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ASYMMETRIC INTRAMOLECULAR ALDOL REACTIONS MEDIATED BY CHIRAL TRIAMINES BEARING A PYRROLIDINE SCAFFOLD TO PROVIDE A WIELAND–MIESCHER KETONE

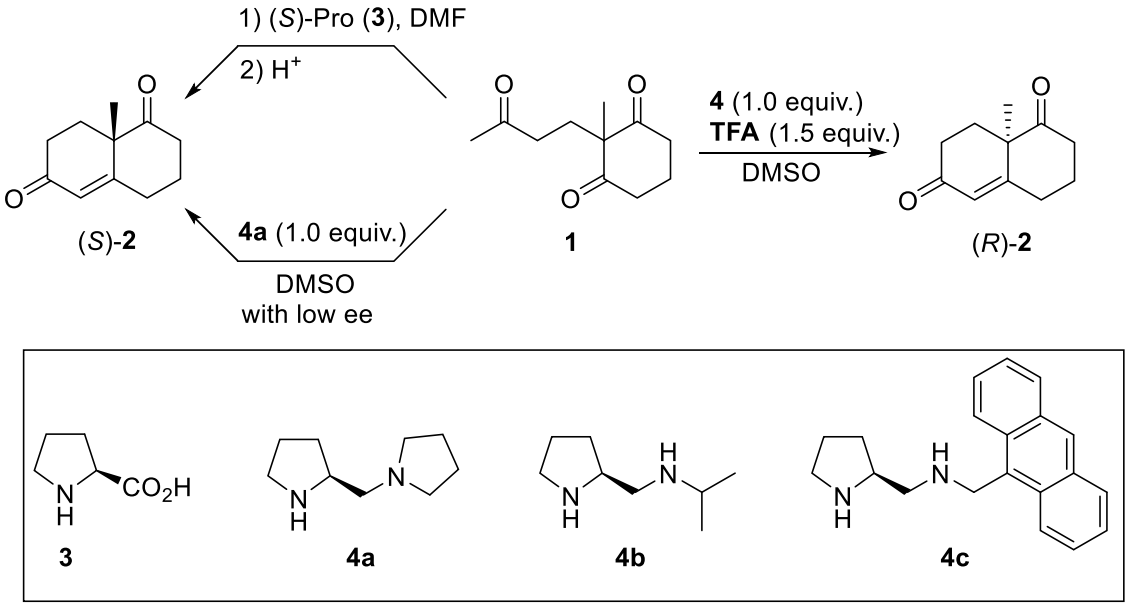
Yuichi Akahane[b] **and Kohei Inomata***[a,b]

[a]Department of Pharmaceutical Sciences, International University of Health and Welfare, 2600-1 Kitakanemaru, Ohtawara 324-8501, Japan, [b]Department of Pharmacy, Tohoku Medical and Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan, E-mail: inomata@iuhw.ac.jp

Abstract – We established a new asymmetric route to provide (*R*)-Wieland–Miescher ketone [(*R*)-**2**] using a combination of trifluoroacetic acid (TFA) and known or new chiral triamines (**7**) bearing a pyrrolidine scaffold. Although the intramolecular aldol reaction of trione (**1**) mediated by chiral prrolidine (**7**) resulted in the production of **2** with low enantioselectivities, a remarkably increased enantioselectivity with a combination of **7b** or **7c** and TFA was observed. We also found that a secondary amine motif existing in the middle of the side chain was important in defining the enantioselectivity.

Wieland–Miescher ketone (**2**) prepared by the (*S*)-proline [(*S*)-Pro, **3**]-mediated asymmetric intramolecular aldol reaction of the trione (**1**) has been a highly useful synthon in the total syntheses of a variety of natural products.[1-6] This asymmetric aldol reaction has been widely recognized to involve an enamine-based mechanism. In this reaction, a hydrogen bond between an oxygen atom on the cyclohaxane and a carboxylic acid in (*S*)-proline (**3**) played very important roles in stabilizing the transition state to achieve a highly enantioselective process.[7,8] Recently, we reported that a combination of (*S*)-2-(pyrrolidinylmethyl)pyrrolidine (**4a**) and TFA successfully mediated the reaction to afford (*R*)-Wieland–Miescher ketone [(*R*)-**2**] accompanied with 81% ee.[9a] Strikingly, the process was characterized by an inversion of enantioselectivity when compared with a similar reaction mediated by **3** to afford (*S*)-**2**.[3] Also, the reaction using **4a** without TFA afforded (*S*)-**2** with lower enantioselectivity (Scheme 1). These results suggested that an ammonium ion that had been produced from **4a** and TFA played a very important role in stabilizing the transition state via hydrogen bonding between the mediator and substrate. This means that an ammonium counterpart in the chiral amine mediator becomes a powerful hydrogen bonding donor

