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SYNTHESIS OF C_2-SYMMETRICAL CHIRAL AROMATIC DIAMINES BY DIASTEREOSELECTIVE ADDITION TO BIS(1,3-OXAZOLIDINYL)AROMATICS WITH GRIGNARD REAGENTS

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Abstract – C_2-Symmetrical chiral bis(1,3-oxazolidinyl)aromatics were prepared by the condensation of aromatic dicarbaldehydes (*p*-benzene, *m*-benzene, 2,6-pyridine, 2,5-furan and 2,5-thiophene) with (*R*)-*N*-2,4,6-trimethoxybenzyl phenylglycinol (**1**). Bulky bis(1,3-oxazolidinyl)aromatics underwent diastereoselective addition with Grignard reagents to give new classes of C_2-symmetrical chiral diaminoaromatics in high yield and diastereoselectivity. The absolute configurations of bulky bis(1,3-oxazolidinyl)aromatics (**3**) and bis(*tert*-amino)aromatics (**10a**) were confirmed by X-Ray spectroscopy.

The nucleophilic addition of organometallic reagents to the C=N bond of imines provides an attractive method for obtaining chiral amine derivatives.[1] 1,3-Oxazolidine derivatives suggest that the reaction proceeds through an iminium ion as a reaction intermediate. We previously reported that 1,3-oxazolidine derived from (*R*)-*N*-2,4,6-trimethoxybenzylphenylglycinol (**1**) is an efficient chiral auxiliary for the diastereoselective addition of Grignard reagent to give the corresponding chiral amine in excellent yield and diastereoselectivity.[2] In this case, the use of a 2,4,6-trimethoxybenzyl (TMB) group as a nitrogen substituent was useful, since its bulkiness gave high diastereoselectivity in the addition and both introduction and removal were simple.

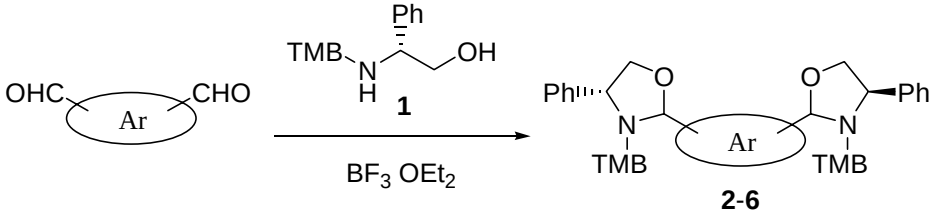
Enantiomerically pure C_2-symmetrical diamines play important roles as chiral auxiliaries in asymmetric synthesis[3] and as ligands[4] in asymmetric catalysis. The search for new methods for the asymmetric synthesis of these compounds is highly interesting. However, since most asymmetrical syntheses of enantiomerically pure diamines give vicinal diamines, a new method for the synthesis of other potential diamines is eagerly anticipated in a broad range of disciplines. Recently, we described an attractive

application of this procedure to develop a diastereoselective synthesis of C_2-symmetrical chiral aliphatic 1,4- and 1,5-diamines by the double addition of Grignard reagent to bis(1,3-oxazolidinyl)alkanes which involving the concomitant conversion of a tertiary diamine to a primary diamine.[5] Despite the fact that the synthesis of some C_2-symmetrical enantiomerically pure aliphatic 1,n-diamines (n>2) has been achieved in asymmetric synthesis,[5, 6] the diastereoselective synthesis of C_2-symmetrical chiral aromatic-joined diamines has not been studied. In this paper, we report the synthesis of novel C_2-symmetrical compounds, chiral bis(aminomethyl)aromatics, using the diastereoselective addition of Grignard reagent to bis(1,3-oxazolidinyl)aromatics.

