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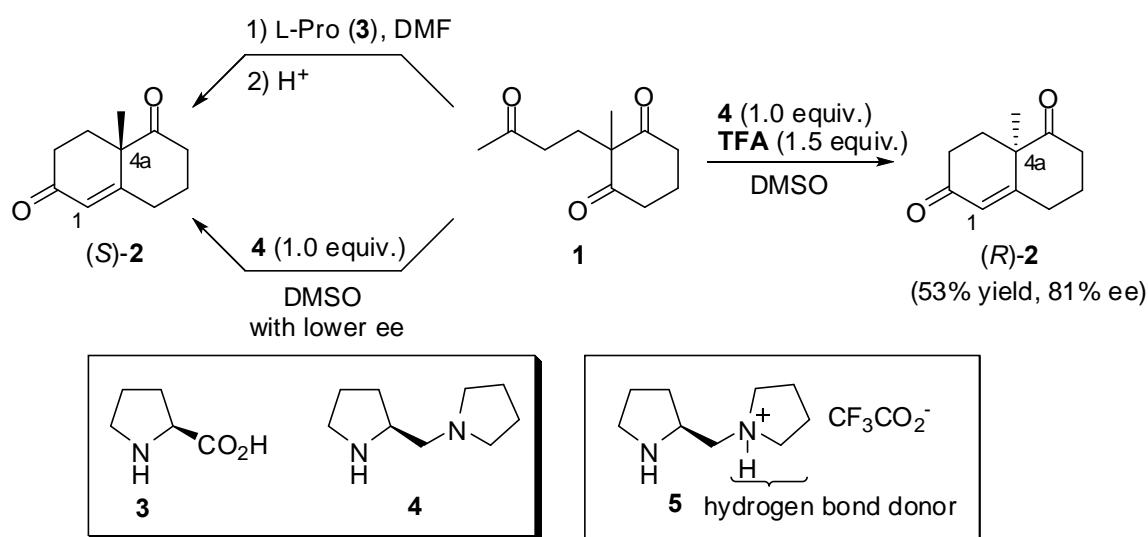
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This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

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-pyrrolidinylmethyl)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 cyclohexane 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).

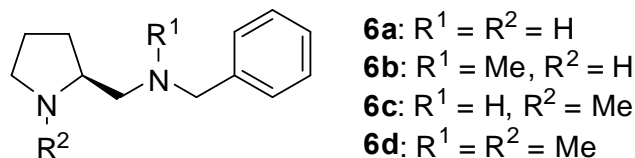
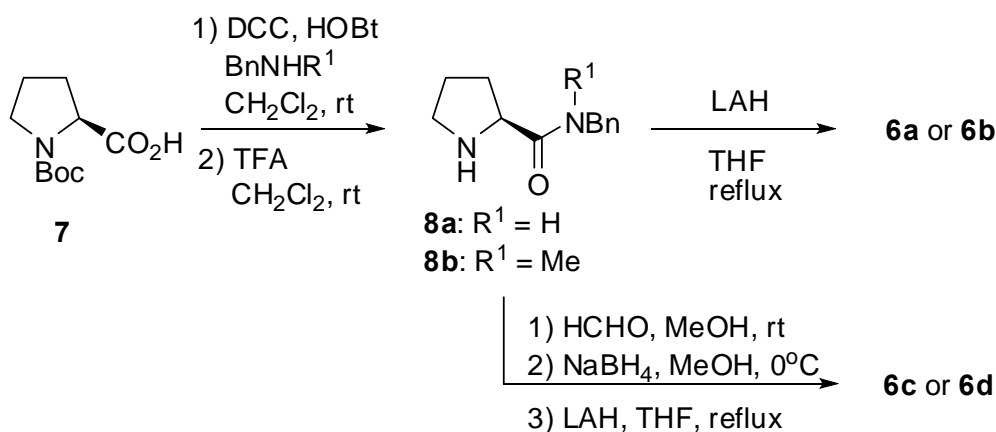