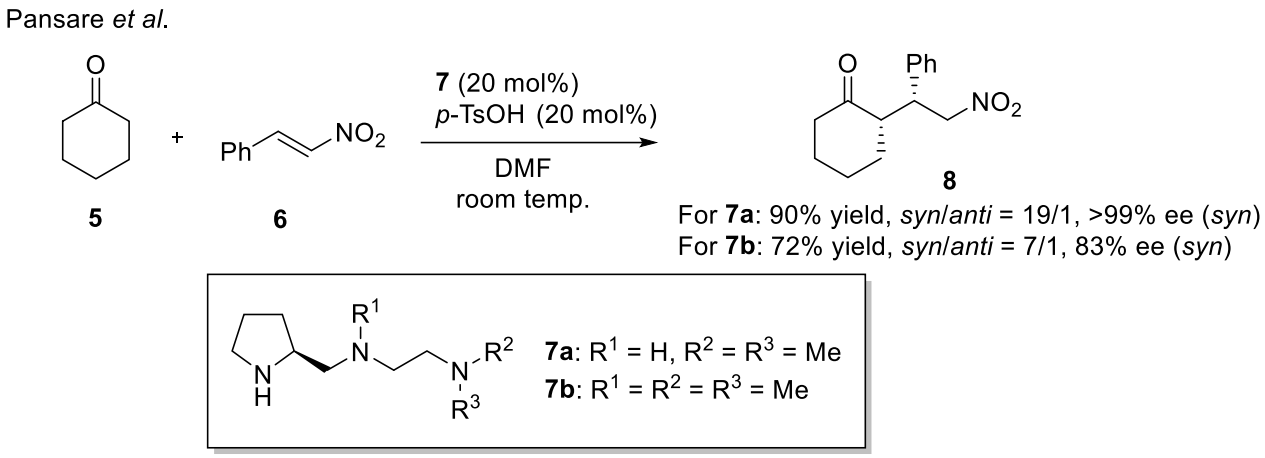
working like a carboxylic acid in an amino acid. We described the details of inverted enantioselectivity using **4a** in our previous report.[9a] Similar results were observed in cases using chiral diamines with a pyrrolidine scaffold bearing a variety of a substituted aminomethyl structures, such as **4b** and **4c**.[9b,9c]



Scheme 1. Asymmetric intramolecular aldol reaction to prepare the Wieland–Miescher ketone (**2**)

In 2006, Pansare reported the enantioselective Michael addition catalyzed by chiral triamines (**7**) under the use of *p*-TsOH to afford **8** accompanied with high *syn*- and enantio-selectivities (Scheme 2).[10] Amine side chain protonation was very important to the selectivity as well as the aldol reaction described above. Thus, they proposed a synclinal transition state (**9**) assembly in which a protonated diamine side chain delivered the nitroalkenes by hydrogen bonding to provide **8**. They also suggested that an internally hydrogen-bonded ethylenediamine unit might explain the enantioselection with **7a** in a noncoordinate solvent (Figure 1).

Inspired by this research, we planned to apply **7** for the aldol reaction of **1**. In addition to known **7a**[11] and **7b**, we designed new triamines (**7c**) and (**7d)** to clarify the effects of terminal amino substituents and conformation of an ethylenediamine unit (Scheme 3). Specifically, **7d** shows a conformationally restricted ethylenediamine motif similar to **10** in Figure 1. Therefore, we could elucidate the effects of conformation in an ethylenediamine unit via comparison to **7a**. Herein, we report the asymmetric intramolecular aldol reaction of **1** mediated by known or new **7** to provide (*R*)-**2**.