RESULTS AND DISCUSSION

Preparation of bis(1,3-oxazolidinyl)aromatics

Our initial attempt to develop a simple synthesis of various bis(1,3-oxazolidinyl)aromatic compounds began with the condensation of aromatic dicarbaldehyde with **1**. *p*-Phthalaldehyde, *m*-phthalaldehyde, and *o*-phthalaldehyde, as arenes, and pyridine-2,6-dicarbaldehyde [7], furan-2,5-dicarbaldehyde [8], and thiophene-2,5-dicarbaldehyde[8], as heterocycles, were selected. Among the reaction conditions examined, we found that the condensation of dicarbaldehyde proceeded slowly by heating with a catalytic amount of BF_3 OEt_2 in CH_2Cl_2 or toluene under nitrogen. In this way, efficient condensations of 1 eq of aromatic dicarbaldehydes with 2 eq of **1** were quantitatively achieved, as shown in Scheme 1. However, the condensation of *o*-phthalaldehyde gave monocondensed product instead of the desired bis(oxazolidinyl)benzene due to steric hindrance. Although it was thought that these compounds may exist in equilibrium with regard to the 1,3-oxazolidine ring, only one diastereomer was observed in $CDCl_3$ by ^1H NMR. We previously reported that the 2- and 4-substituents on the 1,3-oxazolidine ring had a *cis* relationship by X-Ray crystallographic analysis.[9] Similarly, X-Ray crystallographic analysis of **3** confirmed the assigned structure and highlighted the *cis* relationship between the 2- and 4-substituents on each 1,3-oxazolidine ring. Thus, the absolute configurations at the new stereogenic carbons of **2**, **4**–**6** were established to be *R*. **2**–**6** turned out to be acid-sensitive and hence were considered unsuitable for further purification.



Ar = **2**: *p*-benzene, **3**: *m*-benzene, **4**: 2,6-pyridine, **5**: 2,5-furan, **6**: 2,5-thiophene
TMB = 2,4,6-trimethoxybenzyl

Scheme 1

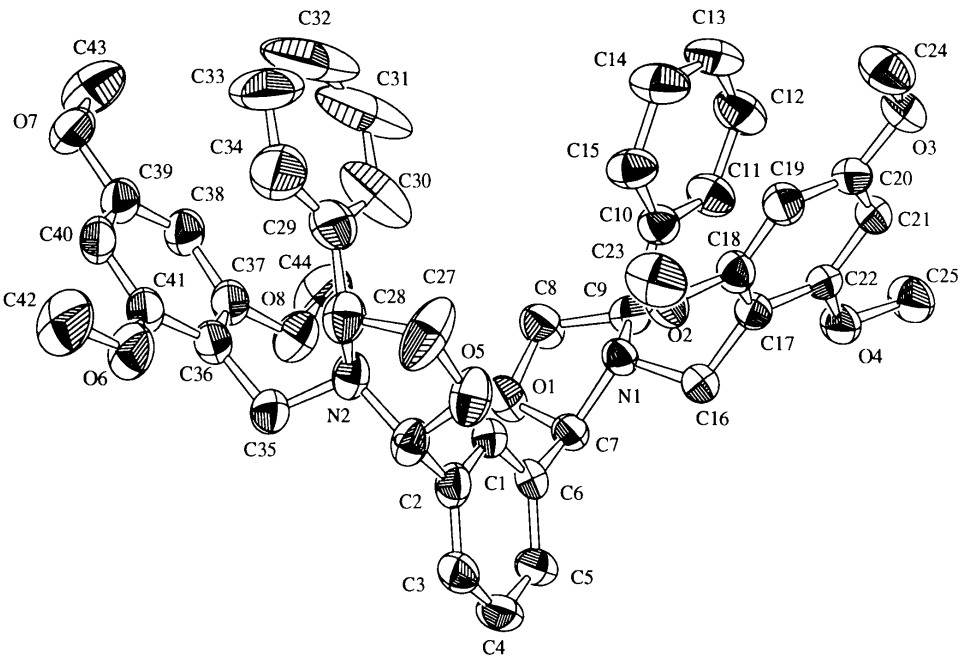


Figure 1 ORTEP drawing of **3**

Diastereoselective addition of Grignard reagents to bis(1,3-oxazolidinyl)aromatics

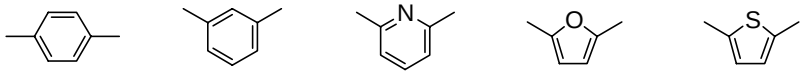
MeMgBr was chosen as a Grignard reagent for nucleophilic addition. The double addition of **2**–**6** with 8 eq of MeMgBr at room temperature for 1 d gave the corresponding diamines (**7**–**11**) in acceptable yields in two steps. The experimental results are summarized in Scheme 2 and Table. The diastereomer ratio of the crude products reflected excellent selectivity. Double arylations of bis(oxazolidinyl)benzenes (**2**, **3**) were also successful to give **12**, **13**. When **12a** and **13a** were treated with silica gel at room temperature in CH_2Cl_2, they decomposed to **12b** and **13b**; i.e., they underwent 2,4,6-trimethoxybenzyl substitution by silica gel purification. Addition of PhMgBr to bis(oxazolidinyl)heterocycles (**4**–**6**) did not give the desired compounds. The absolute configurations at the stereogenic centers of **10a** were confirmed to be *S*, *S* by X-Ray spectroscopy. Thus, the absolute configurations of **7a**–**9a** and **11a**–**13a** were evaluated. A reasonable mechanism for the addition of Grignard reagent to oxazolidine is consistent with previous reports.[9] Similarly, it is considered that the addition to each oxazolidine presumably proceeds *via* an iminium ion as an intermediate.