Figure 1



Scheme 2

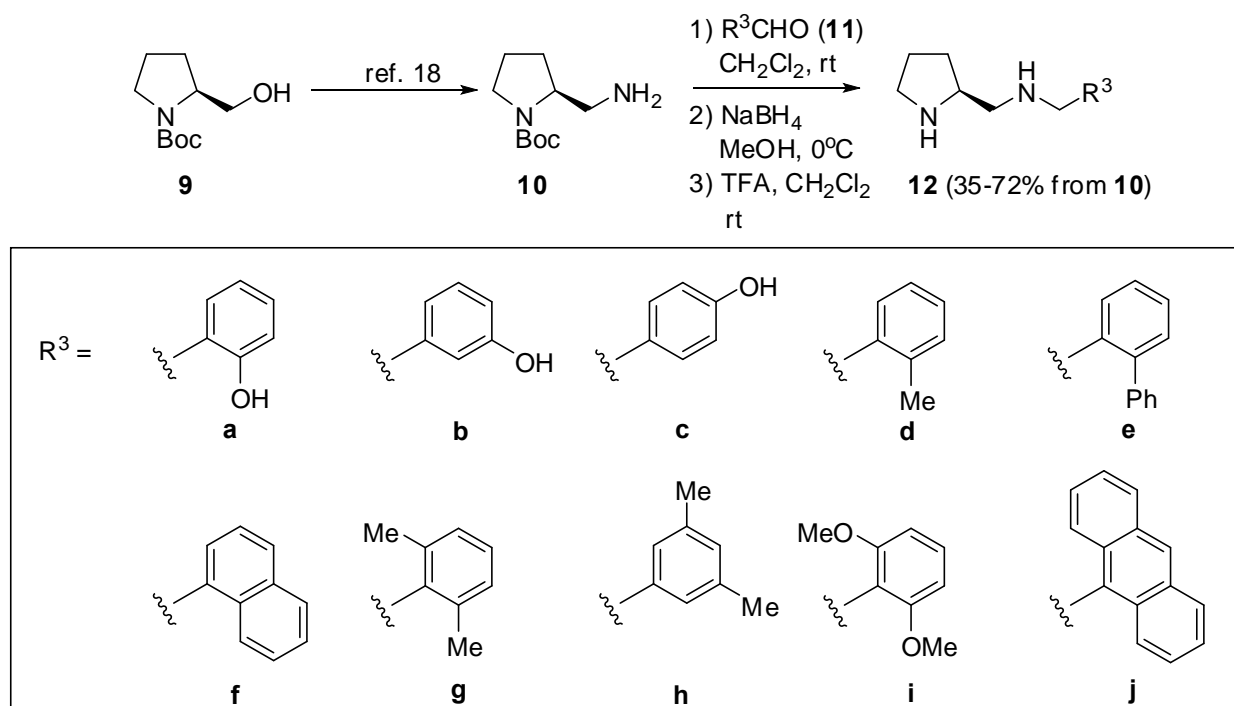
We first screened the amines (**6**) on the aldol reaction of trione (**1**). All of the reactions were carried out under the same conditions in the presence of a stoichiometric amount of **6** with or without 1.5 equiv. of TFA in DMSO at rt.¹⁷ The results were compiled in Table 1. First of all, the 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

$$\begin{array}{c}
 \mathbf{1} \xrightarrow[\text{DMSO, rt}]{\mathbf{6} \text{ (1.0 equiv.) additive}} (\text{S)- or (R)-}\mathbf{2}
 \end{array}$$

Entry	Amine	Additive (equiv.)	Time (h)	Yield ^{a, b} (%)	Ee ^c (%)	Config. ^d
1	6a	none	8	42	44	<i>S</i>
2	6a	TFA (1.5)	11	47	69	<i>R</i>
3	6b	none	9	44	13	<i>S</i>
4	6b	TFA (1.5)	20	50	21	<i>R</i>
5	6c	none	48	7 (41)	4	<i>S</i>
6	6c	TFA (1.5)	48	32 (16)	49	<i>R</i>
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 enantioselectivity 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

$$\begin{array}{c}
 \mathbf{1} \xrightarrow[\text{DMSO, rt}]{\substack{\mathbf{12} \text{ (1.0 equiv.)} \\ \text{TFA (1.5 equiv.)}}} (\mathbf{R})\text{-}\mathbf{2}
 \end{array}$$

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.

