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Synthesis of C_2-symmetrical chiral diamines: diastereoselective addition to bis(1,3-oxazolidinyl)alkanes with Grignard reagents

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Abstract

Asymmetric syntheses of C_2-symmetrical chiral 1,4- and 1,5-diamines with stereogenic centers adjacent to the nitrogen atom have been accomplished. Chiral diamines were prepared by diastereoselective alkylations of bisoxazolidine, which was derived from (*R*)-phenylglycinol. Methyl and phenyl Grignard reagents were employed as alkylating reagents. In addition, tertiary chiral diamines were readily converted to primary diamines in high yield. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Enantiomerically pure diamines are constituents of many natural products, pharmaceutical drugs, agricultural chemicals, polymers and functional materials in organic synthesis. Chiral platinum diamino complexes are being evaluated as antitumor agents that may substitute for cisplatin in reducing toxicity and circumventing drug resistance.[1] C_2-Symmetrical diamines serve as chiral auxiliaries and ligand building blocks for a variety of transition metal catalysts such as Cu,[2] Fe,[3] Os,[4] Pd,[5] Rh,[6] Ru,[7] Se[8] and Cr.[9] In recent years, metal complexes of salen Schiff bases have been reported to bind selectively with DNA.[10] Additionally, the utility of molecules with C_2-symmetrical 1,*n*-diamines ($n=3$–5) as HIV-protease inhibitors has been investigated.[11] Development of novel asymmetric synthesis methods is desirable for obtaining a variety of C_2-symmetrical diamines. Despite numerous studies describing the diastereoselective synthesis of C_2-symmetrical chiral 1,2-diamines by nucleophilic 1,2-addition to C=N bonds,[12] there is little information regarding the synthesis of chiral 1,*n*-diamine ($n>2$).[11b,g,13] Little is known about the diastereoselective synthesis of our target C_2-symmetrical chiral 1,*n*-diamine ($n=4$, 5). As more applications of these interesting compounds become feasible, more convenient and flexible methods for preparative synthesis of chiral 1,*n*-diamines will be required.

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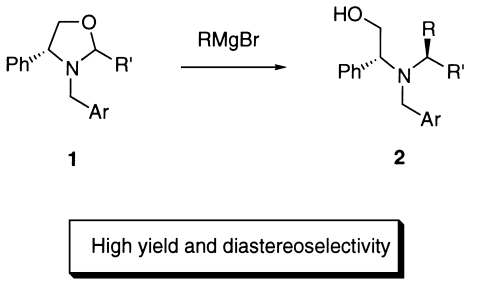
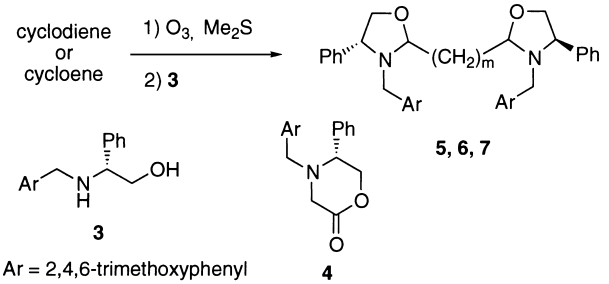
We reported that 1,3-oxazolidines **1**, synthesized easily by condensing (*R*)-*N*-alkylphenylglycinols with carbaldehydes, reacted with various Grignard reagents in highly stereoselective manner providing chiral amines **2** in a high chemical yield and enantiomeric excess (Scheme 1).[14] Similarly, the possible formation of bisoxazolidine by condensing 2 equivalents of (*R*)-*N*-2,4,6-trimethoxybenzylphenylglycinol **3** with 1 equivalent of dialdehyde prompted us to reinvestigate the diastereoselective addition of oxazolidines with Grignard reagents. Here, we describe the preparation of chiral diamines by the diastereoselective addition of bisoxazolidine as well as oxazolidine with Grignard reagents. We also explore the influence of chain length between the oxazolidines on the selectivity of our additions.



Scheme 1.

2. Results and discussion

Our approach to synthesis of C_2-symmetrical chiral 1,*n*-diamines ($n = 2$–6) required the preparation of bisoxazolidines. First, (*R*)-*N*-2,4,6-trimethoxybenzylphenylglycinol **3** as starting material was simply obtained in quantity from (*R*)-phenylglycinol as a chiral auxiliary in two steps. The preparation of dialdehydes except glyoxal was performed in situ by normal ozonolysis of cyclic dienes and enes in anhydrous methanol. After adding dimethyl sulfide at –78°C, (*R*)-*N*-2,4,6-trimethoxybenzylphenylglycinol **3** was added to the methanol solution to yield compounds **5**–**7** in one-pot syntheses (Scheme 2, Table 1). The condensation was successful despite carrying out the reaction in methanol. The condensation of **3** with glyoxal, however, yielded an unexpected morphorin-2-one derivative **4**, which was formed apparently by dehydration. The result of



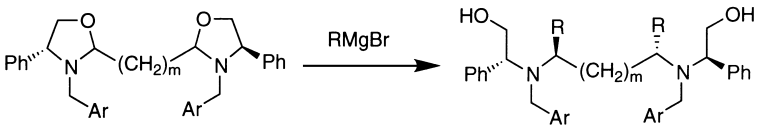
Scheme 2.