In conclusion, novel C_2-symmetrical chiral bis(oxazolidinyl)aromatic compounds were prepared from an enantiomerically pure (*R*)-phenylglycinol derivative and aromatic dicarboxaldehydes. The double addition of Grignard reagents to bis(oxazolidinyl)aromatics gave the corresponding tertiary diamines with excellent diastereoselectivities and yields. The application of this asymmetric reaction and chiral compounds may enable the construction of interesting aromatic structures for various fields.

2-**6** **7**-**13**

TMB = 2,4,6-trimethoxybenzyl
R = Me, Ph

a: X = TMB
b: X = H

Ar = 

2, **7**, **12** **3**, **8**, **13** **4**, **9** **5**, **10** **6**, **11**

Scheme 2

Table. Diastereoselective Addition to **2**-**6** with Grignard Reagents

Run	Substrate	R	Product	Yield(%)[a]	Diastereomer ratio[b]
1	**2**	Me	**7a**	80	88 : 12
2	**3**	Me	**8a**	89	>96 : 4
3	**4**	Me	**9a**	64	>96 : 4
4	**5**	Me	**10a**	63	>96 : 4
5	**6**	Me	**11a**	68	83 : 17
6	**2**	Ph	**12a** + **12b**	61 + 20	>96 : 4
7	**3**	Ph	**13a** + **13b**	67 + 15	>96 : 4

a Isolated yield for two steps.
b The ratios were measured by ^{1}H NMR spectra of the crude product.

EXPERIMENTAL

General Procedures. Melting points were measured with a Yanagimoto Micro melting Point apparatus without correction. IR spectra were recorded on a JASCO FT/IR-200, and major absorption is listed in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded at a JEOL GSX 270 instrument, and chemical sifts values are expressed in ppm relative to TMS (0.0 ppm) for ^{1}H and $CDCl_3$ (77.0 ppm) for ^{13}C in $CDCl_3$ solution. *J*-values are in Hz. MS and High-resolution MS were measured with a JEOL JMS 600 spectrometer in the chemical ionization (CI) with isobutane and electron impact (EI) method. Optical rotations were performed on a JASCO-DIP–1000 polarimeter. Elemental analyses were performed on a Perkin-Elmer 240-B instrument. Column chromatography was performed on silica gel (45–75 μm, Wakogel C-300). Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel F_{254} (Merck). Spot detection was performed with UV 254 nm, iodine vapor, or with a solution mixture of

p-anisaldehyde, sulfuric acid, acetic acid and ethanol (2.5:3.5:1:93). All solvents were freshly distilled before use.