Scheme 2. Asymmetric Michael addition catalyzed by chiral triamines (**7**)

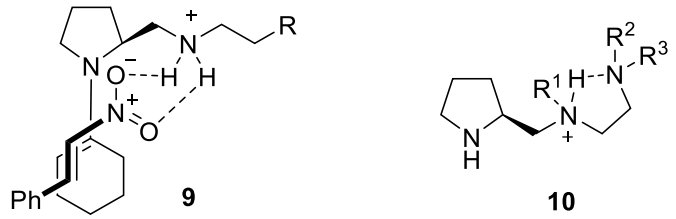
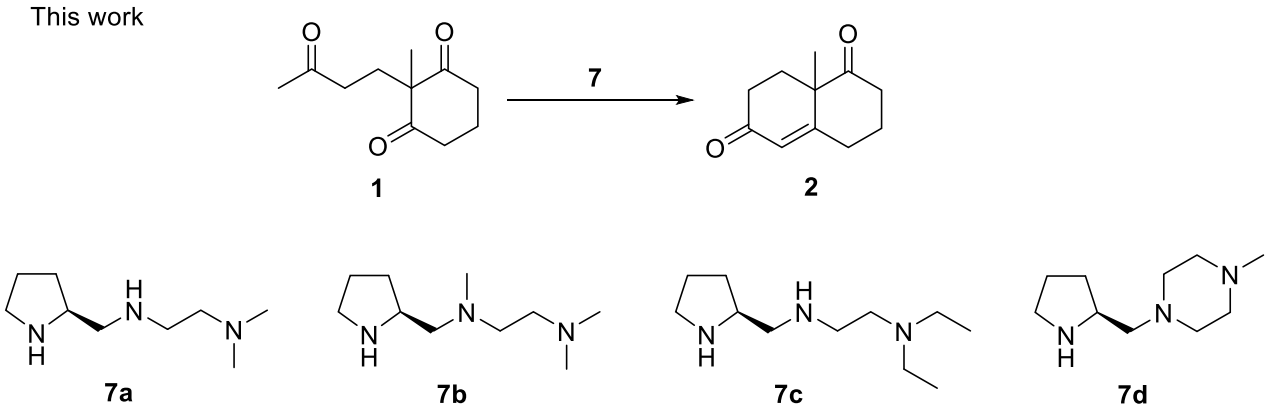
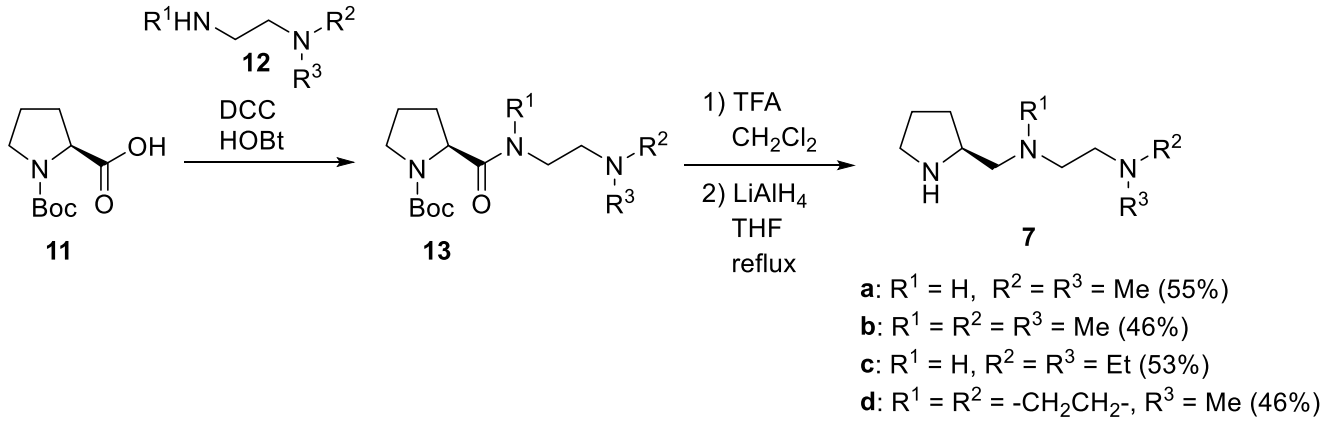


Figure 1. Proposed transition state of asymmetric Michael addition and the possible conformation of ethylenediamine side chain in a protonated **7**



