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A NEW CHIRAL SYNTHESIS OF WIELAND-MIESCHER KETONE CATALYZED BY A COMBINATION OF (*S*)-*N*-BENZYL-*N*-(2-PYRROLIDINYLMETHYL)AMINE DERIVATIVE AND BRØNSTED ACID

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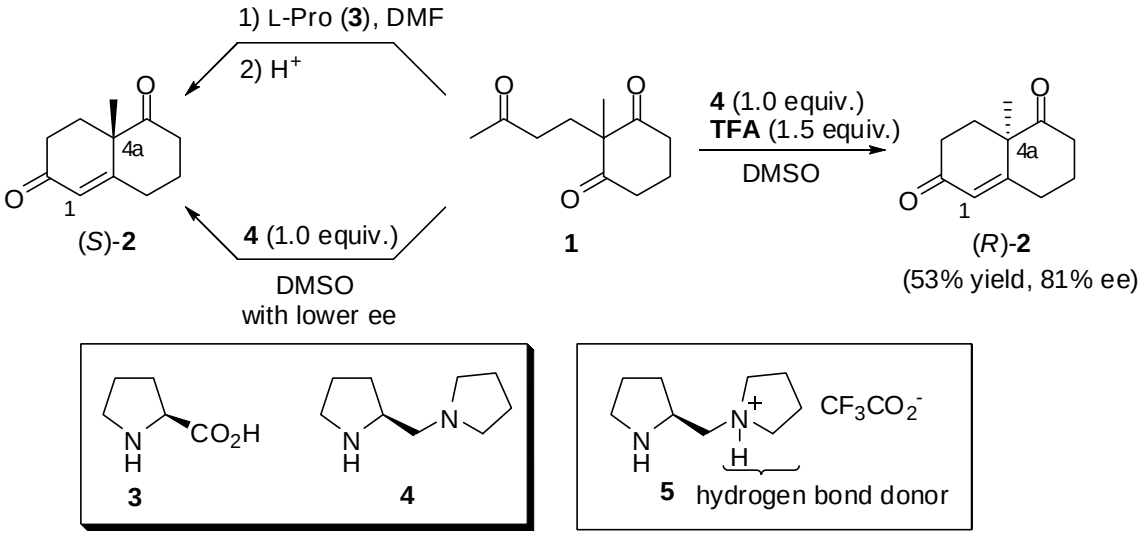
This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

Abstract – New or known *N*-benzyl-*N*-(2-pyrrolidinylmethyl)amine derivatives bearing a variety of substituents on the aromatic ring were easily prepared from *N*-Boc-proline or *N*-Boc-prolinol. The enantioselectivity of the intramolecular asymmetric aldol reaction mediated by a combination of the amine derivative and Brønsted acid to prepare Wieland-Miescher ketone was examined in detail. During the examination, remarkable substitutional effects on the aromatic ring were observed. Development of a catalytic version of the reaction was successfully achieved by the use of *N*-[(9-anthracenyl)methyl]-*N*-(2-pyrrolidinyl-methyl)amine in the presence of dichloroacetic acid.

Wieland-Miescher ketone (**2**), which was prepared by L-proline (L-Pro)-mediated asymmetric intramolecular aldol reaction of the trione (**1**), has been a highly useful synthon in total syntheses of a variety of natural products.[1,2] This asymmetric aldol reaction has become known as the Hajos-Parrish-Eder-Sauer-Wiechert (HPESW) reaction,[3] and has been widely recognized to involve an enamine-based mechanism. In the reaction, a hydrogen bond between an oxygen atom on the cyclohaxane and a carboxylic acid in L-Pro has played a very important role to stabilize a transition state to achieve a highly enantioselective process.[4-6] Recently, we have reported that a combination of (*S*)-2-(pyrrolidinylmethyl)pyrrolidine (**4**) and TFA successfully mediated the HPESW reaction to afford (*R*)-Wieland-Miescher ketone [(*R*)-**2**] accompanied with 81% ee.[7] Strikingly, the process was

characterized by an inversion of enantioselectivity when compared with the similar reaction mediated by L-Pro (**3**). Also, the reaction using **4** without a Brønsted acid afforded (*S*)-**2** with lower enantioselectivity (Scheme 1). These results suggested us that an ammonium moiety in **5** which was produced from **4** and TFA has played a very important role to stabilize a transition state by hydrogen bonds between a mediator and a 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.



Scheme 1

In the area of organocatalysis,[8] (*S*)-2-(pyrrolidinylmethyl)pyrrolidine (**4**) has been employed as a new catalyst to achieve highly efficient asymmetric reactions, including intra- and intermolecular aldol reaction.[9] Amine-Brønsted acid catalysis has also been utilized in asymmetric Diels-Alder reaction and 1,4-addition reaction to construct new chiral centers.[10, 11] However, to our knowledge, there have been few attempts to use amine catalysts in the intramolecular aldol reaction to construct Wieland-Miescher ketone,[12] so our goal was to use some known or new chiral amines based on a structure of L-Pro to synthesize **2** more efficiently. Specifically, we attempted to use known *N*-benzyl amines (**6**), which were easily prepared from L-Pro, containing a secondary and/or a tertiary amine for the HPESW reaction (Figure 1). We report here the new reaction conditions mediated by a combination of Brønsted acid and several known or new *N*-benzylamines.