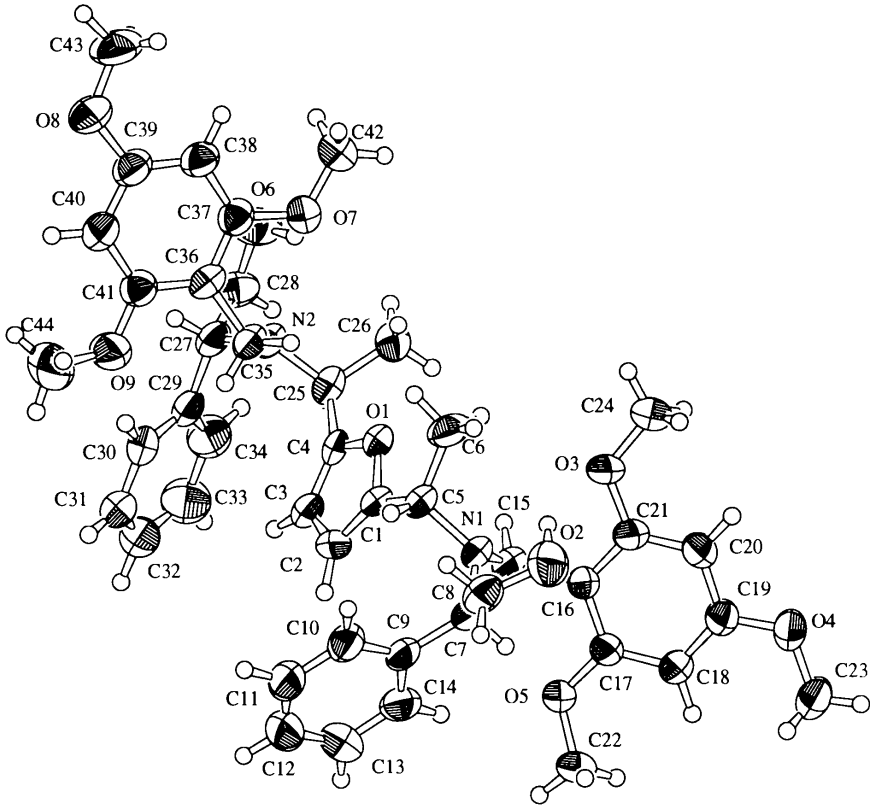


Figure 2 ORTEP drawing of **10a**

General Procedure for the Preparation of Bis(1,3-oxazolidinyl)aromatics (2–6). To a solution of (*R*)-*N*-2,4,6-trimethoxybenzylphenylglycinol (**1**) (634 mg, 2 mmol) and aromatic dicarbaldehydes (1 mmol) in anhydrous CH_2Cl_2 or toluene (10 mL) was added BF_3 diethyl etherate (14 mg, 0.1 mmol) under nitrogen. After being stirred at 60°C (oil bath temperature) for 3 d, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. These crude products but **2** were unstable and used without further purification.

1,4-Bis[(4*R*)-4-phenyl-3-(2,4,6-trimethoxybenzyl)-1,3-oxazolidin-2-yl]benzene (2): CH_2Cl_2 was used as reaction solvent. Pale yellow oil. $[\alpha]^{22}_D$ +13.1° (*c* 1.09, $CHCl_3$). MS *m/z*; EI, 732 (M^+), 181 (base peak). ^{1}H NMR ($CDCl_3$) δ 3.57 (s, 12 H), 3.65–3.83 (m, 6 H), 3.71 (s, 6 H), 4.13 (m, 4 H), 5.28 (s, 2 H), 5.90 (s, 4 H), 7.19–7.34 (m, 6 H), 7.50 (d, 4 H, *J*= 6.7 Hz), 7.63 (s, 4 H). ^{13}C NMR ($CDCl_3$) δ 39.75t, 54.76q, 55.07q, 65.80d, 73.92t, 89.59d, 95.77d, 105.74s, 126.75d, 127.25d, 127.45d, 127.76d, 141.20s, 141.36s, 159.61s, 160.48s. HRMS Calcd for $C_{44}H_{48}N_2O_8$: 732.3410. Found: 732.3401. IR ν (film): 2940, 2840,

1600, 1460, 1230, 1200, 1150 cm^{-1}.

1,3-Bis[(4*R*)-4-phenyl-3-(2,4,6-trimethoxybenzyl)-1,3-oxazolidin-2-yl]benzene (3): CH_2Cl_2 was used as reaction solvent. mp 131°C (AcOEt–hexane). $[\alpha]^{25}_D$ –1.3° (*c* 1.44, $CHCl_3$). MS *m/z*; EI, 732 (M^+), 181 (base peak). ^{1}H NMR ($CDCl_3$) δ 3.56 (s, 12 H), 3.69 (s, 6 H), 3.76–3.79 (m, 6 H), 4.13 (m, 4 H), 5.29 (s, 2 H), 5.88 (s, 4 H), 7.22–7.38 (m, 7 H), 7.50–7.53 (m, 4 H), 7.68 (dd, 2 H, *J*= 1.6, 7.6 Hz), 7.75 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 39.91t, 54.83q, 55.12q, 65.98d, 73.95t, 89.64d, 96.17d, 105.80s, 126.79d, 127.35d, 127.82d, 128.39d, 140.69s, 141.34s, 159.68s, 160.48s. Anal. Calcd for $C_{44}H_{48}N_2O_8$: C, 72.11; H, 6.60; N, 3.82. Found: C, 72.22; H, 6.61; N, 3.78. IR ν (film): 2940, 2840, 1600, 1460, 1230, 1200, 1150 cm^{-1}.

X-Ray Crystal Structure Determinations. A colorless prismatic crystal of $C_{44}H_{48}N_2O_8$ having approximate dimensions of 0.20 x 0.30 x 0.30 mm grown from AcOEt–hexane was used for the data collections of a Rigaku AFC7R diffractometer with graphite monochromated Cu-Kα radiation (λ = 1.54178 Å) and a rotating anode generator. Crystal data of **3**: *M* = 732.87; monoclinic space group $P2_1$ (#4), Z=2 with a=12.116(1) Å, b=10.0009(9) Å, c=16.891(1) Å, ß=104.759(7)°, V=1979.2(3) $Å^3$, and D_{calc}=1.230 g/cm^3. All calculations were performed using the teXsan program. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final R- and Rw-factors after full-matrix least-squares refinement were 0.092 and 0.133, respectively, based on 3143 observed reflections (I>–10.00σ(I)).