Table 1
Preparation of bis(1,3-oxazolidin-2-yl)alkanes

m	ene or diene	product	yield (%) [a]
0	$(CHO)_2$	**4**	75
1		-	0
2		**5**	89
3		**6**	97
4		**7**	90

[a] Isolated yield

1,4-cyclohexadiene ozonolysis was the complex mixture of products. Bisoxazolidines were found to be inseparable thermodynamic mixtures at the 2 position of the 1,3-oxazolidine ring. We previously reported that the relationship of two and four substituents of the 1,3-oxazolidine was assigned as *cis* by X-ray crystallographic analysis.[15] Thus, the absolute stereochemistry of the major bisoxazolidine was assigned as (2*R*,4*R*). The obtained bisoxazolidines **5**–**7** were unstable towards silica gel chromatography and were hence deemed unsuitable for further purification, but could be stored in the freezer in the absence of light without noticeable degradation.



5-7 **8-11**

Ar = 2,4,6-trimethoxyphenyl

Scheme 3.

Table 2
Diastereoselective addition of MeMgBr and PhMgBr to **5**–**7**

substrate	R	product	diastereoisomer ratio [a]	yield (%) [b]
5 (m=2)	Me	**8**	86 : 14	76
5 (m=2)	Ph	**9**	86 : 14	83
6 (m=3)	Me	**10**	86 : 14	80
6 (m=3)	Ph	**11**	90 : 10	86
7 (m=4)	Me	-	-	- [c]

[a] Determined by ^{1}H-NMR spectrum

[b] Isolated yield

[c] Not obtained for decomposition

Grignard reagents were chosen for the nucleophilic reaction component. Generally, to examine both aliphatic and aromatic reagents, commercially available MeMgBr and PhMgBr were employed. Double alkylations and arylations of bisoxazolidines **5**–**7** were carried out by the addition of 6 equivalents of Grignard reagent in THF at room temperature (Scheme 3, Table 2). Diastereoselective addition of Grignard reagent to compound **7** was not achieved due to decomposition. The diastereoisomeric ratio was confirmed by ^{1}H NMR spectroscopy of the crude product mixture, and only two isomers were detected. However, the minor diastereoisomers of **9**–**11** but not **8** were unsuccessfully isolated by chromatographic separation. Compound **9** yielded crystals suitable for X-ray crystallographic analysis (Fig. 1). Furthermore, the absolute configurations of the new stereogenic centers at C9 and C9* of **9** were confirmed to be of form (*R*,*R*). Consequently, the absolute stereochemistry of **11** was presumed to be of form (*R*,*R*,*R*,*R*).

