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ASYMMETRIC INTRAMOLECULAR ALDOL REACTION MEDIATED BY (*S*)-*N*-SUBSTITUTED-*N*-(2-PYRROLIDINYLMETHYL)AMINE TO PREPARE WIELAND-MIESCHER KETONE

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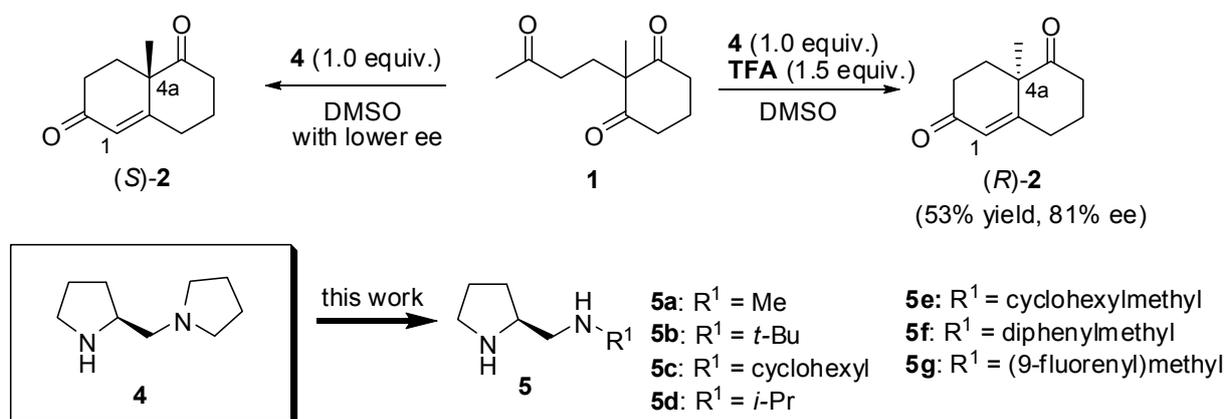
This paper is dedicated to Professor Dr. Albert Eschenmoser on the occasion of his 85th birthday.

Abstract – New or known *N*-substituted-*N*-(2-pyrrolidinylmethyl)amine derivatives bearing a variety of alkyl and aryl substituents were easily prepared from *N*-Boc-proline or *N'*-Boc-*N*-(2-pyrrolidinylmethyl)amine. The enantioselectivity of the intramolecular asymmetric aldol reaction mediated by a combination of the amine derivative and TFA to prepare Wieland-Miescher ketone was examined. During the examination, optimal amount of TFA in the reaction was identified.

Wieland-Miescher ketone (**2**), which was prepared by L-proline-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-proline has played a very important role to stabilize a transition state to achieve a highly enantioselective process.⁴⁻⁶

In the area of organocatalysis,⁷ (*S*)-2-(pyrrolidinylmethyl)pyrrolidine (**4**) has been employed as a new catalyst to achieve highly efficient asymmetric reactions, including intra- and intermolecular aldol reaction.⁸ Amine-Brønsted acid catalysis has also been utilized in asymmetric Diels-Alder reaction and 1,4-addition reaction to construct new chiral centers.^{9,10} However, to our knowledge, there have been few attempts to use a combination of chiral amine and Brønsted acid in the HPESW reaction.¹¹

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.¹² The process was characterized by an inversion of enantioselectivity when compared with the similar reaction mediated by L-Proline. Also, the reaction using **4** without a Brønsted acid afforded (*S*)-**2** with lower enantioselectivity (Scheme 1). We have also established HPESW reaction utilizing *N*-benzyl-*N*-(2-pyrrolidinylmethyl)amine derivatives in the presence of TFA.¹³ In the study, we have observed that steric hindrance around *N*-benzyl moiety was played an important role to achieve higher enantioselectivity. From these aspects, chiral amines bearing various *N*-substituents have been still required to find more effective mediators. We report herein alternative chiral amine mediators in the HPESW reaction. Specifically, we attempted to use known and new *N*-(2-pyrrolidinylmethyl)amine (**5**) containing a variety of substituents such as alkyl, cycloalkyl, branched alkyl and arylalkyl (Scheme 1).