N-Benzyl-*N*-(2-pyrrolidinylmethyl)amine derivatives (**6**) were prepared from *N*-Boc-L-Pro (**7**). Thus, amide (**8**) was obtained by DCC-mediated coupling reaction with **7** and a corresponding *N*-benzylamine and a followed deprotection of Boc-moiety in the presence of TFA. Lithium aluminium hydride (LAH) reduction of amide group afforded **6a**[13] and **6b**[14] respectively. *N*-Methylpyrrolidine derivative (**6c**)[15] or

(**6d**)[16] was easily prepared from **8** by a simple reductive alkylation and a followed LAH reduction (Scheme 2).

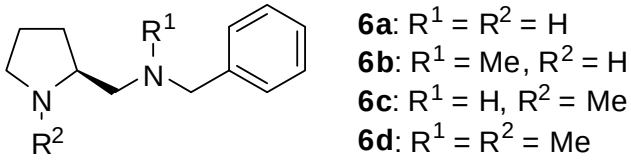
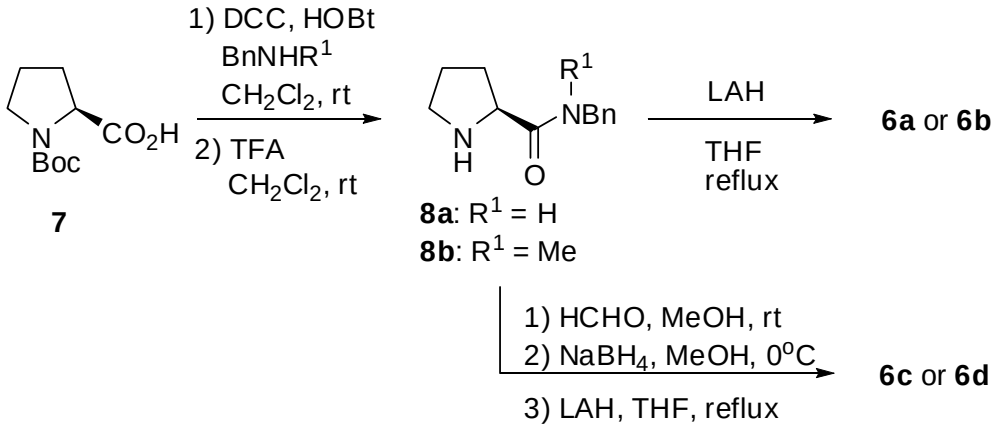


Figure 1

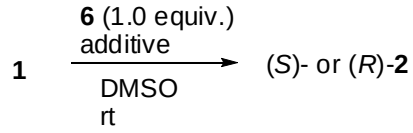


Scheme 2

We first screened the amines (**6**) on the aldol reaction of trione (**1**). All of the reactions were carried out under the same conditions in the presence of a stoichiometric amount of **6** with or without 1.5 equiv. of TFA in DMSO at rt.[17] The results were compiled in Table 1. First of all, the aldol reaction mediated by **6a** afforded (*R*)-**2** in 47% yield accompanied with 69% ee (entry 2). However, the reaction using **6b** bearing a tertiary amino moiety on the side chain afforded (*R*)-**2** in 50% yield accompanied with lower ee (entry 4). The reaction using *N*-methylpyrrolidine derivative (**6c**) or (**6d**) hardly proceeded to afford **2**. From these results, a secondary amine on a pyrrolidine ring was required to achieve the effective reaction. All of the reactions, except for using **6d**, without TFA afforded (*S*)-**2** with moderate or low ee (Table 1). Since the highest ee value was observed in entry 2, **6a** was selected for continued optimization.

We next examined the effects of substituents on the aromatic ring in **6a**. Thus, *N*-benzylamine derivatives (**12**) bearing a variety of substituents shown in Scheme 3 were prepared via a simple reductive alkylation of a known amine **10**, which was easily synthesized from *N*-Boc-prolinol (**9**),[18] with a corresponding benzaldehyde derivative (**11**)[19] in 35-72% yield from **10** (Scheme 3).