Scheme 3. Asymmetric intramolecular aldol reaction mediated by triamine (**7**)

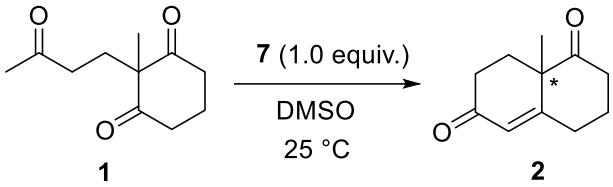
First, triamines (**7**) were prepared from (*S*)-*N*-*tert*-butoxycarbonyl (Boc)-proline (**11**) according to the method reported by Pansare.[10a] Thus, a usual amidation of **11** in the presence of commercially available diamines (**12**) afforded **13**. After deprotection of the Boc moiety, the lithium aluminum hydride (LAH) reduction of amide provided desired **7** in 46%–55% overall yield.



Scheme 4. Preparation of triamines (**7**)

The aldol reaction of **1**[12] mediated by a stoichiometric amount of **7** in dimethyl sulfoxide (DMSO) at 25 °C proceeded to afford **2** in moderate yields and low enantioselectivities. The results were compiled in Table 1. All of **7** except for **7a** provided (*S*)-**2** as a preferred enantiomer. These results showed us that protonation of the amino side chain to form a hydrogen bond might be required.

Table 1. Aldol reaction of **1** mediated by **7**



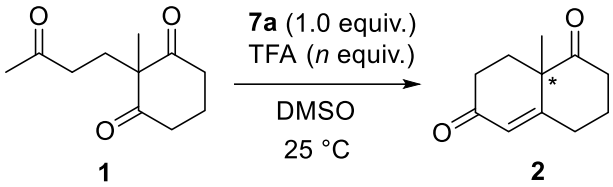
Entry[a]	Amine	Time (h)	Yield[b] (%)	Ee[c] (%)	Config.[d] **2**
1	**7a**	20	47	19	*R*
2	**7b**	48	40	25	*S*
3	**7c**	27	39	8	*S*
4	**7d**	24	60	17	*S*

[a] 100 mg of **1** was used for all reactions.
[b] Isolated yield.
[c] Determined by HPLC equipped with a chiral stationary phase column.
[d] A preferred enantiomer of **2**.

We next ran experiments to understand the effects of an acid in the aldol reaction. Among the triamines **7**, we selected **7a** due to provide (*R*)-**2** shown in Table 1. The aldol reaction using a range of 1.0 to 2.5 equivalent of TFA was performed. The results were shown in Table 2. All of the conditions in the presence of TFA afforded (*R*)-**2** and both the yield and ee were significantly improved. Depending on increasing

TFA, longer reaction time was observed. The reaction in the presence of 1.5 equivalent of TFA afforded (*R*)-**2** in 83% yield accompanied with 67% ee (Entry 2).

Table 2. Aldol reaction of **1** mediated by **7a** in the presence of TFA

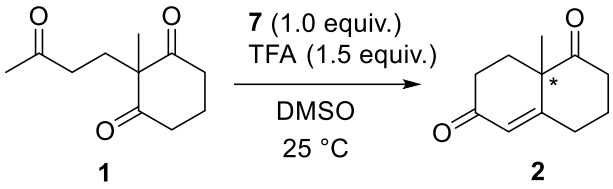


Entry[a]	TFA (equiv.)	Time (h)	Yield[b] (%)	Ee[c] (%)	Config.[d] **2**
1	1.0	12	66	65	*R*
2	1.5	26	83	67	*R*
3	2.0	50	53	59	*R*
4	2.5	125	58	50	*R*

[a] 100 mg of **1** was used for all reactions.
[b] Isolated yield.
[c] Determined by HPLC equipped with a chiral stationary phase column.
[d] A preferred enantiomer of **2**.

