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Diastereoselective Addition of Chiral Imines and 1,3-Oxazolidines with Grignard Reagents; Asymmetric Synthesis of (*R*)-2-Aryl- and (*R,R*)-2,5-Bis(aryl)pyrrolidines

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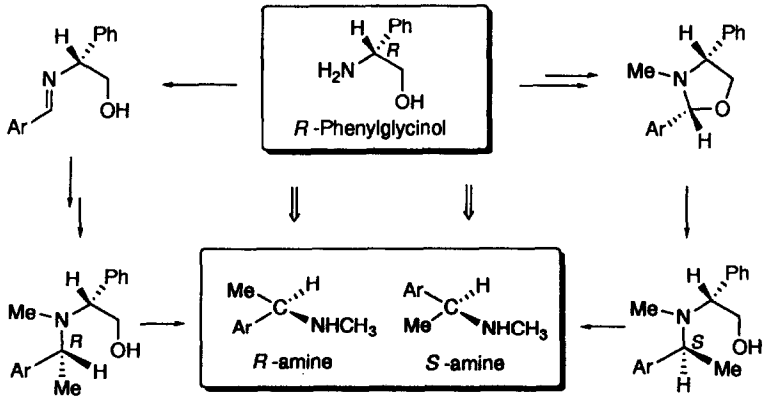
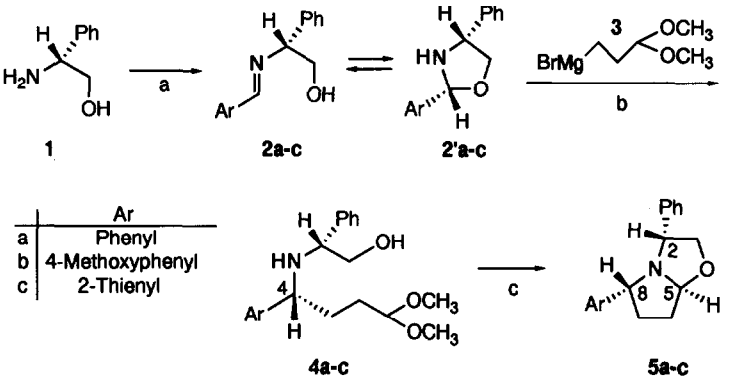
Abstract: Asymmetric syntheses of (*R*)-2-aryl- and (*R,R*)-2,5-bis(aryl)pyrrolidines were described starting from chiral aromatic imines derived from (*R*)-phenylglycinol, in which the diastereoselective additions of Grignard reagents to the chiral imines and 1,3-oxazolidines were used as the key reaction step.

The diastereoselective addition of organometallic reagents to the C=N bond of chiral imines and their derivatives offers an attractive approach for the asymmetric synthesis of chiral amines.[1] Recently, we have developed a synthetic method for the stereoselective preparation of both amine enantiomers starting from the single enantiomeric source using the diastereoselective addition of organometallic reagents to the chiral imines and 1,3-oxazolidines derived from (*R*)-phenylglycinol,[2] and we have also demonstrated its synthetic potential in the asymmetric syntheses of piperidine alkaloids, (-)-coniine and (-)-dihydropinidine.[3]



Scheme 1.

As part of a program aimed at expanding the synthetic utility of this reaction, we have accomplished a practical, asymmetric synthesis of (*R*)-2-arylpyrrolidines and (*R,R*)-2,5-bis(aryl)pyrrolidines, which were useful as a chiral auxiliary for the stereoselective syntheses.[4]



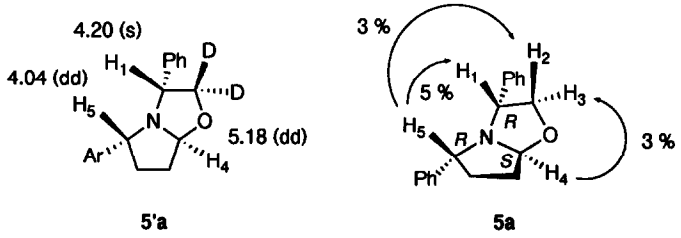
Scheme 2. *Reagents* : (a) aromatic aldehyde (1.0 eq.), C_6H_6, reflux, 4h, **2a**:94%, **2b**:71%, **2c**:98%; (b) Grignard reagent (3.0 eq.), THF, 0°C, 30min, then rt, 15h, **4a**:63%, **4b**:64%, **4c**:58%; (c) MeOH-6N.HCl (pH4), 2days, **5a**:53%, **5b**:49%, **5c**:63%.