Table 1



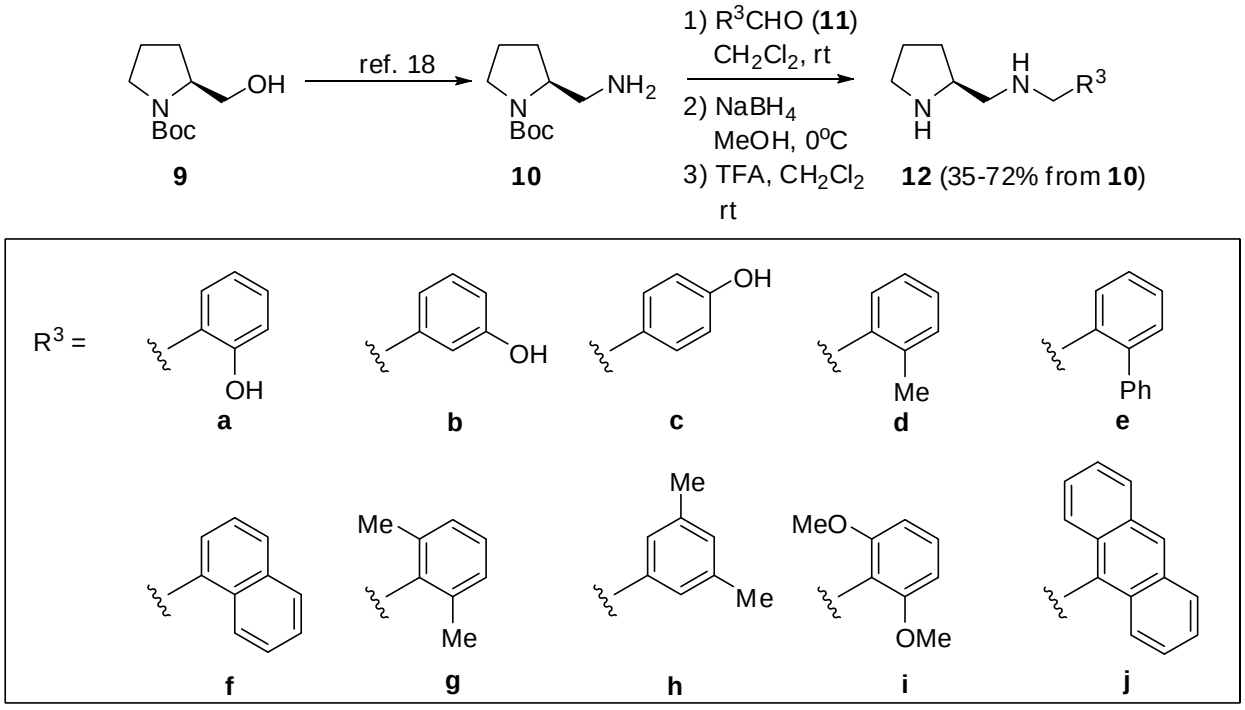
Entry	Amine	Additive (equiv.)	Time (h)	Yield[a, b] (%)	Ee[c] (%)	Config.[d]
1	**6a**	none	8	42	44	*S*
2	**6a**	TFA (1.5)	11	47	69	*R*
3	**6b**	none	9	44	13	*S*
4	**6b**	TFA (1.5)	20	50	21	*R*
5	**6c**	none	48	7 (41)	4	*S*
6	**6c**	TFA (1.5)	48	32 (16)	49	*R*
7	**6d**	none	48	0 (73)	-	-
8	**6d**	TFA (1.5)	48	0 (73)	-	-

[a] Isolated yield.

[b] Yields in parentheses showed the recovery of starting **1**.

[c] Determined by HPLC equipped with a chiral stationary phase column.

[d] Absolute configuration of a major enantiomer of **2**.

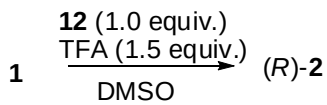


Scheme 3

Next, the aldol reactions of **1** using a stoichiometric amount of **12** in the presence of 1.5 equiv. of TFA to yield (*R*)-**2** were carried out. The results were compiled in Table 2. All of the reactions mediated by **12**

afforded (*R*)-**2** in moderate yield. Amines (**12a**-**12c**) bearing a hydroxyl group on a aromatic ring at *o*-, *m*- and *p*-position, respectively, slightly improved the yield of **2**, but no remarkable effects on the enatioselectivity were observed. Mono alkyl- or aryl-substituted benzyl derivative, such as **12d** and **12e**, and naphthyl derivative **12f** afforded slightly higher ee than the case using **6a**. These results suggested us that the steric hindrance around the aminomethyl moiety improved the enantioselectivity. However, asymmetrical substituted benzene ring in **12d**-**12f** would not be very effective because the substituent might be far away from C-C bond forming site due to the easy rotation of a single bond. From this aspect, we tried to use the symmetrically substituted benzyl derivatives such as **12g**-**12j**. Among those amines, **12g** and **12j** were very effective mediators because of the high ee value over 80%. In comparison with entries 8 and 9, 2,6-dimethyl-substituted benzyl amine (**12g**) was more effective than 3,5-dimethyl-substituted one (**12h**). These results suggested that steric hindrance near the amine moiety obviously affected the enantioselectivity. However, the reaction mediated by **12i** bearing dimethoxy substituents at 2,6-positions required the longer reaction time and hardly affected to the ee value. From these aspects, **12j** was selected as the mediator for continued optimization (Table 2).

Table 2



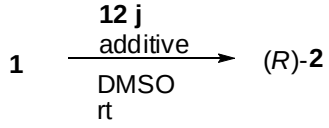
Entry	Amine	Time (h)	Yield[a] (%)	Ee[b] (%)
1[c]	**6a**	11	47	69
2	**12a**	10	60	69
3	**12b**	8	56	69
4	**12c**	9	61	63
5	**12d**	8	53	75
6	**12e**	9	64	72
7	**12f**	7	63	74
8	**12g**	8	53	82
9	**12h**	9	61	61
10	**12i**	36	51	72
11	**12j**	9	51	86

[a] Isolated yield.
[b] Determined by HPLC equipped with a chiral stationary phase column.
[c] Same result in Table 1.