2,6-Bis[(4*R*)-4-phenyl-3-(2,4,6-trimethoxybenzyl)-1,3-oxazolidin-2-yl]pyridine (4): Toluene was used as reaction solvent. Brown oil. $[\alpha]^{25}_D$ –30.4° (*c* 0.84, $CHCl_3$). MS *m/z*; EI, 733 (M^+), 181 (base peak). ^{1}H NMR ($CDCl_3$) δ 3.57 (s, 12 H), 3.68 (s, 6 H), 3.64–3.78 (m, 6 H), 4.16 (m, 4 H), 5.34 (s, 2 H), 5.82 (s, 4 H), 7.21–7.63 (m, 6 H), 7.52 (m, 4 H), 7.63 (m, 1 H), 7.79 (d, 2 H, *J*= 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 40.03t, 54.93q, 55.13q, 66.39d, 74.12t, 89.56d, 96.91d, 105.71s, 120.94d, 126.96d, 127.45d, 127.83d, 136.09d, 141.04s, 158.92s, 159.50s, 160.42s. HRMS Calcd for $C_{43}H_{47}N_3O_8$: 733.3363. Found: 733.3340. IR ν (film): 2940, 2840, 1600, 1460, 1200, 1150 cm^{-1}.

2,5-Bis[(4*R*)-4-phenyl-3-(2,4,6-trimethoxybenzyl)-1,3-oxazolidin-2-yl]furan (5): Toluene was used as reaction solvent. Brown oil. $[\alpha]^{26}_D$ +12.4° (*c* 1.06, $CHCl_3$). MS *m/z*; EI, 722 (M^+), 181 (base peak). ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 12 H), 3.74 (s, 6 H), 3.56–3.89 (m, 6 H), 4.06 (m, 4 H), 5.40 (s, 2 H), 5.98 (s, 4 H), 6.52 (s, 2 H), 7.23–7.35 (m, 6 H), 7.51 (m, 4 H). ^{13}C NMR ($CDCl_3$) δ 39.79t, 55.02q, 55.20q, 65.41d, 73.39t, 88.94d, 89.76d, 105.53s, 107.89d, 127.01d, 127.52d, 127.87d, 140.52s, 155.02s, 159.81s, 160.62s. HRMS Calcd for $C_{42}H_{46}N_2O_9$: 722.3203. Found: 722.3213. IR ν (film): 2940, 2840, 1610, 1460, 1200, 1150 cm^{-1}.

2,5-Bis[(4*R*)-4-phenyl-3-(2,4,6-trimethoxybenzyl)-1,3-oxazolidin-2-yl]thiophene (6): Toluene was

used as reaction solvent. Brown oil. $[\alpha]^{26}_{D}$ +37.2° (*c* 0.91, $CHCl_3$). MS *m/z*; EI, 738 (M^+), 181 (base peak). ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 12 H), 3.73 (s, 6 H), 3.62–3.86 (m, 6 H), 4.07–4.13 (m, 4 H), 5.59 (s, 2 H), 5.95 (s, 4 H), 7.01 (s, 2 H), 7.16–7.39 (m, 6 H) 7.53–7.63 (m, 4 H). ^{13}C NMR ($CDCl_3$) δ 39.35t, 54.69q, 55.02q, 65.45d, 73.39t, 89.61d, 91.15d, 105.41s, 124.75d, 126.86d, 127.37d, 127.75d, 140.61s, 147.54s, 159.67s, 160.53s. HRMS Calcd for $C_{42}H_{46}N_2O_8S$: 738.2974. Found: 738.3002. IR ν (film): 2940, 2840, 1600, 1460, 1200, 1150 cm^{-1}.

General Procedure for Addition of Grignard Reagents Reaction to Bis(1,3-oxazolidinyl)aromatics (2–6).

To a solution of bis(1,3-oxazolidinyl)aromatics (1 mmol) in THF (10 mL) was added a solution of the commercially available Grignard reagent (8 eq) at rt under nitrogen. After being stirred at rt for 1–3 d, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel appropriate solvent as eluent to give the requisite compound in purity.