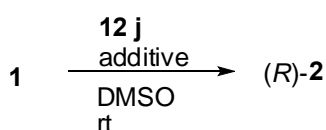
^b Determined by HPLC equipped with a chiral stationary phase column.

^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. ¹H NMR spectra and ¹³C NMR spectra were recorded on a JEOL-AX-400 (¹H 400 MHz, ¹³C 100 MHz) spectrometer and calibrated using trimethylsilane 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 CH₂Cl₂ (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 NaHCO₃ and brine. After drying (Na₂SO₄), the solvent was removed under reduced pressure to afford crude products. To the stirred solution of the crude products in CH₂Cl₂ (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 H₂O. The combined aqueous layer was basified by 10% aqueous NaOH and was extracted with CH₂Cl₂. The combined organic layer was dried (Na₂SO₄) 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 °C. The mixture was further heated under reflux for 16 h. 10 % aqueous NaOH (14 mL) was carefully added to the mixture at 0 °C 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 (CHCl₃/MeOH/NH₄OH =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; ¹H-NMR (400 MHz, CDCl₃) 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); ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₂H₁₈N₂ 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; ¹H-NMR (400 MHz, CDCl₃) 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); ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₃H₂₀N₂ 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, NaBH₄ 444 mg (11.7 mmol) was added as a small portion over 10 min at 0 °C and the mixture was further stirred at the same temperature for 12 h. After adding saturated aqueous NH₄Cl, MeOH was removed under reduced pressure. The residue was dissolved to AcOEt and the mixture was washed with saturated aqueous NaHCO₃ and brine. The organic layer was dried (Na₂SO₄) 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 °C. The mixture was further heated under reflux for 16 h. After cooling, 10% aqueous NaOH was carefully added at 0 °C and the mixture was filtered through a Celite pad. The filtrate was evaporated under reduced pressure. The residue was chromatographed (CHCl₃/MeOH/NH₄OH = 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)

[α]_D²⁹ -57.6 (*c* 1.01, MeOH); IR (film) ν cm⁻¹ 3026, 2942, 2781, 1453; ¹H-NMR (400 MHz, CDCl₃) 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); ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₃H₂₀N₂ 204.1626, found 204.1587.

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

Yield: 51% (yellow oil); [α]_D²⁸ -87.7 (*c* 1.00, MeOH), lit.,¹⁶ [α]_D -83 (*c* 1.0, EtOH); IR (film) ν cm⁻¹ 2944, 2776, 1452; ¹H-NMR (400 MHz, CDCl₃) 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); ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₄H₂₂N₂ 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 CH₂Cl₂ (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 NaBH₄ 469 mg (12.4 mmol) was added to the mixture as a small portion over 10 min at 0 °C. After stirring at 0 °C 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 NaHCO₃ and brine. The organic layer was dried (Na₂SO₄) and the solvent was removed under reduced pressure. The residue was dissolved to CH₂Cl₂ (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 H₂O. The combined aqueous layer was basified by 10% aqueous NaOH and the mixture was extracted with CH₂Cl₂. The combined organic layer was dried (Na₂SO₄) and the solvent was removed under reduced pressure. The residue was chromatographed (CHCl₃/MeOH/NH₄OH =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; ¹H-NMR (400 MHz, CDCl₃) 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); ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₂H₁₈N₂O 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; ¹H-NMR (400 MHz, CDCl₃) 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); ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₂H₁₈N₂O 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; ¹H-NMR (400 MHz, CDCl₃) 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); ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₂H₁₈N₂O 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; ¹H-NMR (400 MHz, CDCl₃) 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); ¹³C-NMR (100 MHz, CDCl₃) 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 C₁₃H₂₀N₂ 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; $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ (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 $\text{C}_{18}\text{H}_{22}\text{N}_2$ 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; $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ (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 $\text{C}_{16}\text{H}_{20}\text{N}_2$ 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; $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ (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 $\text{C}_{14}\text{H}_{22}\text{N}_2$ 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; $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ (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 $\text{C}_{14}\text{H}_{22}\text{N}_2$ 218.1783, found 218.1786.