Finally, we tried to extend this process to be a catalytic version. The reaction using 0.3 equiv of **12j** in the presence of 0.45 equiv of TFA in DMSO at rt (entry 2) did not complete even after 48h and afforded

(*R*)-**2** with lower yield and lower ee than the stoichiometric reaction (entry 1). Since the catalytic reaction using **12j** in the presence of TFA was not successful, the effect of an additive was next probed. Thus, the reaction using a stoichiometric amount of **12j** in the presence dichloroacetic acid (DCA) improved the yield of (*R*)-**2** without serious loss of the ee value (entry 3). Although the catalytic reaction shown in entry 4 required longer reaction time, the result was almost same as the stoichiometric reaction (entry 3). Therefore, we have established a catalytic process using a chiral *N*-benzylamine to prepare (*R*)-**2**.

Table 3



Entry	**12j** (equiv.)	Additive (equiv.)	Time (h)	Yield[a, b] (%)	Ee[c] (%)
1[d]	1.0	TFA (1.5)	9	51	86
2	0.3	TFA (0.45)	48	20 (42)	63
3	1.0	DCA[e] (1.5)	7	75	84
4	0.3	DCA (0.45)	20	68	84

[a] Isolated yield.
[b] The recovery of starting **1** was shown in parentheses.
[c] Determined by HPLC equipped with a chiral stationary phase column.
[d] Same result in Table 2.
[e] Dichloroacetic acid.

In conclusion, we have established a procedure to prepare *N*-benzyl-*N*-(2-pyrrolidinylmethyl)amine derivatives bearing a variety of substituents on the aromatic ring. We also have established a new chiral route to provide (*R*)-Wieland-Miescher ketone [(*R*)-**2**] by using the combination of synthetic chiral amine and Brønsted acid. Furthermore, under optimized conditions, we have achieved the reaction to be a catalytic process. These results may enable the creation of efficient organocatalysts for a wide variety of asymmetric reactions. Further work on a detail of the reaction mechanism and the development of a more efficient catalyst for the reactions is currently in progress.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a JASCO-FT-IR-5000 spectrometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a JEOL-AX-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer and calibrated using trimethysilane as the internal standard. Mass spectra were recorded on a

JEOL-DX-303 or a JEOL-JMS-MS700 spectrometer. Elemental analysis was recorded on a Perkin Elmer CHN-2400 II. Enantiomeric excesses were determined on a Waters-HPLC 600 instrument equipped with a chiral stationary phase column. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter.

Typical procedure of preparation of 6a and 6b

To a stirred solution of *N*-Boc-L-Proline (**7**) 5.0 g (23.3 mmol) in CH_2Cl_2 (50 mL) were added DCC 4.9 g (23.8 mmol) and 1-hydroxybenzotriazole (HOBt) 3.2 g (23.8 mmol) at rt. After stirring at the same temperature for 30 min, *N*-benzylamine 2.5 g (23.3 mmol) was added and the mixture was further stirred at rt for 24 h. The mixture was filtered through a Celite pad and the filtrate was washed with saturated aqueous $NaHCO_3$ and brine. After drying (Na_2SO_4), the solvent was removed under reduced pressure to afford crude products. To the stirred solution of the crude products in CH_2Cl_2 (70 mL) was added TFA 17.7 mL (233 mmol) at rt and the mixture was stirred at the same temperature for 4 h. The mixture was extracted with H_2O. The combined aqueous layer was basified by 10% aqueous NaOH and was extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford crude **8a**. To a stirred suspension of LAH 1.3 g (35 mmol) in THF (50 mL) was added a solution of crude **8a** in THF (20 mL) at 0 ^oC. The mixture was further heated under reflux for 16 h. 10 % aqueous NaOH (14 mL) was carefully added to the mixture at 0 ^oC and the mixture was stirred at rt for 2 h. The mixture was filtered through a Celite pad and the filtrate was evaporated under reduced pressure. The residue was chromatographed ($CHCl_3$/MeOH/NH_4OH =15/1/0.1) to afford **6a** 2.8 g (63% from **7**) as yellow oil.

(*S*)-*N*-Benzyl-*N*-(2-pyrrolidinylmethyl)amine (**6a**)

$[\alpha]_D^{20}$ +14.9 (*c* 1.01, MeOH), lit.,[13] $[\alpha]_D^{20}$ +15.6 (*c* 1.01, EtOH); IR (film) ν cm^{-1} 3301, 2957, 2871, 1454; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32-1.35 (1H, m), 1.62-1.80 (4H, m), 1.85-1.91 (1H, m), 2.53 (1H, dd, *J* = 8.8 Hz, 11.4 Hz), 2.63 (1H, dd, *J* = 4.8 Hz, 11.8 Hz), 2.87-2.92 (2H, m), 3.24 (1H, ddd, *J* = 4.8 Hz, 7.2 Hz, 15.5 Hz), 3.81 (2H, s), 7.23-7.32 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 25.6, 29.6, 46.4, 54.1, 54.6, 58.2, 126.7, 128.0, 128.2, 140.5; EIMS (*m/z*) 190 (M^+), 70 (100%); HRMS calcd. for $C_{12}H_{18}N_2$ 190.1470, found 190.1450.