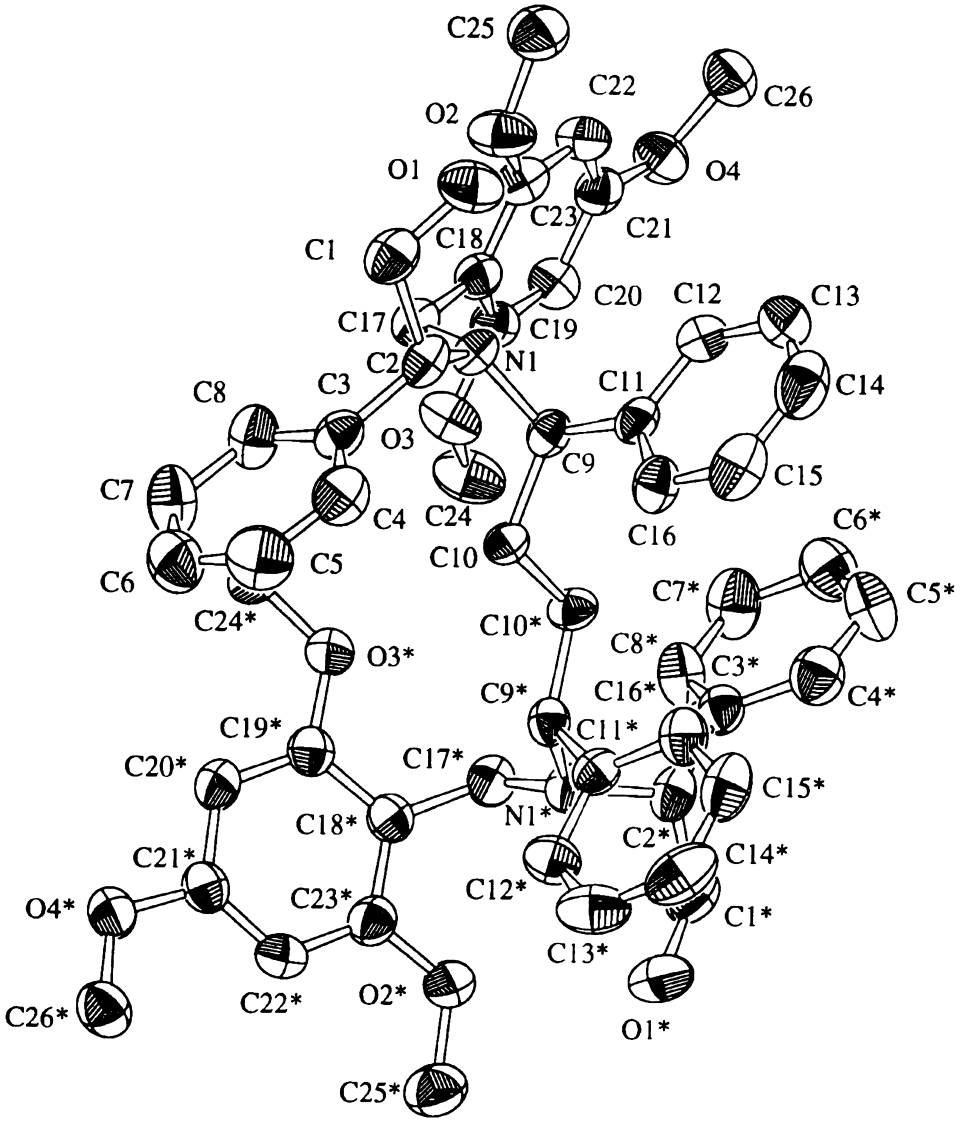


Figure 1. An ORTEP drawing of **9** with crystallographic numbering scheme

The origin of the diastereoselectivity of this reaction is likely to involve steric repulsion between the phenyl and 2,4,6-trimethoxybenzyl functional groups of each oxazolidine part, as we have described previously.[14f,15]

Transformation of tertiary to primary diamines is important for widening applications of these synthetically intriguing diamines. Efficient cleavage of 2,4,6-trimethoxybenzyl groups of **8**–**11** to the corresponding secondary diamines was achieved under TFA conditions in high yield. X-Ray analysis of a single crystal of **12** mono-hydrochloride was also performed and its absolute configurations at C1 and C4 were confirmed to be (*S*,*S*) (Fig. 2). Consequently, the absolute configurations of the new stereogenic centers of **8** and **10** were assumed to be (*S*,*S*). Subsequently, the auxiliary parts were efficiently removed from **12**–**15** by $Pb(OAc)_4$ oxidation[16] to give the desired primary chiral diamine derivatives **16**–**19** as the hydrochloride. Since purification of crude products **16** and **18** was difficult, benzoylation of **16** and **18** to the desired products **20** and **21** was easily achieved by a general method (Scheme 4).

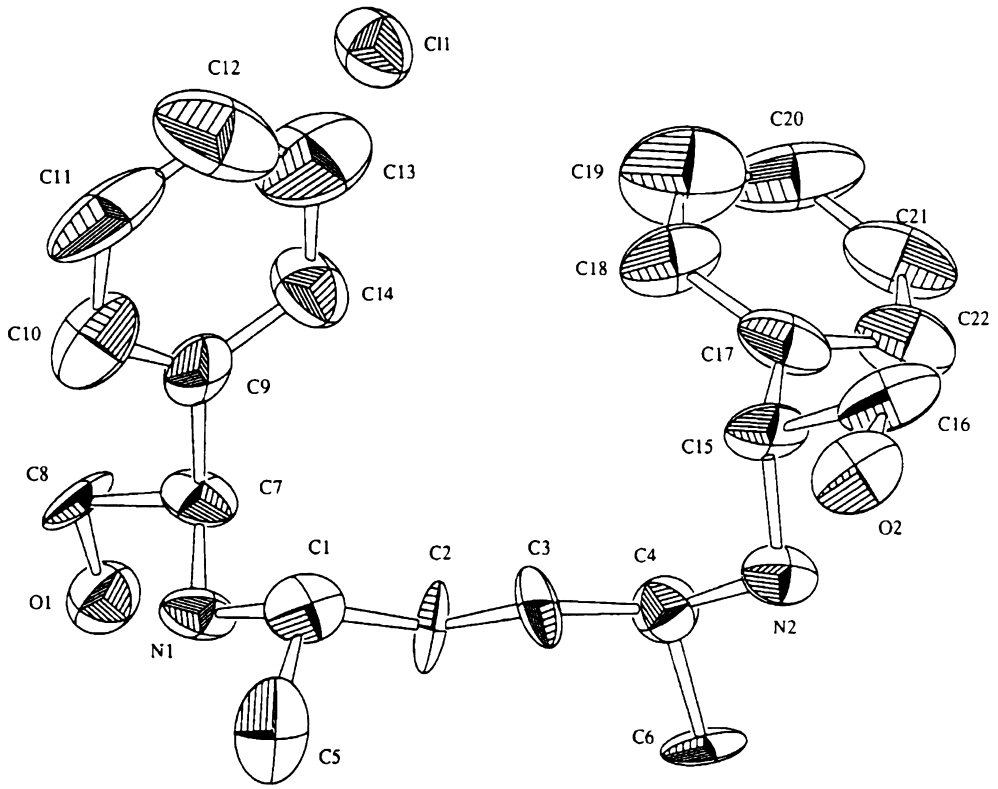
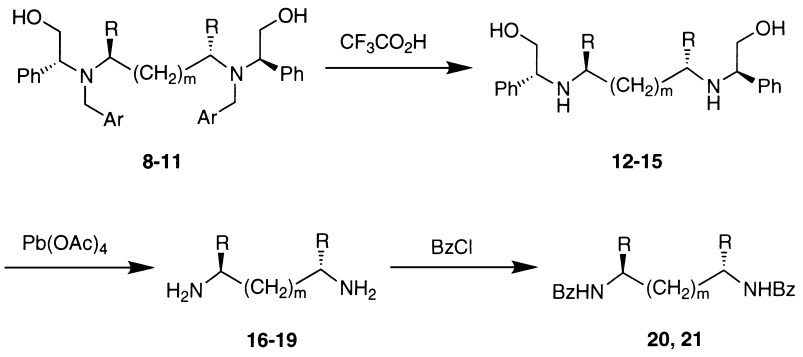