The desired starting material was readily prepared as follows. The condensation of the aromatic aldehyde(benzaldehyde, 4-methoxybenzaldehyde, and 2-thiophen carboxyaldehyde) with (*R*)-phenylglycinol(**1**) by heating in benzene with azeotropic removal of water gave the chiral imines(**2a-c**) as crystals in quantitative yields. However, these products were confirmed to be an equilibrium mixture(90:10) of imines(**2a-c**) and 2-aryl-1,3-oxazolidines(**2'a-c**) from ^{1}H-NMR($CDCl_3$) analyses.[5] The reaction of chiral imines(**2a-c**) with an excessive amount of Grignard reagent(**3**), which was prepared from 3-bromopropionaldehyde dimethyl acetal in THF, afforded the desired products(**4a-c**) in 58-64% yields with very high diastereomeric excesses. Indeed, the ^{1}H-NMR(270MHz) spectra of the crude products did not indicate the presence of any diastereoisomers. The high degree of stereocontrol of this reaction may be attributed to a highly ordered transition state resulting from significant chelation of the alkoxy substituent and imino nitrogen to the magnesium atom and then delivery of the other Grignard reagent from the least hindered side of the carbon-nitrogen double bond.[6]

With the requisite compound in hand, we next carried out the intramolecular cyclization reaction of the acetals(**4a-c**) with 1% methanolic hydrochloric acid to afford the thermodynamically more stable compounds(**5a-c**) as the sole cyclized products in 49-63% yields. The 2*R*,5*S*,8*R*-configuration of **5a-c** have been established using NOE difference spectroscopy and ^{1}H-NMR(270MHz) spectral comparison with deuterated **5'a** obtained from deuterated (*R*)-phenylglycinol, which was derived from (*R*)-phenylglycine by reduction with $LiAlD_4$, in the same manner as described for the preparation of **5a**. Thus, irradiation of the H_5 signal at 4.04ppm caused enhancement of the signals corresponding to H_1 and

H_2 while irradiation of the H_4 signal at 5.18ppm caused enhancement of the signals corresponding to H_3 as shown in Fig 1. The same trend was observed for **5b** and **5c**.

Figure 1. Chemical Shifts of **5'a** and Difference NOE on **5a**



5'a **5a**

Table 1. Selected ^{1}H-NMR Spectral Data of the Bicyclo Compounds(**5a-c**)[a]

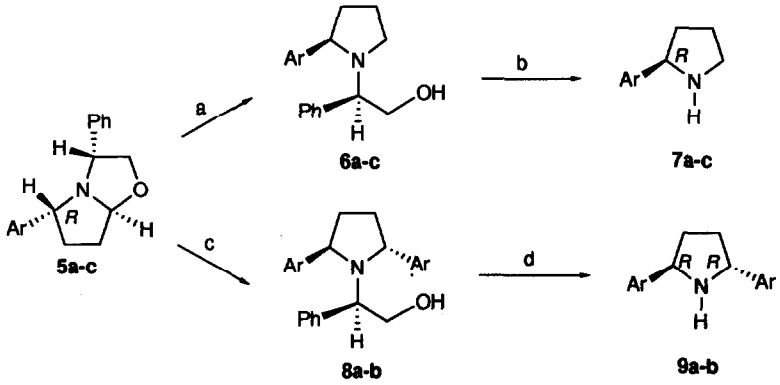
	Chemical Shifts(ppm)				Coupling Constants(Hz)		
	5a	5b	5c		5a	5b	5c
H_1	4.21	4.19	4.30	J_{1-2}	6.7	6.7	7.3
H_2	4.42	4.41	4.40	J_{1-3}	5.5	5.5	5.5
H_3	3.74	3.73	3.73	J_{2-3}	8.5	8.5	8.5
H_4	5.18	5.51	5.12	J_{H4}	2.5, 5.5	2.5, 5.5	1.8, 4.9
H_5	4.04	3.97	4.30	J_{H5}	6.7, 9.8	5.5, 9.8	- b -

a. In $CDCl_3$ at 270MHz. b. Data not available

With the pivotal precursor of the title compounds in hand, we then focused our attention on the conversion of the bicyclo compounds(**5a-c**) into 2-arylpyrrolidines and 2,5-bis(aryl)pyrrolidines. The reduction of **5a-c** with $NaBH_4$ in methanol yielded the alcohol(**6a-c**) in good yields. The removal of the *N*-alkyl substituent from **6a-c** proved to be somewhat difficult even though a wide range of reductive cleavage[7] or oxidative cleavage was attempted.[8] However, according to Meyer's procedure,[9] treatment of **5a-c** with triethylphosphine and diphenyl disulfide yielded the thiophenyl derivatives, which, without isolation, were then treated with the lithium radical anion of 4,4'-di-*tert*-butylbiphenyl to afford the desired (*R*)-2-arylpyrrolidines(**7a-c**). The spectroscopic data of the synthetic **7a** including the specific optical rotation were identical with those already reported. [10]

