 9 h. After neutralized by AcOH, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$ : MeOH = 5 : 1) to give **9** (77 mg, 80 %) as a white solid. $[\alpha]_D^{26}$ +109.8 ° ($CHCl_3$ : MeOH = 5 : 1, *c* 0.1); $^1$H NMR (400 MHz, $CDCl_3$ : $CD_3OD$ = 5 : 1) δ 1.11 (9H, s), 3.55 (1H, d, *J* = 17.4 Hz), 3.92 (1H, d, *J* = 2.4 Hz), 3.98 (1H, d, *J* = 17.4 Hz), 4.88 (1H, brs), 5.62-5.66 (1H, m), 5.72 (1H, d, *J* = 10.1 Hz), 7.38-7.47 (6 H, m), 7.69-7.73 (4H, m); $^{13}$C NMR (100 MHz, $CDCl_3$ : $CD_3OD$ = 5 : 1) δ 18.9, 26.6 (3C), 39.3, 61.4, 63.6, 121.9, 127.0, 127.5 (2C), 127.7 (2C), 129.7 (2C), 129.9 (2C), 132.5, 133.2, 135.5, 135.6, 168.4; IR (KBr): 3409.4, 2932.4, 2857.7, 1635.0, 1567.5, 1112.18, 1060.8 $cm^{-1}$; EI-MS (m/z): 381 ($M^+$); HRMS Calcd for $C_{22}H_{27}NO_3Si$: 381.1760. Found: 381.1764.

**Ethyl (2*S*,3*S*)-3-hydroxypiperidine-2-carboxylate (16).** Compound **16** (191 mg, 88%) was obtained by catalytic hydrogenation of **14** (216 mg, 0.80 mmol) as described in ref 11.

**Ethyl (2*S*,3*S*)-3-(*tert*-butyldiphenylsiloxy)piperidine-2-carboxylate (17).** Compound **17** (syrup, 341 mg, 92 % 2 steps; after purification by silica gel column chromatography: *n*-hexane : AcOEt = 3 : 1) was obtained from **16** (246 mg, 0.90 mmol) by the same procedure described in the synthesis of **15**. $[\alpha]_D^{21}$ +36.0 ° ($CHCl_3$, *c* 1.0); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.01 (9H, s), 1.24 (3H, t, *J* = 7.2 Hz), 1.37-1.46 (1H, m), 1.57 (1H, dt, *J* = 9.7, 3.9 Hz), 1.68-1.72 (2H, m), 2.51 (1H, m), 2.90 (1H, dt, *J* = 13.0, 8.7 Hz), 3.33 (1H, d, *J* = 8.7 Hz), 3.82-3.88 (1H, m), 4.06-4.17 (2H, m), 7.34-7.44 (6H, m), 7.65-7.70 (4H, m) $^{13}$C NMR (100 MHz, $CDCl_3$) δ 13.9, 19.1, 25.4, 26.7 (3C), 33.2, 44.7, 60.8, 66.8, 71.54, 127.4 (2C), 127.5 (2C), 129.5 (2C), 129.6 (2C), 133.4, 134.4, 135.7, 135.8, 172.6; IR (neat): 2932.8, 2857.7, 1734.1, 1428.0, 1192.4, 1111.8, 703.7 $cm^{-1}$; FAB-MS (m/z) : 412 ($M^+$+1); HRMS Calcd for $C_{24}H_{34}NO_3Si$: 412.2308. Found: 412.2293

**(2*S*,3*S*)-3-(*tert*-Butyldiphenylsiloxy)pipecolic acid [(2*S*,3*S*)-3-(*tert*-Butyldiphenylsiloxy)pipecolic acid, 10].** Compound **10** (white solid, 151 mg, 55 % along with 28% recovery of **17**; after purification by silica gel column chromatography: $CHCl_3$ : MeOH = 5 : 1) was obtained from **17** (298 mg, 0.72 mmol) by the

same procedure described in the synthesis of **9**. $[\alpha]_D^{21}$ −19.7 ° ($CHCl_3$ : MeOH = 5 : 1, *c* 0.1); $^1$H NMR (400 MHz, $CDCl_3$ : $CD_3OD$ = 5 : 1) δ 1.13 (9H, s), 1.54 (3H, brs), 2.12 (1H, brs), 3.12 (1H, d, *J* = 13.5 Hz), 3.29 (1H, t, *J* = 11.6), 3.70 (1H, s), 3.81 (1H, brs), 4.68 (1H, s), 7.38-7.47 (6 H, m), 7.65-7.70 (4H, m); IR (KBr): 3446.7, 3047.7, 2934.1, 2858.0, 1635.4, 1562.3, 1371.2, 1111.6, 1060.3, 1018.0 $cm^{-1}$; EI-MS (m/z): 384 ($M^+$+1); HRMS Calcd for $C_{22}H_{29}NO_3Si$: 383.1917. Found: 383.1931.