Figure 2. An ORTEP drawing of **12** HCl with crystallographic numbering scheme

In conclusion, we have studied the synthesis of C_2-symmetrical chiral diamines using double diastereoselective additions of Grignard reagents to bisoxazolidines. Diastereoselective additions proceed independently to each reaction site. The chiral tertiary diamines were easily and conveniently transformed to primary diamines. Our methodology is applicable to the stereocontrolled synthesis of C_2-symmetrical diamine derivatives.



m	R				
2	Me	**8**	**12**	**16**	**20**
2	Ph	**9**	**13**	**17**	
3	Me	**10**	**14**	**18**	**21**
3	Ph	**11**	**15**	**19**	

Scheme 4. Preparation of chiral diamines by removal of benzyl and auxiliary groups

3. Experimental

3.1. General procedures

Ozonolysis was performed on a Nippon Ozone ON-1-2 ozone generator through oxygen gas (50 Nl/h). 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 absorptions are listed in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL GSX 270 instrument, and chemical sift values are expressed in ppm relative to TMS (0.0 ppm) for ^1H and $CDCl_3$ (77.0 ppm) for ^{13}C in $CDCl_3$ solution or HDO (4.65 ppm) for ^1H and 1,4-dioxane (67.4 ppm) in D_2O solution. *J* values are in hertz. Mass spectra and high-resolution mass spectra were measured with a JEOL JMS 600 spectrometer in the chemical ionization (CI) with isobutane and electron impact 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). Tetrahydrofuran were distilled over potassium metal. All other solvent reactants were of the best commercial grade available and used without further purification unless noted.

*3.1.1. (*R*)-5-Phenyl-4-(2,4,6-trimethoxybenzyl)morpholin-2-one **4***

To a solution of 40% glyoxal in water solution (5.2 mL, 36 mmol) in MeOH (100 mL) was added (*R*)-2,4,6-trimethoxybenzylphenylglycinol **3** (3.17 g, 10 mmol) at room temperature. After being stirred overnight, the precipitation was filtered to give the crude product. The crude product was recrystallized with ethyl acetate to give (*R*)-5-phenyl-4-(2,4,6-trimethoxybenzyl)morpholin-2-one **4**

(2.67 g, 75%) as colorless needles, mp 165°C (AcOEt). $[\alpha]_D^{24}$ –50.3 (*c* 1.02, $CHCl_3$). MS *m*/*z*: CI, 358 (M^++1), 181 (base peak); EI, 357 (M^+), 181 (base peak). ^1H NMR ($CDCl_3$) δ 3.18 (d, 1H, J = 11.7 Hz), 3.22 (d, 1H, J = 18.3 Hz), 3.64 (d, 1H, J = 11.7 Hz), 3.69–3.73 (m, 2H), 3.77 (s, 6H), 3.80 (s, 3H), 4.23–4.33 (m, 2H), 6.09 (s, 2H), 7.33–7.53 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 46.18t, 53.40t, 55.27q, 55.42q, 63.78d, 73.20t, 90.35d, 104.94s, 128.39d, 128.59d, 137.02s, 159.88s, 160.94s. IR (film) cm^{-1}: 2960, 2840, 1740, 1500, 1460, 1420. Anal. calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.18; H, 6.55; N, 3.95.