(*S*)-*N*-Benzyl-*N*-methyl(2-pyrrolidinylmethyl)amine (**6b**)

Yield 65% (yellow oil); $[\alpha]_D^{28}$ +8.5 (*c* 1.01, MeOH); IR (film) ν cm^{-1} 3422, 2956, 2788, 1415; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.29-1.36 (1H, m), 1.65-1.72 (2H, m), 1.83-1.91 (2H, m), 2.23 (3H, s), 2.26 (1H, dd, *J* = 4.8 Hz, 12.4 Hz), 2.37 (1H, dd, *J* = 8.8 Hz, 12.4 Hz), 2.79-2.91 (2H, m), 3.25-3.32 (1H, m), 3.45 (1H, d, *J* = 13.2 Hz), 3.58 (1H, d, *J* = 13.2 Hz), 7.23-7.32 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.7, 29.5, 42.5, 45.7, 55.8, 62.6, 62.7, 126.8, 128.1, 128.9, 139.2; EIMS (*m/z*) 204 (M^+), 70 (100%); HRMS calcd. for $C_{13}H_{20}N_2$ 204.1626, found 204.1633.

Typical procedure of preparation of 6c and 6d

To a stirred solution of crude **8a** described above in MeOH (70 mL) was added 37% formalin 2.5 mL (30.3 mmol) at rt. After stirring the mixture at the same temperature for 9 h, $NaBH_4$ 444 mg (11.7 mmol) was added as a small portion over 10 min at 0 ^oC and the mixture was further stirred at the same temperature for 12 h. After adding saturated aqueous NH_4Cl, MeOH was removed under reduced pressure. The residue was dissolved to AcOEt and the mixture was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was dissolved to THF (20 mL) and the solution was added to a stirred suspension of LAH 1.3 g (35 mmol) in THF (50 mL) at 0 ^oC. The mixture was further heated under reflux for 16 h. After cooling, 10% aqueous NaOH was carefully added at 0 ^oC and the mixture was filtered through a Celite pad. The filtrate was evaporated under reduced pressure. The residue was chromatographed ($CHCl_3$/MeOH/NH_4OH = 15/1/0.1) to afford **6c** 2.3 g (48% from **7**) as pale yellow oil.

(*S*)-*N*-Benzyl-*N*-methyl(2-pyrrolidinylmethyl)amine (**6c**)

$[\alpha]_D^{29}$ -57.6 (*c* 1.01, MeOH); IR (film) ν cm^{-1} 3026, 2942, 2781, 1453; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.63-1.78 (1H, m), 1.88-1.94 (1H, m), 2.14-2.21 (1H, m), 2.30 (3H, s), 2.58 (1H, dd, *J* = 6.4 Hz, 11.6 Hz), 2.74 (1H, dd, *J* = 4.0 Hz, 11.6 Hz), 3.01-3.05 (1H, m), 3.79 (1H, d, *J* = 13.6 Hz), 3.84 (1H, d, *J* = 13.6 Hz), 7.23-7.33 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.6, 29.3, 41.1, 52.1, 54.3, 57.5, 65.4, 126.7, 128.0, 128.2, 140.6; EIMS (*m/z*) 204 (M^+), 84 (100%); HRMS calcd. for $C_{13}H_{20}N_2$ 204.1626, found 204.1587.

(*S*)-*N*-Benzyl-*N*, *N'*-dimethyl(2-pyrrolidinylmethyl)amine (**6d**)

Yield: 51% (yellow oil); $[\alpha]_D^{28}$ -87.7 (*c* 1.00, MeOH), lit.,[16] $[\alpha]_D$ -83 (*c* 1.0, EtOH); IR (film) ν cm^{-1} 2944, 2776, 1452; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.52-1.60 (1H, m), 1.66-1.77 (2H, m), 1.96-2.03 (1H, m), 2.12-2.17 (1H, m), 2.20 (3H, s), 2.29-2.35 (2H, m), 2.38 (3H, s), 2.51-2.57 (1H, m), 3.01-3.05 (1H, m), 3.43 (1H, d, *J* = 13.2 Hz), 3.56 (1H, d, *J* = 13.2 Hz), 7.23-7.32 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.4, 30.6, 41.3, 42.9, 57.6, 62.3, 63.1, 63.8, 126.8, 128.1, 128.9, 139.1; EIMS (*m/z*) 218 (M^+), 84 (100%); HRMS calcd. for $C_{14}H_{22}N_2$ 218.1783, found 218.1786.