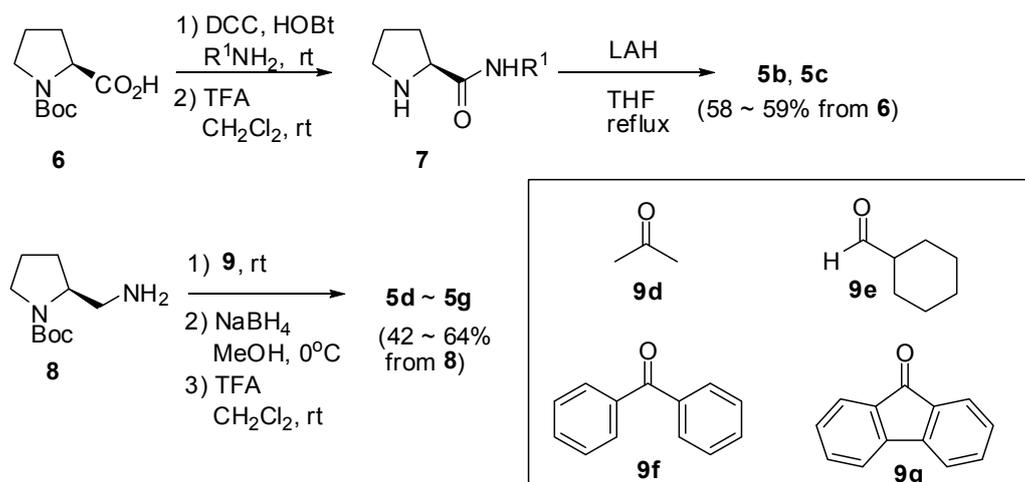


Scheme 1

Among the amines (**5**) shown in scheme 1, **5a** was prepared from *N*-cbz-L-Proline according to the known method reported by Iseki *et al.*¹⁴ Amines (**5b**⁸, **5c**¹⁵) were prepared from *N*-Boc-L-Proline (**6**) respectively in the similar manner reported by Mukaiyama *et al.*¹⁵ Thus, DCC-mediated coupling reaction with **6** and a corresponding amine, and a following deprotection of Boc-moiety in the presence of TFA yielded amide (**7**). Lithium aluminium hydride (LAH) reduction of amide group afforded **5b** and **5c** respectively. The other ones (**5d**,¹⁵ **5e**, **5f**¹⁶ and **5g**) were easily prepared by a simple reductive alkylation of *N*²-Boc-*N*-(2-pyrrolidinylmethyl)amine (**8**)¹³ with corresponding carbonyl compounds (**9**), and a following acidic deprotection of Boc moiety (Scheme 2).

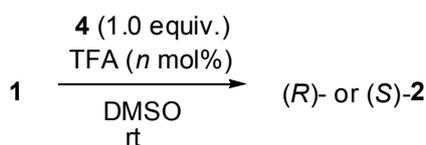
We first examined to determine the optimal amount of TFA in the HPESW reaction mediated by a chiral amine. Thus, the effect of TFA quantities on the yield and ee of **2** in the HPSEW reaction, mediated by **4**, was examined in detail. All reactions were carried out with 1.0 equiv of **4** in DMSO at rt in the presence of TFA over the range of 0 to 170 mol% (Table 1 and Figure 1). Although the yield of **2** revealed almost

same level around 50-65% in all cases, the absolute configuration of **2** was inverted from *S* to *R* at the range of 40-50 mol% of TFA. Higher ee was observed upon increasing the amount of TFA, and the parameter reached to a plateau over 100 mol% of TFA. In the presence of more than 100 mol% of TFA, longer time was required to complete the reaction. From these results, the optimal amount of TFA to achieve a high ee was in the range from 100 mol% to 170 mol%. Since the highest ee value was observed in entry 9, 150 mol% of TFA was selected for further application.