3.2. General procedure for the preparation of bis(1,3-oxazolidinyl)alkane

A solution of cycloene (30 mmol) or cyclodiene (15 mmol) in anhydrous methanol (200 mL) was ozonized at –78°C. After 40 min, the solution turned blue to indicate the completed ozonolysis (excess ozone was removed by bubbling nitrogen into the solution). To this mixture was added dimethyl sulfide (3.3 mL, 45 mmol), and the mixture was stirred at room temperature for 30 min, added (*R*)-2,4,6-trimethoxybenzylphenylglycinol **3** (16.5 g, 52 mmol), and stirred again at the same temperature overnight. After removal of solvents by evaporation, the residue was dissolved in methylene chloride (60 mL) to wash off the byproduct dimethyl sulfoxide with water (3×40 mL). The solution was dried over Na_2SO_4 and concentrated under reduced pressure.

3.2.1. 1,4-Bis[(4R)-4-phenyl-3-(2,4,6-trimethoxybenzyl)1,3-oxazolidin-2-yl]butane ***5***

Yield 89%. Pale yellow needles; mp 36°C (ether–hexane). $[\alpha]_D^{24}$ –47.2 (*c* 1.00, $CHCl_3$). MS *m*/*z*: EI, 684 (M^+), 181 (base peak). ^1H NMR ($CDCl_3$) δ 1.79–2.88 (m, 4H), 3.52 (dd, 2H, J = 7.1, 7.9 Hz), 3.66 (s, 12H), 3.74 (s, 2H), 3.77 (s, 3H), 3.89 (t, 1H, J = 7.3 Hz), 3.99 (t, 1H, J = 7.3 Hz), 4.41 (q, 1H, J = 5.5 Hz), 6.00 (s, 2H), 7.18–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 28.80t, 40.04t, 55.18q, 55.55q, 65.95d, 73.60t, 89.88d, 95.15d, 106.27s, 126.62d, 127.33d, 127.67d, 141.75s, 159.84s, 160.48s. IR (film) cm^{-1}: 2940, 2840, 1600, 1460, 1230, 1200, 1150. HRMS calcd for $C_{40}H_{48}N_2O_8$: 684.3409. Found: 684.3414.

3.2.2. 1,5-Bis[(4R)-4-phenyl-3-(2,4,6-trimethoxybenzyl)-1,3-oxazolidin-2-yl]pentane ***6***

Yield 97%. Pale yellow needles; mp 38°C (ether–hexane). $[\alpha]_D^{23}$ –47.8 (*c* 1.00, $CHCl_3$). MS *m*/*z*: CI, 699 (M^++1), 181 (base peak); EI, 698 (M^+), 181 (base peak). ^1H NMR ($CDCl_3$) δ 1.59–1.78 (m, 6H), 3.54 (dd, 2H, J = 7.1, 7.7 Hz), 3.66 (s, 12H), 3.63–3.81 (m, 4H), 3.77 (s, 6H), 3.93 (dd, 2H, J = 7.1, 7.7 Hz), 4.02 (t, 2H, J = 7.1 Hz), 4.40 (m, 2H), 6.01 (s, 4H), 7.15–7.42 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 19.85t, 35.36t, 40.22t, 55.08q, 55.24q, 66.02d, 73.45t, 89.91d, 95.45d, 106.33s, 126.67d, 127.37d, 127.72d, 141.69s, 159.84s, 160.52s. IR (film) cm^{-1}: 2940, 2840, 1600, 1460, 1230, 1200, 1150. HRMS calcd for $C_{41}H_{50}N_2O_8$: 698.3567. Found: 698.3567.

3.2.3. 1,6-Bis[(4R)-4-phenyl-3-(2,4,6-trimethoxybenzyl)-1,3-oxazolidin-2-yl]hexane 7

Yield 90%. Colorless crystals; mp 130°C (methanol). $[\alpha]_D^{26}$ –50.4 (*c* 1.06, $CHCl_3$). MS *m*/*z*: EI, 712 (M^+), 181 (base peak). ^1H NMR ($CDCl_3$) δ 1.43–1.81 (m, 4H), 3.53 (t, 2H, J = 7.4 Hz), 3.64–3.80 (m, 4H), 3.67 (s, 12H), 3.77 (s, 6H), 3.93 (t, 2H, J = 7.4 Hz), 4.02 (t, 2H, J = 7.4 Hz), 4.39 (m, 2H), 6.01 (s, 4H), 7.17–7.41 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 24.92t, 35.05t, 40.28t, 55.07q, 55.22q, 66.09d, 73.40t, 89.92d, 95.38d, 106.33s, 126.71d, 127.34d, 127.74d, 141.63s, 159.81s, 160.53s. IR (film) 2940, 1610, 1590, 1460, 1150 cm^{-1}. HRMS calcd for $C_{42}H_{52}N_2O_8$: 712.3693. Found: 712.3711. Anal. calcd for $C_{42}H_{52}N_2O_8$: C, 70.76; H, 7.35; N, 3.93. Found: C, 70.42; H, 7.40; N, 4.01.