Typical procedure of preparation of 12

To a stirred solution of **10**[18] 5.5 g, (27.5 mmol) in CH_2Cl_2 (60 mL) was added salicylaldehyde 3.35 g (27.5 mmol) at rt. After stirring at the same temperature, the solvent was removed under reduced pressure. The residue was dissolved to MeOH (60 mL) and $NaBH_4$ 469 mg (12.4 mmol) was added to the mixture as a small portion over 10 min at 0 ^oC. After stirring at 0 ^oC for 1.5 h, the solvent was removed under reduced pressure. The residue was dissolved to AcOEt and the mixture was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was dissolved to CH_2Cl_2 (100 mL) and TFA 30 mL (275 mmol) was added

to the mixture at rt. After stirring at the same temperature for 2 h, the mixture was extracted with H_2O. The combined aqueous layer was basified by 10% aqueous NaOH and the mixture was extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was chromatographed ($CHCl_3$/MeOH/NH_4OH =15/1/0.1) to afford **12a** 3.6 g (63% from **10**) as colorless oil.

(*S*)-*N*-(2-Hydroxybenzyl)-*N*-(2-pyrrolidinylmethyl)amine (**12a**)

$[\alpha]_D^{26}$ +14.3 (*c* 1.01, MeOH); IR (KBr) ν cm^{-1} 3394, 2958, 1454; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.34-1.40 (1H, m), 1.66-1.92 (3H, m), 2.50 (1H, dd, *J* = 8.4 Hz, 11.8 Hz), 2.65 (1H, dd, *J* = 4.4 Hz, 11.6 Hz), 2.84-2.97 (2H, m), 3.29-3.35 (1H, m), 3.94 (1H, d, *J* = 14 Hz), 4.06 (1H, d, *J* = 14 Hz), 4.88 (3H, brm), 6.76 (1H, dt, *J* = 1.2 Hz, 7.2 Hz), 6.82 (1H, dd, *J* = 1.2 Hz, 8.0 Hz), 6.98 (1H, d, *J* = 7.2 Hz), 7.14 (1H, dt, *J* = 1.4 Hz, 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.0, 29.7, 46.6, 52.7, 53.8, 57.5, 116.2, 118.8, 122.6, 128.2, 128.5, 158.3; EIMS (*m/z*) 206 (M^+), 70 (100%); HRMS calcd. for $C_{12}H_{18}N_2O$ 206.1419, found 206.1423.

(*S*)-*N*-(3-Hydroxybenzyl)-*N*-(2-pyrrolidinylmethyl)amine (**12b**)

Yield 50% (yellow solid); $[\alpha]_D^{24}$ +14.0 (*c* 1.00, MeOH); IR (KBr) ν cm^{-1} 3324, 3238, 2967, 1426; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.31-1.40 (1H, m), 1.69-1.96 (3H, m), 2.57 (1H, dd, *J* = 8.8 Hz, 12.0 Hz), 2.72 (1H, dd, *J* = 4.4 Hz, 11.6 Hz), 2.87-2.98 (2H, m), 3.26-3.33 (1H, m), 3.64 (1H, d, *J* = 13.2 Hz), 3.70 (1H, d, *J* = 13.2 Hz), 4.78 (3H, brs), 6.65-6.70 (2H, m), 6.77 (1H, d, *J* = 2.0 Hz), 7.10 (1H t, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 2.53, 29.5, 45.8, 53.5, 53.9, 57.9, 114.9, 115.4, 119.0, 129.5, 141.1, 158.1; EIMS (*m/z*) 206 (M^+), 70 (100%); HRMS calcd. for $C_{12}H_{18}N_2O$ 206.1419, found 206.1399.

(*S*)-*N*-(4-Hydroxybenzyl)-*N*-(2-pyrrolidinylmethyl)amine (**12c**)

Yield: 35% (yellow oil); $[\alpha]_D^{25}$ +12.7 (*c* 1.01, MeOH); IR (film) ν cm^{-1} 3289, 2966, 1456; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.37-1.43 (1H, m), 1.89-1.96 (3H, m), 2.59 (1H, dd, *J* = 8.8 Hz, 11.6 Hz), 2.72 (1H, dd, *J* = 4.4 Hz, 12.0 Hz), 2.92-2.99 (2H, m), 3.26-3.33 (1H, m) 3.67 (2H ,s), 4.75 (3H, brs),6.62 (2H, d, *J* = 8.2 Hz), 7.01 (2H, d, *J* = 8.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 25.4, 29.6, 45.9, 53.3, 53.4, 57.8, 115.7, 129.5, 129.8, 156.8; EIMS (*m/z*) 206 (M^+), 70 (100%); HRMS calcd. for $C_{12}H_{18}N_2O$ 206.1419, found 206.1426.

(*S*)-*N*-(2-Methylbenzyl)-*N*-(2-pyrrolidinylmethyl)amine (**12d**)

Yield: 52% (yellow oil); $[\alpha]_D^{21}$ +14.9 (*c* 1.01, MeOH); IR (film) ν cm^{-1} 3300, 2956, 2870, 1404; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32-1.40 (1H, m), 1.68-1.76 (4H, m), 1.83-1.91 (1H, m), 2.35 (3H, s), 2.58 (1H, dd, *J* = 8.4 Hz, 11.2 Hz), 2.68 (1H, dd, *J* = 4.4 Hz, 11.2 Hz), 2.87-2.94 (2H, m), 3.26 (1H, ddd, *J* = 4.8 Hz, 7.4 Hz, 15.1Hz), 3.78 (2H, s), 7.14-7.30 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.9, 25.6, 29.5, 46.4, 51.7, 54.8, 58.3, 125.7, 126.7, 128.2, 130.1, 136.2, 138.4; EIMS (*m/z*) 204 (M^+), 70 (100%); HRMS calcd. for $C_{13}H_{20}N_2$ 204.1626, found 204.1630.