Scheme 2

Table 1



Entry	TFA (mol %)	Time (h)	Yield ^a (%)	Ee ^{b,c} (%)	Config. ^d 2
1	0	10	55	-19	<i>S</i>
2	20	4	55	-14	<i>S</i>
3	30	4	63	-8	<i>S</i>
4	40	4	61	-1	<i>S</i>
5	50	4	63	9	<i>R</i>
6	60	4	66	17	<i>R</i>
7	80	4	65	49	<i>R</i>
8	100	16	60	77	<i>R</i>
9	150	48	52	81	<i>R</i>
10	170	48	51	78	<i>R</i>

^a Isolated yield.

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

^c Ee of (*S*)-**2** was denoted by a minus sign.

^d Absolute configuration of a major enantiomer of **2**.

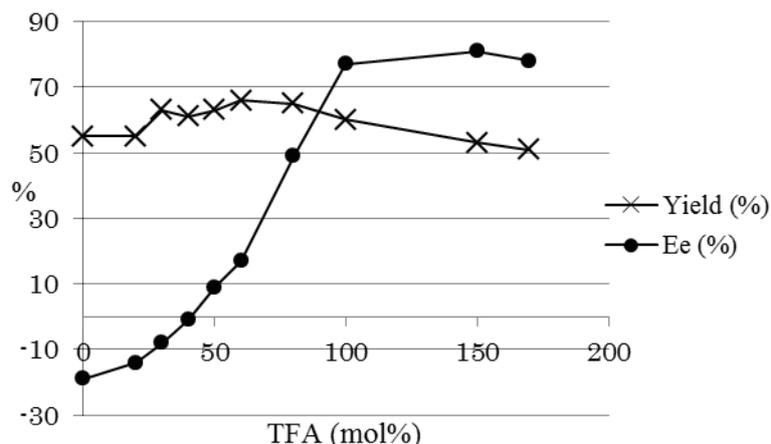
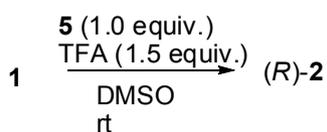


Figure 1. The effects of TFA quantities in the HPESW reaction mediated by amine (**4**)

Table 2



Entry	Amine	Time (h)	Yield ^a (%)	Ee ^b (%)
1	5a	48	44(14)	58
2	5b	9	62	68
3	5c	24	47	68
4	5d	9	67	70
5	5e	10	53	68
6	5f	24	53	50
7	5g	14	55	63

^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 1.

Next, the aldol reactions of **1** using a stoichiometric amount of **5** 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 **5** afforded (*R*)-**2** in moderate yield. The reaction proceeded slowly in the case of **5a** bearing a simple methyl substituent and the reaction was not completed even after 48 h. Cycloalkyl-substituted derivatives such as **5c** and **5e** were not also very effective and (*R*)-**2** was obtained in 47% and 53% yield respectively (entries 3 and 5). However, **5b** and **5d** bearing a tertiary or a secondary branched alkyl substituent respectively improved the yield of (*R*)-**2** (entries 2 and 4). These results suggested us that steric hindrance on

N-substituents in **5** obviously affected the reactivity but not greatly improved the enantioselectivity. In comparison with entries 6 and 7, the reaction mediated by *N*-(9-fluorenyl)methyl derivative (**5g**) revealed slightly higher ee than the case of diphenylmethyl one (**5f**). This result suggested that a planarity and a conformationally restriction of two benzene rings might be very important role to the enantioselectivity. In the previous report, we described that the ammonium moiety, which was produced from an amino substituent and a Brønsted acid, stabilized a transition state by hydrogen bonds between a mediator and a substrate.¹² Since the present mediators bearing various *N*-substituents revealed the slightly lower ee than the case of previous *N*-benzyl derivatives,¹³ the stabilization of a transition state was due to the circumstance around the ammonium moiety. Thus, the mediators substituted by a bulky group directly such as **5b-5g** may inhibit the formation of strong hydrogen bonds to stabilize a favor transition state. These aspects suggested us that *N*-substituents such as a benzyl group having both a moderate steric hindrance and a moderate planarity were a very important structure to achieve higher ee in the HPESW reaction.