1,4-Bis{(1*S*)-[(*R*)-*N*-(2-hydroxy-1-phenylethyl)-*N*-(2,4,6-trimethoxybenzyl)amino]ethyl}benzene (7a): The mixture of **2** and MeMgBr was stirred for 1 d to give **7a** and the diastereomer (88 : 12). Separation by column chromatography on silica gel with CH_2Cl_2–MeOH (30:1~10:1) afforded **7a** in 80 % yield. Pale yellow viscous oil. $[\alpha]^{22}_{D}$ –283.6° (*c* 1.13, $CHCl_3$). MS *m/z*; EI, 733 (M^+–CH_2OH), 181 (base peak). ^{1}H NMR ($CDCl_3$) δ 1.30 (d, 6 H, *J*= 6.6 Hz), 3.53 (m, 2 H), 3.80 (s, 6 H), 3.82 (s, 12 H), 3.73–4.07 (m, 12 H), 6.11 (s, 4 H), 6.79 (s, 4 H), 7.05 (m, 4 H), 7.15 (m, 6 H). ^{13}C NMR ($CDCl_3$) δ 20.43q, 40.31t, 55.10q, 55.25q, 56.09d, 60.97t, 61.98d, 90.40d, 107.87s, 126.74d, 127.30d, 127.72d, 128.80d, 139.09s, 141.73s, 159.53s, 160.42s. IR ν (film): 3440, 3000, 2960, 2940, 1600, 1460, 1230, 1200, 1150, 1130, 760 cm^{-1}. Anal. Calcd for $C_{46}H_{56}N_2O_8$: C, 72.23; H, 7.38; N, 3.66. Found : C, 71.83; H, 7.32; N, 3.57.

1,3-Bis{(*S*)-[(*R*)-*N*-(2-hydroxy-1-phenylethyl)-*N*-(2,4,6-trimethoxybenzyl)amino]ethyl}benzene (8a): The mixture of **3** and MeMgBr was stirred for 3 d to give only **8a**. Separation by column chromatography on silica gel with CH_2Cl_2–MeOH (20:1) afforded **8a** in 89 % yield. Colorless viscous oil. $[\alpha]^{24}_{D}$ –250.9° (*c* 0.94, $CHCl_3$). MS *m/z*; EI, 764 (M^+), 181 (base peak). ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 6 H, *J*= 6.8 Hz), 1.73 (br, 2 H), 3.48 (m, 2 H), 3.80 (s, 6 H), 3.80 (S, 12 H), 3.74–4.05 (m, 10 H), 6.13 (S, 4 H), 6.50 (S, 1 H), 6.91 (s, 3 H), 7.02 (m, 4 H), 7.15 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 20.80q, 40.48t, 55.16q, 55.29q, 56.33d, 60.86t, 61.65d, 90.48d, 108.03s, 126.36d, 126.79d, 126.89d, 127.73d, 127.85d, 128.83d, 139.13s, 143.27s, 159.60s, 160.44s. Anal. Calcd for $C_{46}H_{56}N_2O_8$: C, 72.23; H, 7.38; N, 3.66. Found: C, 71.85; H, 7.44; N, 3.68. IR ν (film): 3430, 3000, 2960, 2940, 1610, 1590, 1460, 1230, 1210, 1150, 1130, 750 cm^{-1}.

2,6-Bis{(*S*)-[(*R*)-*N*-(2-hydroxy-1-phenylethyl)-*N*-(2,4,6-trimethoxybenzyl)amino]ethyl}pyridine (9a): The mixture of **4** and MeMgBr was stirred for 1 d to give only **9a**. Separation by column chromatography

on silica gel with CH_2Cl_2–MeOH (30:1~10:1) afforded **9a** in 64 % yield. Brown oil. $[\alpha]^{25}_D$ –324.4° (*c* 1.06, $CHCl_3$). MS *m/z*; EI, 765 (M^+), 181 (base peak). ^{1}H NMR ($CDCl_3$) δ 1.44 (d, 6 H, *J*= 6.9 Hz), 3.51(m, 2 H), 3.81 (s, 6 H), 3.81 (s, 12 H), 3.75–3.91 (m, 4 H), 4.03–4.09 (m, 8 H) 6.13 (s, 4 H), 6.39 (d, 2 H, *J*= 7.7 Hz), 6.80 (t, 1 H, *J*= 7.7 Hz), 6.90–7.08 (m, 10 H). ^{13}C NMR ($CDCl_3$) δ 19.41q, 39.79t, 55.14q, 55.29q, 56.88d, 60.56t, 61.35d, 90.48d, 107.86s, 120.94d, 126.51d, 127.53d, 128.51d, 134.47d, 139.41s, 159.69s, 160.41s, 160.47s. HRMS Calcd for $C_{45}H_{55}N_3O_8$: 765.3989. Found: 765.3904. IR ν (film): 3420, 2940, 1610, 1590, 1460, 1230, 1200, 1150, 1120 cm^{-1}.