On the other hand, bicyclo compounds(**5a-b**) reacted smoothly with the phenylmagnesium bromide or 4-methoxyphenylmagnesium bromide in THF to give essentially single adducts(**8a-b**) in 82 and 80% yields, respectively, as evidenced by the ^{1}H-NMR(270MHz) spectra of the crude product mixture. The stereochemistry of the newly formed asymmetric center in the adducts(**8a-b**) was assumed to be *R* based on previous results [2] and unambiguously determined by their conversion into 2,5-bis(aryl) pyrrolidines (**9a-b**) in the same manner as described for the preparation of **7a-c**. Namely, the absolute configurations

of **9a-b** should be *R,R* because, first, these compounds exhibited positive optical rotations and, second, the chiral centers of the starting **5a-b** have an *R* configuration at the C-8 position. The observed diastereoselectivity for the Grignard reaction of **5a-b** leading to **8a-b** can be rationalized by assuming that the Grignard reagent approaches the oxygen atom of the 1,3-oxazolidine ring to give a favorable intermediary iminium salt(A), and its nucleophilic attack occurs from the *si*-face of the carbon-nitrogen double bond of the intermediate as shown in Figure 2.[11]



Scheme 3. *Reagents* : (a) $NaBH_4$ (3.0 eq.), MeOH, rt, 2h, **6a**:87%, **6b**:81%,**6c**:76%; (b) 1)PhSSPh(5.0 eq.), Et_3P(5.0eq.), THF, rt, 16h. 2)LiDBB(3.6eq.), THF, -60°C, 15min, then 0°C, 16h, **7a**:62%, **7b**:30%, **7c**:13%; (c) Grignard Reagent(3.0eq.), THF, rt, 2.5h, **8a**:82%, **8b**:80%; (d) In the same manner as (b), **9a**:60%, **9b**:42%

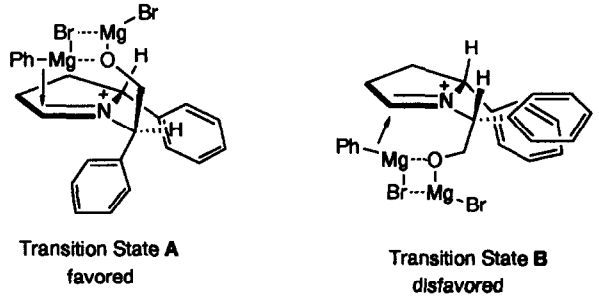


Figure 2. Proposed transition states accounting for the diastereoselectivity.

Thus, we achieved the asymmetric synthesis of (*R*)-2-aryl- and (*R,R*)-2,5-bis(aryl)pyrrolidines by employing the diastereoselective reaction of the chiral imine and 1,3-oxazolidine as the key step. This procedure should be available as an alternative synthetic route to various types of optically active *trans*-2,5-disubstituted pyrrolidines.

Experimental

General Methods. Melting points were measured with a Yanagimoto Micro melting Point apparatus and uncorrected. IR spectra were recorded on a 215 Hitachi Grating I.R. spectrophotometer. ^{1}H-NMR spectra were obtained on a JEOL PMX 270 instrument, and chemical sifts are reported in ppm on the δ-scale from internal Me_4Si. Mass spectra were measured with a JEOL JMS D-300 spectrometer by using the chemical ionization(CI)(isobutane) methods. Optical rotations were taken with a JASCO-DIP-370 polarimeter.

General Procedure for the Reaction of (*R*)-1 with Aromatic Carbaldehydes

An aromatic carbaldehyde [benzaldehyde, 4-methoxybenzaldehyde, or 2-thiophen carboxyaldehyde, (37.0 mmol)] was added to a solution of (*R*)-1(5.0 g, 36.45 mmol) in benzene(50 ml), and the reaction mixture was refluxed for 4 h using a Dean-Stark trap. After cooling, the mixture was concentrated under reduced pressure to give the crude product(**2a-c**), which was purified by recrystallization.

(*E*)-(*R*)-*N*-(2-Hydroxy-1-phenylethyl)-1-phenylmethylideneamine (2a):[2]

Colorless needles, mp 78°C(hexane-ether). Yield, 94%. MS *m/z*; CI, 226(M^++1); EI, 194(M^+-CH_2OH). ^{1}H-NMR($CDCl_3$) δ: 2.03(1H, brs, OH), 3.90(1H, dd, *J*=7.9, 11.0Hz, PhCHC*H*$_2$), 3.97(1H, dd, *J*=4.3, 11.0Hz, PhCHC*H*$_2$), 4.50(1H, dd, *J*=4.3, 7.9Hz, PhC*H*CH$_2$), 7.24-7.82(10H, m, aromatic H), 8.40(1H, s, N=CH). $[\alpha]_D$+48.8°(*c*=1.07, $CHCl_3$). IR($CHCl_3$): 3400(OH), 1640(C=N)cm^{-1}.