We examined the effects of the reaction condition to the other triamines **7**. As shown in Table 3, **7b** and **7d** both bearing a tertiary diamine side chain on a pyrrolidne ring afforded (*S*)-**2** in moderate yields and low enantioselectivities (Entries 2 and 4). Therefore, a tertiary amine motif was hardly suitable for the aldol reaction. Triamine **7d** with a restricted conformation of ethylenediamine unit of **7b**, afforded **2** in almost only racemic forms (Entry 4). However, the effects of conformation were not clear due to the insufficient enatioselectivity of **7b** for comparison (Entry 2). The results showed us that the aldol reaction mediated by **7b** and **7d** might not proceed through a hydrogen-bonded transition state (*vide infra*). Triamine (**7c**) bearing a secondary amino- and diethylamino-side chain on a pyrrolidine ring exhibited almost the same enatioselectivity as **7a** with a moderate yield. The results suggested that the secondary amine structures were required for the aldol reaction, and the possibility that a substituent on the terminal nitrogen atom might not affect to the transition state of the reaction.

Table 3. Aldol reaction of **1** mediated by **7** in the presence of TFA



1 **2**

Entry[a]	Amine	Time (h)	Yield[b] (%)	Ee[c] (%)	Config.[d] **2**
1[e]	**7a**	26	83	67	*R*
2	**7b**	72	45	12	*S*
3	**7c**	24	49	60	*R*
4	**7d**	24	49	6	*S*

[a] 100 mg of **1** was used for all reactions.
[b] Isolated yield.
[c] Determined by HPLC equipped with a chiral stationary phase column.
[d] A preferred enantiomer of **2**.
[e] Same result shown in Table 2.

From our previous report,[9a] the transition states predicted for the aldol reaction are shown in Figure 2. In the presence of TFA, the ethylenediamine moiety in **7** would need to be protonated to generate a corresponding ammonium ion. We devised two transition state models (**14**, **15**) to give (*S*)- and (*R*)-**2** respectively.[6] As similar enantioselectivities were observed in comparison with **7a** and **7c**, we believe that the terminal amino group (-NR^2R^3) is far from the C-C bond forming site. The hydrogen in the ammonium ion could hydrogen-bond to the carbonyl oxygen atom originating from 1,3-diketone functionality. In the cases of using **7b** and **7d**, severe steric repulsions between an alkyl substituent (R^1) on the ammonium moiety and an angular methyl group or a carbonyl functionality are observed. However, the results suggested the possibility that the sterically subtle differences around the tertiary amino-side chain might affect the enantioselectivities in comparison to the fact **7a** aforded (*R*)-**2** with high ee. Therefore, the reactions using **7b** and **7d** might proceed through a non-hydrogen bonded transition state to afford **2** with very low enantioselectivities. In the case of **7a** or **7c** (both R^1 = H), the steric repulsion in **15** is relieved due to the planar carbonyl functionality. Consequently, **15** should be most favored which would give rise to (*R*)-**2** after dehydration (Figure 2).

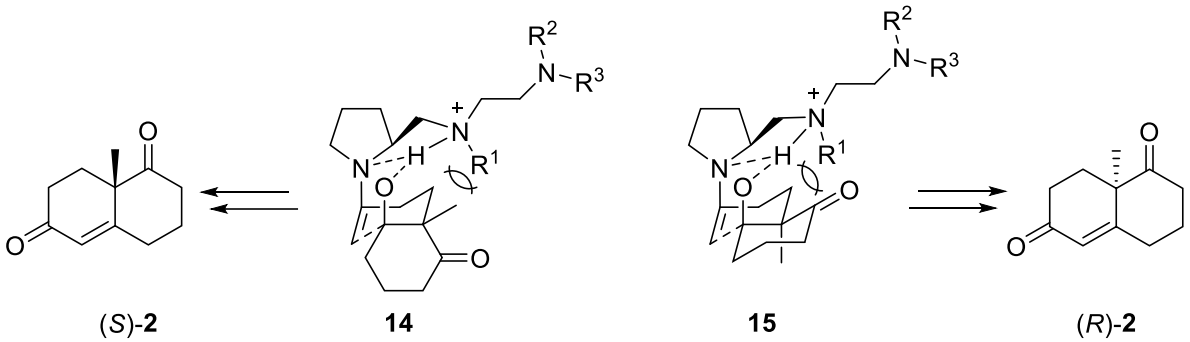


Figure 2. Proposed transition state of the aldol reaction mediated by **7**

In conclusion, we have established a new chiral route to provide (*R*)-Wieland–Miescher ketone [(*R*)-**2**] by using a combination of TFA and known or new chiral triamines (**7**) bearing a pyrrolidine scaffold. Although the intramolecular aldol reaction of trione (**1**) mediated by **7** resulted in **2** with low enantioselectivities, a remarkable increase enantioselectivity with a combination of TFA and **7a** or **7c** was observed. We also found that a secondary amine motif existing in the middle of the side chain was important in determining enantioselectivity. These results may enable the creation of efficient organocatalysts for a wide variety of asymmetric reactions. Further work on the detail of the reaction mechanism and the development of a more efficient mediator for the reactions are currently in progress.

EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer Spectorum One FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL-AX-400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer. All ^{1}H-NMR spectra were reported in ppm downfield of tetramethylsilane (TMS) as an internal standard. All ^{13}C-NMR spectra were reported in ppm relative to $CDCl_3$ (77 ppm) and were obtained with ^{1}H decoupling. MS spectra were recorded on a JEOL-JMS-700V spectrometer. Optical purities were determined using a Hitachi HPLC ELITE LaChrom instrument equipped with a chiral stationary phase column. Optical rotations were measured with a JASCO D-2300 digital polarimeter. All reactions were performed under an argon atmosphere.

Typical procedure of the preparations of triamine 7

To a stirred suspension of Boc-(*S*)-proline (**11**, 6.5 g, 30.0 mmol), 1-hydroxybenzotriazole (HOBt, 4.1 g, 30.6 mmol) and *N*,*N*-dicyclohexylcarbodiimide (DCC, 6.3 g, 30.6 mmol) in anhydrous CH_2Cl_2 (60 mL) was added a solution of a commercially available amine **12a** (3.3 mL, 30.0 mmol) in CH_2Cl_2 (30 mL) at 25 °C. The mixture was stirred at the same temperature for 24 h. After filtering through a Celite pad, the filtrate was washed with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted twice with CH_2Cl_2 (25 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced

pressure. TFA (22.8 mL, 300 mmol) was added to a solution of the residue in anhydrous CH_2Cl_2 (100 mL) at 25 °C, and the solution was stirred for 4 h at the same temperature. After removing the solvent under reduced pressure, the residue was dissolved to CH_2Cl_2, and the mixture was extracted with H_2O (30 mL × 3). The combined aqueous layers were basified with granulated NaOH. The mixture was extracted with CH_2Cl_2 (30 mL × 3) and the combined organic layers were dried (Na_2SO_4). The solvent was removed under reduced pressure. A solution of the residue in anhydrous THF (40 mL) was slowly added to a suspension of LAH (1.7 g, 45 mmol) in THF (70 mL) over 20 min at 0 °C. After stirring for 30 min at 25 °C, the mixture was further heated under reflux for 13 h. The reaction was quenched with H_2O (0.81 mL) and 10% (w/v) aqueous NaOH (18 mL) at 0 °C. The mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was chromatographed ($CHCl_3$/MeOH/NH_4OH = 10/1/0.1) to afford 2.8 g (55%) of **7a** as a colorless oil.

(*S*)-*N*^{1},*N*^{1}-Dimethyl-*N*^{2}-[(pyrrolidin-2-yl)methyl]ethane-1,2-diamine (7a)

$[\alpha]_D^{23}$ +13.2 (*c* 1.00, $CHCl_3$), lit.[9a] +13.0 (*c* 1.00, $CHCl_3$). IR (film) ν cm^{-1} 3390, 2950, 2825, 2779, 1462. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.33-1.36 (1H, m), 1.69-1.79 (2H, m), 1.87-1.89 (1H, m), 2.05 (2H, m), 2.22 (6H, s), 2.40 (2H, t, *J* = 6.3 Hz), 2.55 (1H, dd, *J* = 8.3 Hz, 11.5 Hz), 2.63 (1H, dd, *J* = 4.9 Hz, 11.7 Hz), 2.71 (2H, t, *J* = 6.3 Hz), 2.89-2.94 (2H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 25.5, 29.6, 45.5, 46.3, 47.5, 55.2, 58.3, 59.1. FABMS (*m*/*z*) 172 (M^++H, 100%). HRMS (FAB) calcd. for $C_9H_{22}N_3$ (M^++H) 172.1814. Found 172.1812.