In conclusion, we have established a procedure to prepare *N*-(2-pyrrolidinylmethyl)amine derivatives (**5**) bearing a variety of alkyl and aryl substituents. We also have established a new chiral route to provide (*R*)-Wieland-Miescher ketone [(*R*)-**2**] by using the combination of synthetic **5** and TFA. Furthermore, we have determined the optimal amount of TFA in HPESW reaction mediated by a chiral amine. 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. 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.

(*S*)-*N*-*t*-Butyl-*N*-(2-pyrrolidinylmethyl)amine (**5b**)

To a stirred solution of *N*-Boc-L-Proline (**6**) 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, *t*-butylamine 1.7 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 product. To the stirred solution of the crude product 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 10 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 **7**. To a stirred suspension of LAH 1.3 g (35 mmol) in THF (70 mL) was added a solution of **7** in THF (20 mL) at 0 °C. The mixture was further heated under reflux for 24 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 ($\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH} = 15/1/0.1$) to afford **5b** 2.1 g (58% from **6**) as a yellow oil.

$[\alpha]_{\text{D}}^{27} +11.8$ (c 1.00, CHCl_3), [lit.,^{8a} $[\alpha]_{\text{D}}^{25} +12.0$ (c 1.98, CHCl_3)]; IR (film) ν cm^{-1} 3429, 2980, 1407; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.09 (9H, s), 1.29-1.37 (1H, m), 1.65-1.81 (4H, m), 1.84-1.92 (1H, m), 2.47 (1H, dd, $J = 8.4$ Hz, 11.2 Hz), 2.55 (1H, dd, $J = 4.8$ Hz, 11.2 Hz), 2.84-2.94 (2H, m), 3.11-3.17 (1H, m); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 25.5, 28.9, 29.7, 46.3, 47.7, 49.9, 59.0; EIMS (m/z) 156 (M^+), 70 (100%); HRMS calcd. for $\text{C}_9\text{H}_{20}\text{N}_2$ 156.1626, found 156.1623.

(S)-N-Cyclohexyl-N-(2-pyrrolidinylmethyl)amine (5c)

In the similar manner described for **5b**, **5c** was obtained by the use of cyclohexylamine instead of *t*-butylamine.

Yield 59% (yellow oil); $[\alpha]_{\text{D}}^{28} +9.8$ (c 1.00, EtOH), [lit.,¹⁵ $[\alpha]_{\text{D}}^{24} +10.3$ (c 1.01, EtOH)]; IR (film) ν cm^{-1} 3401, 2931, 2856, 1408; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.03-1.34 (6H, m), 1.60-1.63 (1H, m), 1.67-1.78 (6H, m), 1.84-1.91 (3H, m), 2.37-2.43 (1H, m), 2.49 (1H, dd, $J = 8.8$ Hz, 11.6 Hz), 2.66 (1H, dd, $J = 4.8$ Hz, 11.2 Hz), 2.86-2.92 (2H, m), 3.19 (1H, ddd, $J = 4.8$ Hz, 7.4 Hz, 15.6 Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 25.0, 25.6, 29.7, 33.4, 33.4, 46.3, 52.0, 57.0, 58.5; EIMS (m/z) 182 (M^+), 70 (100%); HRMS calcd. for $\text{C}_{11}\text{H}_{22}\text{N}_2$ 182.1783, found 182.1786.

(S)-N-Isopropyl-N-(2-pyrrolidinylmethyl)amine (5d)

To a stirred solution of **8**¹³ 3.5 g (17.5 mmol) in acetone (30 mL) at rt. After stirring at the same temperature for 8 h, the solvent was removed under reduced pressure. The residue was dissolved to MeOH (30 mL) and NaBH_4 333 mg (8.75 mmol) was added to the mixture as a small portion over 10 min at 0 °C. After stirring at 0 °C for 7 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 (70 mL) and TFA 13 mL (175 mmol) was added to the mixture at rt. After stirring at the same temperature for 15 h, the mixture was extracted with H_2O . 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 =10/1/0.1) to afford **5d** 1.6 g (64% from **8**) as a yellow oil.