(*E*)-(*R*)-*N*-(2-Hydroxy-1-phenylethyl)-1-(4-methoxyphenyl)-methylideneamine (2b):

Colorless needles, mp 62°C(hexane-ether). Yield, 71%. MS *m/z*; CI, 256(M^++1); EI, 224(M^+-CH_2OH). ^{1}H-NMR ($CDCl_3$) δ: 2.21(1H, brs, OH), 3.85(3H, s, OCH_3), 3.83-3.99(2H, m, PhCHC*H*$_2$), 4.46(1H, dd, *J*=4.9, 7.9Hz, PhC*H* CH_2), 6.91 (2H, d, *J*=6.1Hz, aromatic H), 7.26-7.45(5H, m, aromatic H), 7.73(2H, d, *J*=6.1Hz, aromatic H), 8.44(1H, s, N=CH). $[\alpha]_D$ +110.7° (*c*=1.00, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.33; H, 6.69; N, 5.50. IR($CHCl_3$): 3400(OH), 1640(C=N)cm^{-1}.

(*E*)-(*R*)-*N*-(2-Hydroxy-1-phenylethyl)-1-(2-thienyl)methylideneamine (2c):

Colorless prisms, mp 101°C(hexane-ether). Yield, 98%. MS *m/z*; CI, 232(M^++1); EI, 200(M^+-CH_2OH). ^{1}H-NMR($CDCl_3$) δ: 2.39(1H, brs, OH), 3.83-3.99(2H, m, PhCHC*H*$_2$), 4.47(1H, dd, *J*=4.3, 8.8Hz, PhC*H* CH_2), 7.05(1H, dd, *J*= 3.7, 4.9Hz, aromatic H), 7.25-7.42(7H, m, aromatic H), 8.44(1H, s, N=CH). $[\alpha]_D$ +150.5° (*c*=1.00, $CHCl_3$). *Anal.* Calcd for $C_{13}H_{13}NOS$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.36; H, 5.70; N, 6.17. IR ($CHCl_3$): 3400(OH), 1620(C=N)cm^{-1}.

General Procedure for the Reaction of (*R*)-2a-c with Grignard reagent

To a stirred solution of Grignard reagent, prepared from 3.2 g (17.5 mmol) of 3-bromopropionaldehyde dimethyl acetal and 0.43 g (17.7 mmol) of Mg, in THF (30 ml) was added dropwise at 0 °C a solution of chiral imine(**2a-c**)(5.84 mmol) in THF(50 ml) under nitrogen over a period of 30min. After the reaction mixture was stirred for 15 h at room temperature, the mixture was poured into 30 ml of saturated ammonium chloride, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate(3 x 20 ml). The combined extracts were dried over Na_2SO_4 and concentrated to give a residue,

which was subjected to column chromatography on silica gel with CH_2Cl_2-MeOH (10:1). The acetal (**4a-c**) was obtained as a yellowish oil, which was not stable enough to obtain a satisfactory microanalysis.

(4*R*-1'*R*)-4-(2'-Hydroxy-1'-phenylethylamino)-4-phenylbutanal dimethyl acetal (4a):
Yellow oil. Yield, 63%. MS *m/z*; CI, 330(M^++1). ^{1}H-NMR($CDCl_3$) δ: 1.44-1.50(2H, m, PhCHC*H*$_2$), 1.51-1.80[2H, m, C*H*$_2$CH(OCH_3)$_2$], 1.90(2H, brs, NH,OH), 3.23(3H, s, OCH_3), 3.24(3H, s, OCH_3), 3.52(1H, dd, *J*=7.3, 11.0Hz, C*H*$_2$OH), 3.62(1H, dd, *J*=5.5, 7.3Hz, PhC*H*CH$_2$OH), 3.74(1H, dd, *J*=5.5, 11.0Hz, C*H*$_2$OH), 3.85 (1H, dd, *J*=5.5, 7.3Hz, NC*H*CH$_2$), 4.54[1H, t, *J*=5.5Hz, CH$_2$C*H*(OCH_3)$_2$], 7.17-7.32(10H, m, aromatic H). $[\alpha]_D$ -22.7° (*c*=1.59, EtOH).