(*S*)-*N*-(2-Phenylbenzyl)-*N*-(2-pyrrolidinylmethyl)amine (**12e**)

Yield: 53% (yellow oil); $[\alpha]_D^{22}$ +6.4 (*c* 1.00, MeOH); IR (film) ν cm^{-1} 3299, 2958, 2870, 1403; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.20-1.29 (1H, m), 1.62-1.83 (3H, m), 2.16 (2H, brs), 2.42 (1H, dd, *J* = 8.4 Hz, 11.6 Hz), 2.51 (1H, dd, *J* = 4.8 Hz, 11.8 Hz), 2.81-2.91 (2H, m), 3.13 (1H, ddd, *J* = 4.8 Hz, 7.2 Hz, 15.1 Hz), 3.72 (1H, d, *J* = 13.2 Hz), 3.77 (1H, d, *J* = 13.2 Hz), 7.25-7.34 (3H, m), 7.35-7.47 (6H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 25.3, 29.3, 46.2, 51.5, 53.9, 58.2, 126.8, 127.0, 127.4, 128.1, 129.0, 130.0, 137.6, 141.2, 141.7; EIMS (*m/z*) 266 (M^+), 70 (100%); HRMS calcd. for $C_{18}H_{22}N_2$ 266.1783, found 266.1787.

(*S*)-*N*-(1-Naphthylmethyl)-*N*-(2-pyrrolidinylmethyl)amine (**12f**)

Yield: 63% (orange color oil); $[\alpha]_D^{22}$ +8.8 (*c* 1.00, MeOH); IR (film) ν cm^{-1} 3297, 2956, 1400; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.31-1.40 (1H, m), 1.63-1.76 (4H, m), 1.83-1.92 (1H, m), 2.65 (1H, dd, *J* = 8.4 Hz, 11.2 Hz), 2.76 (1H, dd, *J* = 4.8 Hz, 11.6 Hz), 2.84-2.94 (2H, m), 3.23-3.30 (1H, m), 4.25 (2H, s), 7.40-7.55 (4H, m), 7.76 (1H, d, *J* = 8.4 Hz), 7.85 (1H, d, *J* = 8.0 Hz), 8.14 (1H, d, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 25.5, 29.6, 46.3, 51.7, 54.9, 58.3, 123.7, 125.3, 125.5, 126.0, 127.6, 128.6, 131.7, 133.8, 136.0; EIMS (*m/z*) 240 (M^+), 70 (100%); HRMS calcd. for $C_{16}H_{20}N_2$ 240.1626, found 240.1629.

(*S*)-*N*-(2,6-Dimethylbenzyl)-*N*-(2-pyrrolidinylmethyl)amine (**12g**)

Yield: 71% (pale yellow oil); $[\alpha]_D^{27}$ +16.8 (*c* 1.01, MeOH); IR (film) ν cm^{-1} 3069, 2959, 2923, 2853, 1411; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.30-1.39 (1H, m), 1.65-1.79 (4H, m), 1.83-1.91 (1H, m), 2.40 (6H, s), 2.62 (1H, dd, *J* = 8.2 Hz, 11.4 Hz), 2.70 (1H, dd, *J* = 4.8 Hz, 11.6 Hz), 2.82-2.95 (2H, m), 3.19-3.25 (1H, m), 3.76 (1H, d, *J* = 12.1 Hz), 3.80 (1H, d, *J* = 11.6 Hz), 6.99-7.07 (3H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.5, 25.4, 29.5, 46.3, 47.9, 55.2, 58.2, 126.8, 128.1, 136.7, 136.9; EIMS (*m/z*) 218 (M^+), 70 (100%); HRMS calcd. for $C_{14}H_{22}N_2$ 218.1783, found 218.1781.

(*S*)-*N*-(3,5-Dimethylbenzyl)-*N*-(2-pyrrolidinylmethyl)amine (**12h**)

Yield: 60% (pale yellow oil); $[\alpha]_D^{28}$ +10.0 (*c* 1.00, MeOH); IR (film) ν cm^{-1} 3418, 2920, 1408; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.28-1.37 (1H, m), 1.64-1.76 (4H, m), 1.83-1.91 (1H, m), 2.30 (6H, s), 2.53 (1H, dd, *J* = 8.8 Hz, 11.6 Hz), 2.63 (1H, dd, *J* = 4.4 Hz, 11.4 Hz), 2.86-2.93 (2H, m), 3.20-3.27 (1H, m), 3.72 (2H, s), 6.88 (1H, s), 6.93 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.2, 25.6, 29.6, 46.4, 54.1, 54.7, 58.2, 125.9, 128.4, 137.8, 140.3; EIMS (*m/z*) 218 (M^+), 70 (100%); HRMS calcd. for $C_{14}H_{22}N_2$ 218.1783, found 218.1786.