(S)-N-(2,6-Dimethoxybenzyl)-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; $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ (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; 1H -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 μ L (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 $^{\circ}C$, lit.,^{4b} 48.6-49.4 $^{\circ}C$; $[\alpha]_D^{25} -100$ (c 1.00, benzene), lit.[(*S*)-**2**],^{3l} $[\alpha]_D^{25} +100$ (c 1.40, benzene); IR (film) ν cm^{-1} 1714, 1668; 1H -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 μ L (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.

REFERENCES

- (a) P. Wieland and K. Miescher, *Helv. Chim. Acta*, 1950, **33**, 2215. (b) S. Ramachandran and M. S. Newman, *Organic Syntheses*, 1961, **41**, 38. (c) J. Gutzwiller, P. Buchschacher, and A. Fürst, *Synthesis*, 1977, 167. (d) R. Uma, S. Swaminathan, and K. Rajagopalan, *Tetrahedron Lett.*, 1984, **25**, 5825. (e) G. Ottolina, G. Gonzalo, G. Carrea, and B. Danieli, *Adv. Synth. Catal.*, 2005, **347**, 1035. (f) Y. Kasai, K. Shimanuki, S. Kuwahara, M. Watanabe, and N. Harada, *Chirality*, 2006, **18**, 177.
- Recent applications of **2**: (a) N. Shah and T. S. Scanlan, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5199. (b) S. Díaz, A. González, B. Bradshaw, J. Cuesta, and J. Bonjoch, *J. Org. Chem.*, 2005, **70**, 3749. (c) H. Liu, D. R. Siegel, and S. J. Danishefsky, *Org. Lett.*, 2006, **8**, 423. (d) A. B. Smith, L. Kürti, A. H. Davulcu, and Y. S. Cho, *Org. Proc. Res. Dev.*, 2007, **11**, 19. (e) K. P. Kaliappan and V. Ravikumar, *Org. Lett.*, 2007, **9**, 2417. (f) B. Bradshaw, G. Etxebarria-Jardí, and J. Bonjoch, *Org. Biomol. Chem.*, 2008, **6**, 772.