(4*R*-1'*R*)-4-(2'-Hydroxy-1'-phenylethylamino)-4-(4-methoxyphenyl)-butanal dimethyl acetal (4b):
Yellow oil. Yield, 64%. MS *m/z*; CI, 360(M^++1). ^{1}H-NMR($CDCl_3$) δ: 1.42-1.77(2H, m, PhCHC*H*$_2$), 1.81-1.94[2H, m, C*H*$_2$CH(OCH_3)$_2$], 2.13(2H, brs, NH,OH), 3.22(3H, s, OCH_3), 3.24(3H, s, OCH_3), 3.51 (1H, dd, *J*=7.3, 11.0Hz, C*H*$_2$OH), 3.56(1H, dd, *J*=5.5, 7.3Hz, PhC*H*CH$_2$OH), 3.74(1H, dd, *J*=5.5, 11.0Hz, C*H*$_2$ OH), 3.78(3H, s, OCH_3), 3.83(1H, dd, *J*=5.5, 7.3Hz, NC*H*CH$_2$), 4.27[1H, t, *J*=5.5Hz, CH$_2$C*H*(OCH_3)$_2$], 6.81(2H, d, *J*=8.5Hz, aromatic H), 7.10(2H, d, *J*=8.5Hz, aromatic H), 7.16-7.33(5H, m, aromatic H). $[\alpha]_D$ -32.5° (*c*=1.23, EtOH).

(4*R*-1'*R*)-4-(2'-Hydroxy-1'-phenylethylamino)-4-(2-thienyl)-butanal dimethyl acetal (4c):
Yellow oil. Yield, 58%. MS *m/z*; CI, 335(M^++1). ^{1}H-NMR($CDCl_3$) δ: 1.52-1.69(2H, m, PhCHC*H*$_2$), 1.71-1.81[2H, m, C*H*$_2$CH(OCH_3)$_2$], 2.20(2H, brs, NH,OH), 3.26(3H, s, OCH_3), 3.27(3H, s, OCH_3), 3.57(1H, dd, *J*=7.3, 11.0Hz, C*H*$_2$OH), 3.75(1H, dd, *J*=5.5, 11.0Hz, C*H*$_2$OH), 3.91(1H, dd, *J*=5.5, 7.3Hz, PhC*H*CH$_2$OH), 3.96 (1H, dd, *J*=5.5, 7.3Hz, NC*H*CH$_2$), 4.30[1H, t, *J*=5.5Hz, CH$_2$C*H*(OCH_3)$_2$], 6.83(1H, dd, *J*=1.2, 3.7Hz, aromatic H), 6.90(1H, dd, *J*=3.7, 4.9Hz, aromatic H), 7.18(1H, dd, *J*=1.2, 4.9Hz, aromatic H), 7.23-7.34 (5H, m, aromatic H). $[\alpha]_D$ -23.2° (*c*=1.7, EtOH).

General Procedure for the Formation of 2,8-Dialkyl-1-aza-4-oxabicyclo[3.3.0]octane (5a-c)
A solution of acetal(**3a-c**)(1.49 mmol) in methanol(100 ml) was acidified with aqueous 6N HCl solution to pH 4 and stirred at ambient temperature. After 2 days, the reaction mixture was basified with aqueous 10% NaOH solution to pH 8, and poured into a separatory funnel together with EtOAc(300 ml) and brine (300 ml). The layers were separated, and the organic phase was washed with brine(4 x 50 ml), dried over $MgSO_4$, and evaporated to give the crude product, which was subjected to column chromatography on silica gel with hexane-EtOAc(10:3) to give bicyclo compounds(**5a-c**).

(2*R*,5*S*, 8*R*)-2,8-Diphenyl-1-aza-4-oxabicyclo[3.3.0]octane (5a):
Colorless needles, mp 51°C (ether). Yield, 53%. MS *m/z*; CI, 266(M^++1). ^{1}H-NMR($CDCl_3$) δ: 1.78-2.37 (4H, m, PhCHC*H*$_2$C*H*$_2$), 3.74 (1H, dd, *J*=5.5, 8.5Hz, PhCHC*H*$_2$O), 4.04(1H, dd, *J*=6.7, 9.8Hz, PhCHN), 4.21(1H, dd, *J*=5.5, 6.7Hz, PhC*H*CH$_2$O), 4.42(1H, dd, *J*=6.7, 8.5Hz, PhCHC*H*$_2$O), 5.18(1H, dd, *J*=2.5, 5.5Hz, NCHO), 7.20-7.41 (10H, m, aromatic H). $[\alpha]_D$ -32.5° (*c*=1.05, EtOH). *Anal.* Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.14; H, 7.24; N, 5.12.

(2*R*,5*S*, 8*R*)-8-(4-Methoxyphenyl)-2-phenyl-1-aza-4-oxabicyclo[3.3.0] octane (5b):
Yellow oil. Yield, 49%. MS *m/z*; CI, 296(M^++1). ^{1}H-NMR($CDCl_3$) δ 1.75-2.05(2H, m, PhCHCH_2CH_2), 2.21-2.32(2H, m, PhCHCH_2CH_2), 3.73(1H, dd, *J*=5.5, 8.5Hz, PhCHCH_2O), 3.75(3H, s, OCH_3), 3.97(1H, dd, *J*=5.5, 9.8 Hz, ArCHN), 4.19(1H, dd, *J*=5.5, 6.7Hz, PhC*H*CH_2O), 4.41(1H, dd, *J*=6.7, 8.5Hz, PhCH CH_2O), 5.51(1H, dd, *J*=2.2, 5.5Hz, NCHO), 6.79(2H, d, J=9.2 Hz, aromatic H), 7.20-7.33(7H, m, aromatic H). $[\alpha]_D$ -23.3° (*c*=1.23, EtOH). *Anal.* Calcd for $C_{19}H_{21}NO_2$: C, 77.34; H, 7.23; N, 4.52. Found: C, 77.26; H, 7.17; N, 4.74.