(*S*)-*N*-(2,6-Dimethoxylbenzyl)-*N*-(2-pyrrolidinylmethyl)amine (**12i**)

Yield: 53% (yellow oil); $[\alpha]_D^{19}$ +6.6 (*c* 1.00, MeOH); IR (film) ν cm^{-1} 3402, 2938, 2837, 1475; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.31-1.38 (1H, m), 1.71-1.78 (2H, m), 1.84-1.91 (1H, m), 2.52 (1H, dd, *J* = 8.4 Hz, 12.4 Hz), 2.64 (1H, dd, *J* = 5.6 Hz, 12.0 Hz), 2.92 (2H, t, *J* = 6.8 Hz), 3.03 (2H, brs), 3.28-3.33 (1H, m), 3.82 (6H, s), 3.89 (2H, s), 6.54 (2H, d, *J* = 8.8 Hz), 7.18 (1H, t, *J* = 8.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$)

δ 25.1, 29.3, 41.3, 45.9, 52.9, 55.6, 58.2, 103.5, 115.8, 128.3, 158.6; EIMS (*m/z*) 250 (M^+), 151 (100%); HRMS calcd. for $C_{14}H_{22}N_2O_2$ 250.1681, found 250.1683.

(*S*)-*N*-(9-Anthracenylmethyl)-*N*-(2-pyrrolidinylmethyl)amine (**12j**)

Yield: 72% (yellow oil); $[\alpha]_D^{22}$ +19.0 (*c* 1.00, MeOH); IR (film) ν cm^{-1} 3302, 2954, 2869, 1445, 1405; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.33-1.42 (1H, m), 1.61-1.74 (2H, m), 1.81-1.89 (1H, m), 2.79-2.97 (4H, m), 3.28-3.35 (3H, m), 4.70 (2H, s), 7.42-7.53 (4H, m), 7.99 (2H, d, *J* = 8.4 Hz), 8.33 (2H, d, *J* = 8.8 Hz), 8.39 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 25.4, 29.5, 46.0, 46.3, 55.4, 58.3, 124.2, 124.9, 126.0, 127.1, 129.1, 130.3, 131.5, 131.8; EIMS (*m/z*) 290 (M^+), 70 (100%); HRMS calcd. for $C_{20}H_{22}N_2$ 290.1783, found 290.1773.

Typical procedure of intramolecular aldol reaction of 1

To a stirred solution of **12j** 203 mg (0.70 mmol) and TFA 80 μL (1.05 mmol) in DMSO (1.4 mL) was added **1** 137 mg (0.70 mmol) at rt. After stirring at the same temperature for 9 h, the mixture was diluted with AcOEt and the mixture was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was chromatographed (AcOEt/CH_2Cl_2/hexane = 1/1/4) to afford (*R*)-**2** 63 mg (51%) as pale yellow oil. The optical purity was determined to be 86% ee by HPLC with a chiral stationary phase column. HPLC conditions: Chiralcel OD (Daicel Chemical Industries, LTD), 2-propanol/hexane = 1/10 (v/v), flow rate 1.0 mL/min. detected by UV at 254 nM, t_R = 14.6 min for (*S*)-**2**, 15.7 min for (*R*)-**2**. According to the procedure reported previously,[7a] the optically pure material (>99% ee) was obtained by a single recrystallization from Et_2O/hexane as colorless needles.

M.p. 49.5-50 °C, lit.,[4b] 48.6-49.4 °C; $[\alpha]_D^{25}$ -100 (*c* 1.00, benzene), lit.[(*S*)-**2**],[3l] $[\alpha]_D^{25}$ +100 (*c* 1.40, benzene); IR (film) ν cm^{-1} 1714, 1668; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.46 (3H, s), 1.67-1.78 (1H, m), 2.10-2.19 (3H, m), 2.44-2.53 (4H, m), 2.68-2.77 (2H, m), 5.87 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.8, 23.2, 29.6, 31.7, 33.5, 37.6, 50.5, 125.8, 165.8, 198.2, 211.0; EIMS (*m/z*) 178 (M^+, 100%); HRMS calcd. for $C_{11}H_{14}O_2$ 178.0994, found 178.0988; Anal. Calcd for $C_{11}H_{14}O_2$ C, 74.13; H, 7.92. Found C, 74.03; H, 8.16.

Typical procedure of catalytic intramolecular aldol reaction of 1

To a stirred solution of **12j** 65 mg (0.23 mmol) and DCA 28 μL (0.34 mmol) in DMSO (1.4 mL) was added **1** 147 mg (0.75 mmol) at rt. After stirring at the same temperature for 20 h, the mixture was diluted with AcOEt and the mixture was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was chromatographed (AcOEt/CH_2Cl_2/hexane = 1/1/4) to afford (*R*)-**2** 91 mg (68%) as pale yellow oil. The optical purity was determined to be 84% ee by the same procedure described above.

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