- (a) Z. G. Hajos and D. R. Parrish, German Patent DE 2102623, 1971. (b) U. Eder, G. Sauer and R. Wiechert, German Patent DE 2014757, 1971. (c) U. Eder, G. Sauer, and R. Wiechert, *Angew. Chem.*, 1971, **83**, 492. (d) Z. G. Hajos and D. R. Parrish *J. Org. Chem.*, 1973, **38**, 3239. (e) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1615. (f) R. A. Micheli, Z. G. Hajos, N. Cohen, D. R. Parrish, L. A. Portland, W. Sciamanna, M. A. Scott, and P. A. Wehri, *J. Org. Chem.*, 1975, **40**, 675. (g) P. Buchschacher and A. Fuerst, *Organic Syntheses*, 1985, **63**, 37. (h) Z. G. Hajos and D. R. Parrish, *Organic Syntheses*, Wiley: New York, 1990, Collect. Vol. VII, p. 363. (i) N. Harada, T. Sugioka, H. Uda, and T. Kuriki, *Synthesis*, 1990, 53. (j) D. Rajagopal, K. Rajagopalan, and S. Swaminathan, *Tetrahedron: Asymmetry*, 1996, **7**, 2189. (k) T. Bui and C. F. Barbas III, *Tetrahedron Lett.*, 2000, **41**, 6951. (l) D. Rajagopal, R. Narayanan, and S. Swaminathan, *Tetrahedron Lett.*, 2001, **42**, 4887.
- (a) G. Zhong, T. Hoffmann, R. A. Lerner, S. Danishefsky, and C. F. Barbas III, *J. Am. Chem. Soc.*, 1997, **119**, 8131. (b) K. Fuhshuku, N. Funo, T. Akeboshi, H. Ohta, H. Hosomi, S. Ohba, and T. Sugai, *J. Org. Chem.*, 2000, **65**, 129. (c) H. Hioki, T. Hashimoto, and M. Kodama, *Tetrahedron: Asymmetry*, 2000, **11**, 829. (d) A. Gassama, J. d'Angelo, C. Cavé, J. Mahuteau, and C. Riche, *Eur. J. Org. Chem.*, 2000, 3165. (e) S. G. Davies, R. L. Sheppard, A. D. Smith, and J. E. Thomson, *Chem. Commun.*, 2005, 3802. (f) M. Hosseini, N. Stiasni, V. Barbieri, and C. O. Kappe, *J. Org. Chem.*, 2007, **72**, 1417. (g) S. Sulzer-Mossé, M. Laars, K. Kriis, T. Kanger, and A. Alexakis, *Synthesis*, 2007, 1729.
- (a) K. L. Brown, L. Damm, J. D. Dunitz, A. Eschenmoser, R. Hobi, and C. Kratky, *Helv. Chim. Acta*, 1978, **61**, 3108. (b) C. Agami and H. Sevestre, *J. Chem. Soc., Chem. Commun.*, 1984, 1385. (c) C. Agami, C. Puchot, and H. Sevestre, *Tetrahedron Lett.*, 1986, **27**, 1501. (d) C. Agami and C. Puchot, *J. Mol. Catal.*, 1986, **38**, 341. (e) C. Agami, N. Platzter, and H. Sevestre, *Bull. Soc. Chim. Fr.*, 1987, 358. (f) C. Agami, *Bull. Soc. Chim. Fr.*, 1988, 499. (g) N. Gathaergood, *Austr. J. Chem.*, 2002, **55**, 615.