(2*R*,5*S*, 8*R*)-2-Phenyl-8-(2-thienyl)-1-aza-4-oxabicyclo[3.3.0]octane (5c):
Yellow oil. Yield, 63%. MS *m/z*; CI, 272(M^++1). ^{1}H-NMR($CDCl_3$) δ 1.91-2.08(2H, m, PhCHCH_2CH_2), 2.22-2.43(2H, m, PhCHCH_2CH_2), 3.73(1H, dd, *J*=5.5, 7.3Hz, PhCHCH_2O), 4.30(2H, dd, *J*=5.5, 7.3Hz, ArCHN and PhC*H*CH_2O), 4.40(1H, dd, *J*=7.3, 8.5Hz, PhCHCH_2O), 5.12(1H, dd, *J*=1.8, 4.9Hz, NCHO), 6.87(1H, d, *J*=1.2Hz, aromatic H), 6.90(1H, dd, *J*=1.2, 3.7Hz, aromatic H), 7.12(1H, d, *J*=3.7Hz, aromatic H), 7.17-7.37(5H, m, aromatic H). $[\alpha]_D$ -60.9° (*c*=0.87, EtOH). *Anal.* Calcd for $C_{16}H_{17}NOS$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.82; H, 6.30; N, 5.13.

General Procedure for the Reduction of 5a-c with $NaBH_4$
To a solution of bicyclo compound(**4a-c**)(0.83 mmol) in methanol(20 ml) was added portionwise $NaBH_4$ (2.5 mmol). After stirred for 2 h, the reaction mixture was quenched with water and the aqueous layer was extracted with EtOAc(3 x 20 ml). The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated to give the crude product, which was subjected to column chromatography on silica gel with hexane-EtOAc(10:4) to give C-2 substituted pyrrolidines(**6a-c**).

(2*R*,1'*R*)-*N*-2'-Hydroxy-1'-phenylethyl-2-phenylpyrrolidine (6a):
Colorless plates, mp 80°C (hexane-ether). Yield, 87%. MS *m/z*; CI, 268(M^++1). ^{1}H-NMR($CDCl_3$) δ: 1.62-2.18(4H, m, pyrrolidine H), 2.00(1H, brs, OH), 2.90(1H, dd, *J*=9.2, 15.9Hz, CH_2N), 3.26(1H, m, CH_2N), 3.57(2H, d, *J*=6.7Hz, CH_2 OH), 3.71(1H, m, PhCHN), 3.93(1H, t, *J*=6.7Hz, PhC*H*CH_2OH), 7.12-7.36 (10H, m, aromatic H). $[\alpha]_D$ +75.8° (*c*=0.84, EtOH). *Anal.* Calcd for $C_{18}H_{21}NO$: C, 80.56; H, 7.96; N, 5.20. Found: C, 80.86; H, 7.92; N, 5.24.

(2*R*,1'*R*)-*N*-2'-Hydroxy-1'-phenylethyl-2-(4-methoxyphenyl) pyrrolidine (6b):
Colorless plates, mp 75°C(hexane-ether). Yield, 81%. MS *m/z*; CI, 298(M^++1). ^{1}H-NMR($CDCl_3$) δ: 1.65-1.72(2H, m, pyrrolidine H), 1.92-2.07(2H, m, pyrrolidine H), 2.00(1H, brs, OH), 2.85(1H, dd, *J*=9.2, 15.9 Hz, CH_2N), 3.20(1H, m, CH_2N), 3.57(2H, d, *J*=6.7Hz, CH_2OH), 3.64(1H, m, ArCHN), 3.80(3H, s, OCH_3), 3.90(1H, t, *J*=6.7Hz, PhC*H*CH_2OH), 6.84(2H, d, J=9.2, aromatic H), 7.14-7.33(7H, m, aromatic H). $[\alpha]_D$ +50.5° (*c*=0.95, EtOH). *Anal.* Calcd for $C_{19}H_{23}NO_2$: C, 76.80; H, 7.85; N, 4.63. Found: C, 76.73; H, 7.80; N, 4.71.