$[\alpha]_D^{28} +16.0$ (*c* 1.00, MeOH), [lit.,¹⁵ $[\alpha]_D^{26} +16.5$ (*c* 1.07, EtOH)]; IR (film) ν cm⁻¹ 3401, 2977, 1411; ¹H-NMR (400 MHz, CDCl₃) δ 1.05 (3H, d, *J* = 4.3 Hz), 1.06 (3H, d, *J* = 4.3 Hz), 1.28-1.37 (1H, m), 1.68-1.76 (4H, m), 1.84-1.91 (1H, m), 2.46 (1H, dd, *J* = 4.8 Hz, 11.4 Hz), 2.63 (1H, dd, *J* = 4.8 Hz, 11.4 Hz), 2.75-2.81 (1H, m), 2.88-2.92 (2H, m), 3.20 (1H, ddd, *J* = 4.8 Hz, 7.4 Hz, 15.9 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 23.0, 25.7, 29.8, 46.4, 48.8, 52.9, 58.5; EIMS (*m/z*) 142 (M⁺), 70 (100%); HRMS calcd. for C₈H₁₈N₂ 142.1470, found 142.1437.

(S)-N-Cyclohexylmethyl-N-(2-pyrrolidinylmethyl)amine (**5e**)

To a stirred solution of **8** 3.5 g, (17.5 mmol) in dichloromethane (35 mL) was added cyclohexanecarboxaldehyde 2.3 mL (19.3 mmol) at rt. After stirring at the same temperature for 9 h, the solvent was removed under reduced pressure. The residue was dissolved to MeOH (35 mL) and NaBH₄ 333 mg (8.75 mmol) was added to the mixture as a small portion over 10 min at 0 °C. After stirring at 0 °C for 7 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 (70 mL) and TFA 13 mL (175 mmol) was added to the mixture at rt. After stirring at the same temperature for 15 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 =10/1/0.1) to afford **5e** 1.6 g (47% from **8**) as a yellow oil.

$[\alpha]_D^{28} +12.1$ (*c* 1.00, MeOH); IR (film) ν cm⁻¹ 3400, 2924, 2851, 1409; ¹H-NMR (400 MHz, CDCl₃) δ 0.85-0.94 (2H, m), 1.10-1.36 (4H, m), 1.40-1.49 (1H, m), 1.65-1.78 (9H, m), 1.83-1.91 (1H, m), 2.44 (2H, dd, *J* = 2.4 Hz, 6.8 Hz), 2.49 (1H, dd, *J* = 8.2 Hz, 11.6 Hz), 2.59 (1H, dd, *J* = 4.8 Hz, 11.8 Hz), 2.85-2.95 (2H, m), 3.18-3.25 (1H, m); ¹³C-NMR (100 MHz, CDCl₃) δ 25.6, 26.0, 26.6, 29.7, 31.3, 37.8, 46.4, 55.3, 56.9, 58.2; EIMS (*m/z*) 196 (M⁺), 70 (100%); HRMS calcd. for C₁₂H₂₄N₂ 196.1939, found 196.1916.

(S)-N-Diphenylmethyl-N-(2-pyrrolidinylmethyl)amine (**5f**)

In the similar manner described for **5e**, **5f** was obtained by the use of benzophenone instead of cyclohexanecarboxaldehyde.