3.3. General procedure for addition of Grignard reagents to bis(1,3-oxazolidinyl)alkane

To a solution of bis(1,3-oxazolidinyl)alkane compounds **5** and **6** in THF (20 mL) was added dropwise a solution of the commercially available Grignard reagent (6 equivalents). After being stirred at room temperature for 1 to 2 days, the reaction mixture was quenched with water and the organic solution was decanted from the insoluble solid. The residue was extracted with CH_2Cl_2 (30 mL), then the extract solution was combined, dried over Na_2SO_4, and concentrated under reduced pressure to give crude products. The crude products were subjected to column chromatography on silica gel using the appropriate solvent as eluent to give the requisite compounds **8**–**11** in purity.

3.3.1. (2S,5S)-Bis[(R)-N-(2-hydroxy-1-phenylethyl)-N-(2,4,6-trimethoxybenzyl)]hexane-2,5-diamine **8**

A 3 mol/L solution of methylmagnesium bromide in Et_2O was added to **5** to give **8** and diastereoisomer (86:14) in 89% yield. Separation by column chromatography on silica gel with CH_2Cl_2:MeOH:NH_4OH (200:10:1) gave **8** as colorless needles; mp 72°C (ether–hexane). $[\alpha]_D^{20}$ –116.6 (*c* 1.00, $CHCl_3$). MS *m*/*z*: EI, 685 (M^+–CH_2OH), 181 (base peak). ^1H NMR ($CDCl_3$) δ 0.72 (m, 4H), 0.83 (d, 6H, $J=6.6$ Hz), 1.74 (br, 2H), 2.37 (m, 2H), 3.34 (m, 2H), 3.71 (s, 12H), 3.83 (s, 3H), 3.67–3.98 (m, 8H), 6.10 (s, 4H), 7.25–7.32 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 19.14q, 30.93t, 37.67t, 52.02d, 55.26q, 55.52q, 60.27t, 61.29d, 90.32d, 107.70s, 127.12d, 127.99d, 129.15d, 139.88s, 159.68s, 160.44s. Anal. calcd for $C_{42}H_{56}N_2O_8$: C, 70.36; H, 7.87; N, 3.91. Found: C, 70.06; H, 7.87; N, 4.02. IR (film): 3400, 2960, 2940, 1600 cm^{-1}. Diastereoisomer of **8**: colorless amorphous; $[\alpha]_D^{20}$ –108.6 (*c* 1.10, $CHCl_3$). MS *m*/*z*: EI, 716 (M^+). ^1H NMR ($CDCl_3$) δ 0.91 (d, 6H, $J=6.6$ Hz), 1.18–1.33 (m, 4H), 1.64 (br, 2H), 2.76 (m, 2H), 3.35 (m, 2H), 3.82 (s, 3H), 3.85 (s, 12H), 3.55–4.12 (m, 8H), 6.16 (s, 4H), 7.24–7.45 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 19.23q, 27.57t, 37.65t, 52.03d, 55.16q, 55.30q, 59.80t, 61.65d, 90.53d, 107.59s, 127.31d, 128.18d, 128.78d, 139.79s, 159.74s, 160.56s. IR (film): 3400, 2940, 2960, 1600 cm^{-1}. HRMS calcd for $C_{42}H_{56}N_2O_8$: 716.4036. Found: 716.4031.

3.3.2. (1R,4R)-Bis[(R)-N-(2-hydroxy-1-phenylethyl)-N-(2,4,6-trimethoxybenzyl)]-1,4-diphenylbutane-1,4-diamine **9**

A 2 mol/L solution of phenylmagnesium bromide in THF was added to **5** to give **9** and diastereoisomer (86:14) in 99% yield. Separation by column chromatography on silica gel with CH_2Cl_2:MeOH (100:1) gave **9** as colorless needles; mp 191–192°C (AcOEt–hexane). $[\alpha]_D^{25}$ –49.2 (*c* 0.98, $CHCl_3$). FAB–MS *m*/*z*, 841 (M^++1), 121(base peak). ^1H NMR ($CDCl_3$) δ 0.88–0.97 (m, 2H), 1.22–1.44 (m, 2H), 1.68 (br, 2H), 3.17 (m, 2H), 3.31 (m, 2H), 3.41 (m, 2H), 3.54 (s, 12H), 3.83 (s, 6H), 3.58–3.88 (m, 6H), 6.05 (s, 4H), 6.89 (m, 4H), 7.22–7.33 (m, 16H). ^{13}C NMR ($CDCl_3$) δ 26.70t, 38.43t, 55.06q, 55.21q, 60.73t, 61.04d, 61.47d, 90.23d, 107.52s, 126.41d, 127.01d, 127.67d, 127.95d, 128.76d, 129.17d, 139.78s, 142.64s, 159.65s, 160.53s. Anal. calcd for $C_{52}H_{60}N_2O_8$: C, 74.26; H, 7.19; N, 3.33. Found: C, 74.23; H, 7.13; N, 3.29. IR (film): 3460, 2940, 1600 cm^{-1}.