2,5-Bis{(*S*)-[(*R*)-*N*-(2-hydroxy-1-phenylethyl)-*N*-(2,4,6-trimethoxybenzyl)amino]ethyl}furan (10a): The mixture of **5** and MeMgBr was stirred for 1 d to give only **10a**. Separation by column chromatography on silica gel with CH_2Cl_2–MeOH (30 : 1) afforded **10a** in 74 % yield. mp 157°C (CH_2Cl_2–hexane). $[\alpha]^{25}_D$ –250.4° (*c* 1.40, $CHCl_3$). MS *m/z*; EI, 754 (M^+), 181 (base peak). ^{1}H NMR ($CDCl_3$) δ 1.33 (d, 6 H, *J*= 7.1 Hz), 3.45 (m, 2 H), 3.78 (s, 12 H), 3.82 (s, 6 H), 3.69–3.97 (m, 10 H), 5.23 (s, 2 H), 6.14 (s, 4 H), 7.04–7.15 (m, 10 H). ^{13}C NMR ($CDCl_3$) δ 19.14q, 39.80t, 48.92d, 55.16q, 55.24q, 60.70t, 61.05d, 90.40d, 107.05d, 107.71s, 126.71d, 127.64d, 128.80d, 139.07s, 154.42s, 159.76s, 160.48s. HRMS Calcd for $C_{44}H_{54}N_2O_9$: 754.3829. Found: 754.3841. IR ν (film): 3450, 2940, 1610, 1590, 1460, 1230, 1200, 1150, 1120, 760 cm^{-1}. **X-Ray Crystal Structure Determinations.** A colorless prismatic crystal of $C_{44}H_{54}N_2O_9$ having approximate dimensions of 0.10 x 0.10 x 0.10 mm grown from CH_2Cl_2–hexane was used for the data collections of a Rigaku AFC7R diffractometer with graphite monochromated Cu-Kα radiation (λ = 1.54178 Å) and a rotating anode generator. Crystal data of **10a**: *M* = 754.92; monoclinic space group $P2_1$ (#4), Z=2 with a=10.260(1) Å, b=7.424(1) Å, c=26.522(1) Å, ß=95.167(6) °, V=2011.8(3) $Å^3$, and D_{calc}=1.246 g/cm^3. All calculations were performed using the teXsan program. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final R- and Rw-factors after full-matrix least-squares refinement were 0.095 and 0.139, respectively, based on 3266 observed reflections (I>–10.00σ(I)).

2,6-Bis{(*S*)-[(*R*)-*N*-(2-hydroxy-1-phenylethyl)-*N*-(2,4,6-trimethoxybenzyl)amino]ethyl}thiophene (11a): The mixture of **6** and MeMgBr was stirred for 1 d to give **11a** and the diastereomer (83 : 17). Separation by column chromatography on silica gel with CH_2Cl_2–MeOH (30 : 1) afforded **11a** in 68 % yield. Pale yellow oil. $[\alpha]^{25}_D$ –166.2° (*c* 1.13, $CHCl_3$). MS *m/z*; EI, 770 (M^+), 181 (base peak). ^{1}H NMR ($CDCl_3$) δ 1.41 (d, 6 H, *J*= 6.9 Hz), 3.42 (m, 2 H), 3.71 (s, 12 H), 3.82 (s, 6 H), 3.74–4.05 (m, 10 H), 6.12 (s, 4 H), 6.52 (s, 2 H), 6.84 (m, 4 H), 6.97–7.24 (m, 6 H). ^{13}C NMR ($CDCl_3$) δ 21.51q, 39.53t, 50.58d, 55.11q, 55.14q, 60.90d, 60.97t, 90.18d, 107.32s, 122.85d, 126.42d, 127.28d, 128.94d, 138.47s, 146.31s, 159.74s, 160.49s. HRMS Calcd for $C_{44}H_{54}N_2O_8S$: 770.3600. Found: 770.3553. IR ν (film): 3450, 2940,

1610, 1590, 1460, 1230, 1200, 1150, 1140, 760 cm^{-1}.