**Procedures for asymmetric Mannich reactions.** Following the procedure reported by Barbas *et al*.,[9] the asymmetric Mannich reaction was done. After purification, by silica gel column chromatography, the optical purities of the products were analyzed by HPLC using a chiral column. Typically, ethyl 4-(methoxyphenylimino)acetate (103 mg, 0.5 mmol) was dissolved in a solvent (5 mL) and aldehyde (0.75 mmol) was dropwise added to the mixture at rt. After addition of catalyst (10 mol%), the mixture was stirred at room temperature. The reaction was quenched with *aq*. $NH_4Cl$, and the whole mixture was extracted with AcOEt×3, then dried ($Na_2SO_4$). After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (*n*-hexane : AcOEt = 9-5 : 1).

**Ethyl 3-formyl-2-(*p*-methoxyphenylamino)-4-methylpentanoate ((2*S*,3*S*)-20 and (2*S*,3*R*)-21).** $^1$H-NMR (400 MHz, $CDCl_3$): purified 1 : 0.8 mixture of diastereomers, * denotes *anti* diastereomer δ 1.03 (1.7H, d, *J* = 6.8 Hz), 1.08 (1.3H*, d, *J* = 6.8 Hz), 1.13 (1.3H*, d, *J* = 6.8 Hz), 1.17 (1.7H, d, *J* = 7.2 Hz), 1.22 (3H, t × 2, *J* = 7.2 Hz), 2.06-2.15 (0.44H*, m), 2.27-2.36 (0.55H, m), 2.53-2.62 (1H, m), 3.74 (3H, s), 3.80-3.92 (1H, m), 4.16 (2H, q×2, *J* = 7.2 Hz), 4.30-4.34 (1H, m), 6.66 (2H, d, *J* = 8.7 Hz), 6.76-6.79 (2H, m), 9.75 (0.44H, d, *J* = 3.4 Hz), 9.78 (0.55H, d, *J* = 2.9 Hz); HPLC: CHIRALPAK AS-H, hexane : *i*-PrOH = 99 : 1, Flow Rate 1.0 mL/ min, Retention Time; *syn* major enantiomer = 22.9 min, *syn* minor enantiomer = 35.2 min, *anti* major enantiomer = 19.4 min, *anti* minor enantiomer = 31.7 min, 35 °C, 254 nm.

**Ethyl 3-formyl-2-(*p*-methoxyphenylamino)heptanoate ((2*S*,3*S*)-22 and (2*S*,3*R*)-23).** $^1$H-NMR (400 MHz, $CDCl_3$): purified 1 : 0.9 mixture of diastereomers, * denotes *anti* diastereomer δ 0.87~0.92 (3H, m), 1.23 (1.4H*, t, *J* = 7.2 Hz), 1.24 (1.6H, t, *J* = 7.2 Hz), 1.29-1.49 (4H, m), 1.53-1.65 (1H, m), 1.68-1.75 (0.5H*, m), 1.83-1.90 (0.5H, m), 2.68-2.77 (1H, m), 3.74 (3H, s), 4.00 (1H, brs), 4.13-4.22 (2H, m), 4.26 (0.5H*, d, *J* = 6.3 Hz), 4.35 (0.5H, d, *J* = 4.8 Hz), 6.65 (2H, d, *J* = 9.2 Hz), 6.78 (2H, dd, *J* = 8.7, 1.9 Hz), 9.66 (0.5H, d, *J* = 2.4 Hz), 9.71 (0.5H, d, *J* = 1.9 Hz); HPLC: CHIRALPAK AS-H, hexane : *i*-PrOH = 100 : 1, Flow Rate 0.6 mL / min, Retention Time; *syn* major enantiomer = 45.7 min, *syn* minor enantiomer = 60.9 min, *anti* major enantiomer = 37.8 min, *anti* minor enantiomer = 43.7 min, 32 °C, 254 nm.

## ACKNOWLEDGEMENTS

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12. The absolute stereochemistries of the Mannich products were determined by the comparison of retention times of chiral HPLC analysis with the data shown in ref 9b.