3.3.3. (2S,6S)-Bis[(R)-N-(2-hydroxy-1-phenylethyl)-N-(2,4,6-trimethoxybenzyl)]heptane-2,6-diamine **10**

A 3 mol/L solution of methylmagnesium bromide in Et_2O was added to **6** to give **10** and diastereoisomer (86:14) in 94% yield. Separation by column chromatography on silica gel with CH_2Cl_2:MeOH:NH_4OH (150:10:1) gave **10** as colorless needles; mp 160°C (AcOEt–hexane). $[\alpha]_D^{22}$

–181.9 (*c* 1.05, $CHCl_3$). MS *m/z*: EI, 699 (M^+–CH_2OH), 181 (base peak). ^1H NMR ($CDCl_3$) δ 0.55 (m, 6H), 1.03 (d, 6H, $J=7.3$ Hz), 1.59 (br, 2H), 2.58 (m, 2H), 3.31 (dd, 2H, $J=3.6$, 9.1 Hz), 3.80 (s, 12H), 3.82 (s, 3H), 3.66–3.92 (m, 8H), 6.14 (s, 4H), 7.29 (s, 10H). ^{13}C NMR ($CDCl_3$) δ 19.10q, 26.15t, 32.46t, 37.47t, 51.68d, 55.20q, 55.25q, 59.91t, 61.37d, 90.38d, 107.51s, 127.29d, 128.04d, 129.02d, 139.51s, 159.74s, 160.54s. IR (film): 3440, 2960, 2940, 1600, 1460, 1420, 1230, 1200, 1150, 1130 cm^{-1}. Anal. calcd for $C_{43}H_{58}N_2O_8$: C, 70.66; H, 8.00; N, 3.83. Found: C, 70.36; H, 8.0; N, 3.73.

*3.3.4. (1*R*,5*R*)-Bis[(*R*)-*N*-(2-hydroxy-1-phenylethyl)*-N*-(2,4,6-trimethoxybenzyl)]-1,5-diphenylpentane-1,5-diamine **11***

A 2 mol/L solution of phenylmagnesium bromide in THF was added to **6** to give **11** and diastereoisomer (90:10) in 99% yield. Separation by column chromatography on silica gel with CH_2Cl_2:MeOH (50:1) gave **11** as colorless needles; mp 219–220°C (AcOEt–hexane). $[\alpha]_D^{21}$ –172.5 (*c* 1.01, $CHCl_3$). FAB–MS *m/z*, 854 (M^+), 183 (base peak). ^1H NMR ($CDCl_3$) δ 0.50 (m, 2H), 0.62 (m, 2H), 1.49 (m, 2H), 1.58 (br, 2H), 3.23 (dt, 2H, $J=4.6$, 9.9 Hz), 3.49–3.66 (m, 4H), 3.55 (s, 12H), 3.81 (s, 6H), 3.76–3.81 (m, 2H), 3.94–4.03 (m, 4H), 6.06 (s, 4H), 6.92 (m, 4H, $J=5.77$ Hz), 7.17–7.43 (m, 16H). ^{13}C NMR ($CDCl_3$) δ 24.82t, 25.33t, 37.53t, 55.11q, 55.16q, 59.06d, 60.31t, 60.83d, 90.30d, 107.17s, 126.25d, 127.44d, 127.90d, 128.33d, 128.92d, 129.06d, 140.04s, 141.35s, 159.79s, 160.59s. Anal. calcd for $C_{53}H_{62}N_2O_8$: C, 74.45; H, 7.31; N, 3.28. Found: C, 74.23; H, 7.34; N, 3.20. IR (film): 3460, 2940, 1600, 1150, 1140 cm^{-1}.

3.4. General procedure for removal of 2,4,6-trimethoxybenzyl to tertiary diamines

To a solution of tertiary amines **8**–**11** in TFA was stirred for 1 to 2 days. The reaction mixture was alkalized with 1 mol/L NaOH solution, extracted with CH_2Cl_2 for three times, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure, followed by column chromatography on silica gel using the appropriate solvent as eluent to give the corresponding secondary amines **12**–**15** in purity.