(2*R*,1'*R*)-*N*-2'-Hydroxy-1'-phenylethyl-2-(2-thienyl)pyrrolidine (6c):
Yellow oil. Yield, 76%. MS *m/z*; CI, 274(M^++1). ^{1}H-NMR($CDCl_3$) δ 1.75-1.80(2H, m, pyrrolidine H), 1.93-2.09(2H, m, pyrrolidine H), 2.00(1H, brs, OH), 2.85(1H, dd, *J*=8.5, 15.3Hz, CH_2N), 3.14(1H, m, CH_2

N), 3.72(2H, m, CH_2OH), 3.89 (1H, dd, *J*=6.1, 7.3Hz, ArCHN), 4.23(1H, m, PhC*H*CH_2OH), 6.78(1H, d, *J*=3.1Hz, aromatic H), 6.89(1H, dd, *J*=3.1, 4.9Hz, aromatic H), 7.16-7.35(6H, m, aromatic H). $[\alpha]_D$ +37.1° (*c*=1.16, EtOH). *Anal.* Calcd for $C_{16}H_{19}NOS$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.18; H, 7.04; N, 5.00.

General Procedure for the Preparation of (*R*)-2-arylpyrrolidine (7a-c)

The title products were prepared according to the method described by Meyers.[9] To a stirred solution of **5a-c**(1.65 mmol) and diphenyldisulfide(1.80 g, 8.25 mmol) in dry THF(50 ml) was added dropwise triethylphosphine(1.2 ml, 8.25 mmol) at ambient temperature. After being stirred for 16 h, the solution was concentrated to leave a residue, which was purified through a short silica gel column with hexane-EtOAc (10:1). The thiophenyl derivative was obtained, which, without further purification, was used for the next reaction. A solution of the thiophenyl derivative obtained above in THF(5 ml) was added dropwise to a stirred solution of radical anion, prepared from 4,4'-di-tert-butylbiphenyl(1.6 g, 6 mmol) and piece of metallic lithium (35 mg, 5.04 mmol), in THF(20 ml) at -60 °C under argon atmosphere. After being stirred for 15min at the same temperature, the solution was allowed to warm to 0 °C and further stirred for 16 h. The reaction mixture was treated with water and extracted with EtOAc(3 x 30 ml). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was subjected to column chromatography on silica gel with hexane-EtOAc(10:1-1:10) to give (*R*)-2-arylpyrrolidines(**7a-c**) as a yellowish oil.

(*R*)-2-Phenylpyrrolidine (7a):

Yellow oil. Yield, 62%. MS *m/z*; CI, 148(M^++1). ^{1}H-NMR ($CDCl_3$) δ: 1.63-2.26(4H, m, pyrrolidine H), 2.72(1H, brs, NH), 2.98-3.07(1H, m, CH_2N), 3.17-3.46(1H, m, CH_2N), 4.13(1H, t, *J*=7.3Hz, PhCHN), 7.20-7.39(5H, m, aromatic H). HCl salt; Colorless plates, mp 105°C(ether). $[\alpha]_D$ -15.7° (*c*=0.96, MeOH) [lit [10] $[\alpha]_D$ -15.3° (*c*=0.86, MeOH)]. *Anal.* Calcd for $C_{10}H_{13}N$· HCl: C, 65.38; H, 7.68; N, 7.62. Found: C, 65.11; H, 7.74; N, 7.51.

(*R*)-2-(4-Methoxyphenyl)pyrrolidine (7b):

Yellow oil. Yield, 30%. MS *m/z*; CI, 178(M^++1). ^{1}H-NMR ($CDCl_3$) δ: 1.62-1.71(1H, m, pyrrolidine H), 1.79-2.12(3H, m, pyrrolidine H and NH), 2.13-2.19(1H, m, pyrrolidine H), 2.94-3.15(1H, m, CH_2N), 3.17-3.24(1H, m, CH_2N), 3.79(3H, s, OCH_3), 4.05(1H, t, *J*= 7.3 Hz, ArCHN), 6.86(2H, d, *J*=9.2Hz, aromatic H), 7.29(2H, d, *J*=9.2Hz, aromatic H). HCl salt; Colorless plates, mp 168°C(ether). $[\alpha]_D$ -14.3° (*c*=0.98, MeOH). *Anal.* Calcd for $C_{11}H_{15}N$·HCl: C, 61.81; H, 7.55; N, 6.55. Found: C, 61.56; H, 7.46; N, 6.48.

(*R*)-2-(2-Thienyl)pyrrolidine (7c):

Yellow oil. Yield, 13%. MS *m/z*; CI, 154(M^++1). ^{1}H-NMR ($CDCl_3$) δ: 1.73-2.07(3H, m, pyrrolidine H), 2.18(1H, brs, NH), 2.19-2.28(1H, m, pyrrolidine H), 2.94-3.04(1H, m, CH_2N), 3.13-3.22(1H, m, CH_2N), 4.40(1H, t, *J*=6.7Hz, ArCHN), 6.90-6.96(2H, m, aromatic H), 7.17(1H, dd, *J*=1.8, 4.9Hz, aromatic H). $[\alpha]_D$ +14.8° (*c*=1.07, EtOH). HCl salt; Colorless plates, mp 160°C(ether). *Anal.* Calcd for $C_8H_{11}NS$·HCl: C, 50.66; H, 6.38; N, 7.38. Found: C, 50.88; H, 6.43; N, 7.19.