6. (a) S. Bahmanyar and K. N. Houk, [J. Am. Chem. Soc., 2001, 123, 11273](#). (b) S. Bahmanyar and K. N. Houk, [J. Am. Chem. Soc., 2001, 123, 12911](#). (c) L. Hoang, S. Bahmanyar, K. N. Houk, and B. List, [J. Am. Chem. Soc., 2003, 125, 16](#). (d) S. Bahmanyar, K. N. Houk, H. J. Martin, and B. List, [J. Am. Chem. Soc., 2003, 125, 2475](#). (e) B. List, L. Hoang, and H. J. Martin, [Proc. Nat. Acad. Sci. U. S. A., 2004, 101, 5839](#). (f) B. List, [Acc. Chem. Res., 2004, 37, 548](#). (g) C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong, and K. N. Houk, [Acc. Chem. Res., 2004, 37, 558](#). (h) P. H.-Y. Cheong and K. N. Houk, [Synthesis, 2005, 1533](#).
7. (a) Y. Akahane, N. Inage, T. Nagamine, K. Inomata, and Y. Endo, [Heterocycles, 2007, 74, 637](#). (b) T. Nagamine, K. Inomata, and Y. Endo, [Heterocycles, 2008, 76, 1191](#).
8. For reviews: (a) B. List, [Tetrahedron, 2002, 58, 5573](#). (b) W. Notz, F. Tanaka, and C. F. Barbas III, [Acc. Chem. Res., 2004, 37, 580](#). (c) P. I. Dalko and L. Moisan, [Angew. Chem. Int. Ed., 2004, 43, 5138](#). (d) A. Berkessel and H. Gröger, [Asymmetric Organocatalysis](#), Wiley-VCH: Weinheim, 2005. (e) B. List, [Chem. Commun., 2006, 819](#). (f) H. Pellissier, [Tetrahedron, 2007, 63, 9267](#). (g) G. Guillena, C. Nájera, and D. J. Ramón, [Tetrahedron: Asymmetry, 2007, 18, 2249](#). (h) A. Dondoni and A. Massi, [Angew. Chem. Int. Ed., 2008, 47, 4638](#).
9. (a) S. Saito, M. Nakadai, and H. Yamamoto, [Synlett, 2001, 1245](#). (b) M. Nakadai, S. Saito, and H. Yamamoto, [Tetrahedron, 2002, 58, 8167](#). (c) S. Saito and H. Yamamoto, [Acc. Chem. Res., 2004, 37, 570](#). (d) S. Saito, N. Momiyama, and H. Yamamoto, [J. Synth. Org. Chem., Jpn 2008, 66, 774](#).
10. (a) K. Ishihara and K. Nakano, [J. Am. Chem. Soc., 2005, 127, 10504](#) and [13079](#). (b) A. Sakakura, K. Suzuki, K. Nakano, and K. Ishihara, [Org. Lett., 2006, 8, 2229](#). (c) A. Sakakura, K. Suzuki, and K. Ishihara, [Adv. Synth. Catal., 2006, 348, 2457](#). (d) H. Sundén, R. Rios, Y. Xu, L. Eriksson, and A. Córdova, [Adv. Synth. Catal., 2007, 349, 2549](#).
11. (a) S. Mossé, M. Laars, M. Kriis, T. Kanger, and A. Alexakis, [Org. Lett., 2006, 8, 2559](#). (b) S. Mossé and A. Alexakis, [Chem. Commun., 2007, 3123](#). (c) H. Chen, Y. Wang, S. Wei, and J. Sun, [Tetrahedron: Asymmetry, 2007, 18, 1308](#).
12. (a) T. Kanger, K. Kriis, M. Laars, T. Kailas, A-M. Müürisepp, T. Pehk, and M. Lopp, [J. Org. Chem., 2007, 72, 5168](#). (b) E. Lacoste, E. Vaique, M. Berlande, I. Pianet, J-M. Vincent, and Y. Landais, [Eur. J. Org. Chem., 2007, 167](#). (c) M. Laars, K. Kriis, T. Kailas, A-M. Müürisepp, T. Pehk, T. Kanger, and M. Lopp, [Tetrahedron: Asymmetry, 2008, 19, 641](#).
13. M. Amedjkouh and P. Ahlberg, [Tetrahedron: Asymmetry, 2002, 13, 2229](#).
14. F. Sternfeld, A. R. Guiblin, R. A. Jelley, V. G. Matassa, A. J. Reeve, P. A. Hunt, M. S. Beer, A. Heald, J. A. Stanton, B. Sohal, A. P. Watt, and L. J. Street, [J. Med. Chem., 1999, 42, 677](#).
15. R. H. Reitsema, [J. Am. Chem. Soc., 1949, 71, 2041](#).
16. D. Terakado, H. Koutaka, and T. Oriyama, [Tetrahedron: Asymmetry, 2005, 16, 1157](#).

17. In our previous report about the aldol reaction using **4**, addition of 1.5 equiv. of TFA as a Brønsted acid has afforded a highest enantioselectivity. See ref. 7a.
18. (a) A. Slaitas and E. Yeheškiely, [Eur. J. Org. Chem., 2002, 2391](#). (b) N. Dahlin, A. Bøgevig, and H. Adolfsson, [Adv. Synth. Catal., 2004, 346, 1101](#). (c) E. Bellis, K. Vasilatou, and G. Kokotos, [Synthesis, 2005, 2407](#).
19. All of the substituted benzaldehyde derivatives have been commercially available.