1,4-Bis{(*R*)-[(*R*)-*N*-(2-hydroxy-1-phenylethyl)-*N*-(2,4,6-trimethoxybenzyl)amino]phenylmethyl}benzene (12a): The mixture of **2** and PhMgBr was stirred for 3 d to give **12a** and **12b**. Separation by column chromatography on silica gel with CH_2Cl_2–MeOH (60:1) afforded **12a** and **12b** in 61 and 20 % yields. Pale yellow viscous oil. $[\alpha]^{22}_D$ –177.2° (*c* 1.02, $CHCl_3$). MS *m/z*; EI 888 (M^+), 64 (base peak). ^{1}H NMR ($CDCl_3$) δ 3.45 (br, 2 H), 3.59–4.24 (m, 10 H), 3.69 (s, 12 H), 3.73 (s, 6 H), 4.81 (s, 2 H), 5.92 (s, 4 H), 6.90–7.33 (m, 24 H). ^{13}C NMR ($CDCl_3$) δ 42.14t, 55.10q, 55.19q, 61.52t, 62.36d, 69.43d, 90.27d, 108.03s, 126.04d, 126.72d, 127.02d, 127.81d, 128.15d, 128.92d, 129.11d, 138.34s, 140.41s, 144.14s, 159.09s, 160.30s. Anal. Calcd for $C_{56}H_{60}N_2O_8$: C, 75.65; H, 6.80; N, 3.15. Found: C, 75.47; H, 6.81; N, 3.06. IR ν (film): 3460, 3000, 2940, 2840, 1600, 1460, 1230, 1200, 1150, 1140, 760, 700 cm^{-1}.

1,4-Bis{(*R*)-[(*R*)-*N*-(2-hydroxy-1-phenylethyl)amino]phenylmethyl}benzene (12b): Pale yellow oil. $[\alpha]^{22}_D$ –152.5° (*c* 0.91, $CHCl_3$). MS *m/z*; EI, 528 (M^+), 392 (base peak). ^{1}H NMR ($CDCl_3$) δ 2.51 (br, 4 H), 3.51–3.80 (m, 6 H), 4.70 (s, 2 H), 7.15–7.37 (m, 24 H). ^{13}C NMR ($CDCl_3$) δ 61.49d, 63.25d, 66.70t, 127.10d, 127.20d, 127.27d, 127.65d, 127.82d, 128.47d, 128.68d, 140.27s, 141.46s, 144.07s. HRMS Calcd for $C_{36}H_{36}N_2O_2$: 528.2776. Found: 528.2776. IR ν (film): 3400, 3030, 2930, 1600, 1490, 1450, 1050, 1030, 760, 700 cm^{-1}.

1,3-Bis{(*R*)-[(*R*)-*N*-(2-hydroxy-1-phenylethyl)-*N*-(2,4,6-trimethoxybenzyl)amino] phenylmethyl}benzene (13a): The mixture of **3** and PhMgBr was stirred for 2 d to give **13a** and **13b**. Separation by column chromatography on silica gel with CH_2Cl_2–MeOH (50:1~30:1) afforded **13a** and **13b** in 67 and 15 % yields. Pale yellow viscous oil. $[\alpha]^{24}_D$ –142.1° (*c* 1.41, $CHCl_3$). MS *m/z*; EI 888 (M^+), 103 (base peak), CI 889 (M^++1), 113 (base peak). ^{1}H NMR ($CDCl_3$) δ 3.44 (br, 2 H), 3.66–3.99 (m, 4 H), 3.63 (s, 12 H), 3.73 (s, 6 H), 4.09–4.26 (m, 6 H), 4.70 (s, 2 H), 5.85 (s 4 H), 6.92–7.24 (m, 24 H). ^{13}C NMR ($CDCl_3$) δ 41.70t, 54.99q, 55.21q, 61.37t, 62.22d, 71.15d, 90.16d, 108.25s, 126.03d, 126.65d, 126.84d, 127.09d, 127.86d, 128.18d, 129.20d, 129.48d, 137.74s, 143.01s, 144.00s, 158.88s, 160.21s. HRMS Calcd for $C_{56}H_{60}N_2O_8$: 888.4349. Found: 888.4338. IR ν (film): 3470, 3000, 2960, 2940, 2840, 1610, 1600, 1470, 1450, 1230, 1200, 1150, 1140, 760 cm^{-1}.

1,3-Bis{(*R*)-[(*R*)-*N*-(2-hydroxy-1-phenylethyl)amino]phenylmethyl}benzene (13b): Pale yellow oil. $[\alpha]^{24}_D$ –97.9° (*c* 1.13, $CHCl_3$). MS *m/z*; EI, 528 (M^+), 360 (base peak). ^{1}H NMR ($CDCl_3$) δ 3.44 (br, 4 H), 3.59–3.74 (m, 6 H), 4.69 (s, 2 H), 7.16–7.37 (m, 24 H). ^{13}C NMR ($CDCl_3$) δ 61.74d, 63.33d, 66.66t, 126.54d, 127.02d, 127.14d, 127.30d, 127.34d, 127.60d, 128.36d, 128.60d, 128.93d, 140.05s, 142.76s, 143.87s. HRMS Calcd for $C_{36}H_{36}N_2O_2$: 528.2776. Found: 528.2769. IR ν (film): 3390, 3030, 2930, 1600, 1490, 1450, 1150, 1140, 1050, 1030, 760 cm^{-1}.

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