(*S*)-*N*^{1},*N*^{1}-Dimethyl-*N*^{2},*N*^{2}-[(pyrrolidin-2-yl)methyl]methylethane-1,2-diamine (7b)

Yield 46%, colorless oil. $[\alpha]_D^{23}$ +14.3 (*c* 1.02, $CHCl_3$). IR (film) ν cm^{-1} 3387, 2950, 2820, 2778, 1459. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.30-1.35 (1H, m), 1.70-1.89 (3H, m), 2.16-2.20 (1H, m), 2.24 (6H, s), 2.27 (3H, s), 2.29-2.58 (6H, m), 2.82-3.00 (2H, m), 3.21-3.25 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.7, 29.6, 43.0, 45.7, 56.0, 56.1, 57.3, 63.4. FABMS (*m*/*z*) 186 (M^++H, 100%). HRMS (FAB) calcd. for $C_{10}H_{24}N_3$ (M^++H) 186.1970. Found 186.1958.

(*S*)-*N*^{1},*N*^{1}-Diethyl-*N*^{2}-[(pyrrolidin-2-yl)methyl]ethane-1,2-diamine (7c)

Yield 53%, pale yellow oil. $[\alpha]_D^{18}$ +11.1 (*c* 1.00, $CHCl_3$). IR (film) ν cm^{-1} 3368, 2968, 1407. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.01 (6H, t, *J* = 7.2 Hz), 1.30-1.35 (1H, m), 1.67-1.90 (5H. m), 2.50-2.57 (7H, m), 2.61 (1H, dd, *J* = 4.8 Hz, 11.6 Hz), 2.69 (2H, t, *J* = 6.4 Hz), 2.87-2.95 (2H, m), 3.20-3.23 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.6, 25.4, 29.5, 46.2, 46.9, 47.7, 52.5, 55.3, 58.1. FABMS (*m*/*z*) 200 (M^++H, 100%). HRMS (FAB) calcd. for $C_{11}H_{26}N_3$ (M^++H) 200.2127. Found 200.2124.

(*S*)-1-Methyl-4-(pyrrolidin-2-ylmethyl)piperazine (7d)

Yield 46%, pale yellow oil. $[\alpha]_D^{18}$ +16.5 (*c* 1.03, MeOH). IR (film) ν cm^{-1} 3386, 2944, 2808, 1411. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.27-1.36 (1H, m), 1.69-1.76 (2H, m), 1.83-1.89 (1H, m), 2.06 (1H, brs), 2.28 (3H, s), 2.28-2.30 (3H, m), 2.31-2.36 (2H, m), 2.44-2.58 (6H, brm), 2.81-2.88 (1H, m), 2.96-3.01 (1H, m),

3.23-3.28 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.9, 29.9, 46.0, 55.1, 55.2, 63.9. EIMS (*m*/*z*) 183 (M^+), 70 (100%). HRMS calcd. for $C_{10}H_{21}N_3$ 183.1735. Found 180.1726.

Typical procedure of triamine-mediated aldol reaction of 1.

To a stirred solution of **1** (100 mg, 0.51 mmol) in DMSO (1.0 mL) were added a solution **7a** (87 mg, 0.51 mmol) and TFA (59 μL, 0.77 mmol) in DMSO (0.5 mL) at 25 °C. The mixture was stirred at the same temperature for 26 h and was diluted with AcOEt. The mixture was washed with saturated aqueous $NaHCO_3$ and brine, respectively. After drying (Na_2SO_4), the solvent was removed under reduced pressure and the residue was chromatographed (AcOEt/CH_2Cl_2/hexane = 1/1/4) to afford 75 mg (83%) of (*R*)-**2** as colorless crystals. The spectroscopic data for **2** agreed with that reported in refs. 9. The enantiomeric excess of **2** was determined by HPLC equipped with a chiral stationary phase column (Chiralcel OD) to be 67% ee. HPLC conditions: Chiralcel OD, 2-propanol/hexane = 1/10 (v/v), flow rate 1.0 mL/min, detected at 254 nm, t_R = 14.6 min for (*S*)-**2**, 15.7 min for (*R*)-**2**.

(*R*)-**2**: $[\alpha]_D^{25}$ –66.0 (*c* 1.00, benzene, 67% ee), lit.[9b] $[\alpha]_D^{25}$ –100 (*c* 1.00, benzene, > 99% ee).

ACKNOWLEDGEMENTS

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