General Procedure for the Reaction of 5a and 5b with ArMgBr

Grignard reagent (C_6H_5MgBr or 4-$CH_3OC_6H_4MgBr$, 3.39 mmol) in THF was added dropwise to a stirred solution of **5a-b**(1.13 mmol) in THF(50 ml) at ambient temperature under nitrogen over a period of 15 min. After the reaction mixture was stirred for 2.5 h, the resulting dark orangish solution was poured into 100 ml of saturated ammonium chloride, the organic layer was separated, and aqueous layer was extracted with EtOAc(3 x 30 ml). The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated to give a residue, which was subjected to column chromatography on silica gel with hexane-EtOAc(10:4) to give 2,5- disubstituted pyrrolidines(**8a-b**) as a viscous oil.

(2*R*,5*R*,1'*R*)-*N*-2'-Hydroxy-1'-phenylethyl-2,5-bisphenylpyrrolidine (8a):

Colorless oil. Yield, 82%. MS *m/z*; CI, 344(M^++1). ^{1}H-NMR($CDCl_3$) δ: 1.56(1H, brs, OH), 1.70-1.81(2H, m, pyrrolidine H), 2.52-2.67(2H, m, pyrrolidine H), 3.45-3.59(2H, m, C*H*$_2$OH), 4.02(1H, t, *J*=6.7Hz, Ph C*H*CH$_2$OH), 4.49 (2H, d, *J*=5.5Hz, PhCHN), 6.74-7.37(15H, m, aromatic H). $[\alpha]_D$ +45.3° (*c*=1.10, EtOH), which was not stable enough to give a satisfactory microanalysis.

(2*R*,5*R*,1'*R*)-*N*-2'-Hydroxy-1'-phenylethyl-2,5-bis(4-methoxyphenyl) pyrrolidine (8b):

Colorless oil. Yield, 80%. MS *m/z*; CI, 404(M^++1). ^{1}H-NMR($CDCl_3$) δ 1.67-1.79(2H, m, pyrrolidine H), 2.31(1H, brs, OH), 2.47-2.59(2H, m, pyrrolidine H), 3.40-3.57(2H, m, C*H*$_2$OH), 3.82(3H, s, OCH_3), 3.98(1H, t, *J*= 6.7 Hz, PhC*H*CH$_2$OH), 4.41(2H, d, *J*=5.5Hz, ArCHN), 6.74-6.86(6H, m, aromatic H), 7.04-7.15(7H, m, aromatic H). $[\alpha]_D$ +60.6° (*c*=0.94, EtOH). *Anal.* Calcd for $C_{26}H_{29}NO_3$: C, 77.39; H, 7.24; N, 3.47. Found: C, 77.11; H, 7.33; N, 3.17.

General Procedure for the Preparation of (*R,R*)-2,5-Diarylpyrrolidine (9a,b).

In the same manner as described for the preparation of (*R*)-**7**.

(*R,R*)-2,5-Bis(phenyl)pyrrolidine (9a):

Yellow oil. Yield, 60%. MS *m/z*; CI, 224(M^++1). ^{1}H-NMR ($CDCl_3$) δ: 1.85-1.99(2H, m, pyrrolidine H), 2.35-2.47(2H, m, pyrrolidine H), 3.75(1H, brs, NH), 4.61(2H, t, *J*=5.5Hz, PhCHN), 7.07-7.49(10H, m, aromatic H). $[\alpha]_D$ +80.6° (*c*=0.60, MeOH), identical with authentic sample.[12]

(*R,R*)-2,5-bis-(4-Methoxyphenyl)pyrrolidine (9b):

Colorless prisms, mp 54°C(hexane-ether). Yield, 42%. MS *m/z*; CI, 284(M^++1). ^{1}H-NMR($CDCl_3$) δ: 1.84-1.91(2H, m, pyrrolidine H), 2.04(1H, brs, NH), 2.30-2.39(2H, m, pyrrolidine H), 3.80(6H, s, OCH_3), 4.48 (2H, t, *J*=6.7Hz, PhCHN), 6.88(4H, d, *J*= 8.5Hz, aromatic H), 7.33(4H, d, *J*=8.5Hz, aromatic H). $[\alpha]_D$ +103.8° (*c*=0.87, MeOH). *Anal.* Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.06; H, 7.48; N, 4.78.

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