Yield 42% (yellow oil); $[\alpha]_D^{20} +19.2$ (*c* 0.84, MeOH), [lit.,¹⁶ $[\alpha]_D^{25} +20.0$ (*c* 1.0, MeOH)]; IR (film) ν cm⁻¹ 3283, 2956, 2869, 1452, 1405; ¹H-NMR (400 MHz, CDCl₃) δ 1.30-1.37 (1H, m), 1.65-1.92 (3H,

m), 2.48 (1H, dd, $J = 8.4$ Hz, 11.6 Hz), 2.59 (1H, dd, $J = 4.8$ Hz, 11.8 Hz), 2.87-2.91 (2H, m), 3.27 (1H, ddd, $J = 4.8$ Hz, 7.2 Hz, 11.7 Hz), 4.81 (1H, s), 7.19-7.21 (2H, m), 7.29 (4H, dt, $J = 2.0$ Hz, 7.2 Hz), 7.38-7.41 (4H, m); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 25.4, 29.5, 46.2, 52.8, 58.5, 67.6, 126.9, 127.2, 128.4, 144.0; 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*-(9-Fluorenyl)-*N*-(2-pyrrolidinylmethyl)amine (**5g**)

In the similar manner described for **5e**, **5g** was obtained by the use of 9-fluorenone instead of cyclohexanecarboxaldehyde.

Yield 48% (yellow oil); $[\alpha]_{\text{D}}^{21}$ -8.6 (c 1.00, CHCl_3); IR (film) ν cm^{-1} 3285, 2926, 2871, 144.7, 1403; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 1.17-1.26 (1H, m), 1.61-1.68 (2H, m), 1.72-1.80 (1H, m), 2.08 (2H, brs), 2.22 (1H, dd, $J = 8.0$ Hz, 11.8 Hz), 2.34 (1H, dd, $J = 4.8$ Hz, 11.8 Hz), 2.82-2.86 (2H, m), 3.09-3.15 (1H, m), 4.96 (1H, s), 7.33-7.39 (4H, m), 7.59-7.62 (2H, m), 7.69-7.71 (2H, m); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 25.4, 29.3, 46.2, 48.6, 58.9, 63.4, 119.8, 124.7, 127.2, 127.8, 140.6, 145.6; EIMS (m/z) 264 (M^+), 70 (100%); HRMS calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_2$ 264.1626, found 264.1624.

The effect of quantities of TFA in the HPESW reaction

To a stirred solution of the trione (**1**) 147 mg (0.75 mmol) in DMSO (1.5 mL) was added the amine (**4**) 121 μL (0.75 mmol) and TFA 86 μL (1.1 mmol) at rt. The reaction mixture was stirred at rt for 48 h, then diluted with ethyl acetate (AcOEt), washed with saturated aqueous NaHCO_3 and brine, and dried (MgSO_4). The solvent was removed under reduced pressure. The crude product was chromatographed on silica gel (AcOEt/ CH_2Cl_2 /hexane = 1/1/4) to afford (*R*)-**2** 70 mg (52%) as a pale yellow oil. The optical purity was determined to be 81% ee by HPLC with a chiral stationary phase. HPLC conditions: Chiralcel OD, 2-propanol/hexane = 1/10 (v/v), flow rate 1.0 mL/min, detected at 254 nm, $t_{\text{R}} = 14.6$ min for (*S*)-**2**, 15.7 min for (*R*)-**2**. The results in Table 1 were obtained by the same manner changing the amount of TFA in the range from 0 to 170 mol%.

Typical procedure of HPESW reaction mediated by chiral amine (**5**)

To a stirred solution of **5d** 203 mg (0.70 mmol) and TFA 86 μL (1.13 mmol) in DMSO (1.5 mL) was added **1** 147 mg (0.75 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** 84 mg (67%) as a pale yellow oil. The optical purity was determined to be 70% ee by the same manner described above.

$[\alpha]_{\text{D}}^{25}$ -69.1: 70% ee (c 1.00, benzene), [lit., [(*S*)-**2**],^{3f} $[\alpha]_{\text{D}}^{25}$ +100 (c 1.40, benzene)]; IR (film) ν cm^{-1} 1714, 1668; $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ (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 $C_{11}H_{14}O_2$ 178.0992, found 178.0988.

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