*3.4.1. (2*S*,5*S*)-Bis[(*R*)-*N*-2-hydroxy-1-phenylethyl]hexane-2,5-diamine **12***

The reaction was performed as described in general procedures by stirring TFA (60 mL) and tertiary amine **8** (4.80 g, 6.7 mmol) at room temperature for 2 days. Column chromatography on silica gel with CH_2Cl_2:MeOH, 6:1–1:1, gave 2.05 g (86%) of the title compound as colorless needles; mp 46°C (ether–hexane). $[\alpha]_D^{24}$ –103.5 (*c* 1.16, $CHCl_3$). MS *m/z*: EI, 356 (M^+), 308 (base peak). ^1H NMR ($CDCl_3$) δ 0.97 (d, 6H, $J=6.4$ Hz), 1.33–1.46 (m, 4H), 2.53 (br, 4H), 2.60 (m, 2H), 3.47 (dd, 2H, $J=8.7$, 10.7 Hz), 3.66 (dd, 2H, $J=4.4$, 10.7 Hz), 3.85 (dd, 2H, $J=4.4$, 8.7 Hz), 7.23–7.37 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 21.44q, 30.90t, 50.31d, 61.97d, 66.67t, 127.12d, 127.49d, 128.61d, 141.40s. IR (film): 3300, 2930 cm^{-1}. HRMS calcd for $C_{22}H_{32}N_2O_2$: 356.2464. Found: 356.2495. **12** Monohydrochloride; mp 223°C (EtOH–acetone). Anal. calcd for $C_{22}H_{33}N_2O_2Cl$: C, 67.24; H, 8.46; N, 7.13. Found: C, 67.06; H, 8.57; N, 7.16.

*3.4.2. (1*R*,4*R*)-Bis[(*R*)-*N*-2-hydroxy-1-phenylethyl]-1,4-diphenylbutane-1,4-diamine **13***

The reaction was performed as described in general procedures by stirring TFA (3 mL) and tertiary amine **9** (0.44 g, 0.53 mmol) at room temperature for 1 day. Column chromatography on silica gel with CH_2Cl_2:MeOH, 20:1, gave 0.24 g (96%) of the title compound as a yellow oil. $[\alpha]_D^{24}$ –63.3 (*c* 1.83, $CHCl_3$). MS *m/z*: EI, 480 (M^+), 106 (base peak). ^1H NMR ($CDCl_3$) δ 1.40–1.74 (m,

4H), 2.32 (br, 4H), 3.39–3.74 (m, 8H), 7.05–7.27 (m, 20H). ^{13}C NMR ($CDCl_3$) δ 32.14t, 59.72d, 61.06d, 65.56t, 127.01d, 127.07d, 127.12d, 127.34d, 128.40d, 128.43d, 140.99s, 142.64s. IR (film): 3340 cm^{-1}. HRMS calcd for $C_{32}H_{36}N_2O_2$: 480.2776. Found: 480.2759.

3.4.3. (2S,6S)-Bis[(R)-N-2-hydroxy-1-phenylethyl]heptane-2,6-diamine ***14***

The reaction was performed as described in general procedures by stirring TFA (20 mL) and tertiary amine **10** (4.89 g, 6.7 mmol) at 50°C for 1 day. Column chromatography on silica gel with CH_2Cl_2:MeOH, 8:1, gave 2.49 g (99%) of the title compound as a yellow oil. $[\alpha]_D^{22}$ –92.0 (*c* 1.08, $CHCl_3$). MS *m*/*z*; EI, 370 (M^+), 339 (base peak). ^{1}H NMR ($CDCl_3$) δ 0.97 (d, 6H, J = 6.43 Hz), 1.30–1.46 (m, 6H), 2.63 (br, 6H), 3.48 (dd, 2H, J = 8.73, 10.71 Hz), 3.67 (dd, 2H, J = 4.45, 10.71 Hz), 3.84 (dd, 2H, J = 4.45, 8.73 Hz), 7.25–7.38 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 21.23t, 21.75q, 36.57t, 50.52d, 62.17d, 66.45t, 127.06d, 127.48d, 128.59d, 141.40s. HRMS calcd for $C_{23}H_{34}N_2O_2$: 370.2620. Found: 370.2638. IR (film): 3300, 2930, 1600, 1490, 1450, 1380, 1060, 1020, 760, 700 cm^{-1}.

3.4.4. (1R,5R)-Bis[(R)-N-2-hydroxy-1-phenylethyl]-1,5-diphenylpentane-1,5-diamine ***15***

The reaction was performed as described in general procedures by stirring TFA (50 mL) and tertiary amine **11** (4.60 g, 5.38 mmol) at room temperature for 2 days. Column chromatography on silica gel with CH_2Cl_2:MeOH, 20:1, gave 2.51 g (94%) of the title compound as a yellow oil. $[\alpha]_D^{31}$ –53.1 (*c* 1.11, EtOH). MS *m*/*z*, (CI) 495 (M^++1, base peak). ^{1}H NMR ($CDCl_3$) δ 1.07 (m, 2H), 1.60 (m, 2H), 1.73 (m, 2H), 2.32 (br, 4H), 3.42–3.75 (m, 8H), 7.05–7.29 (m, 20H). ^{13}C NMR ($CDCl_3$) δ 22.39t, 36.62t, 60.00d, 61.24d, 65.40t, 126.97d, 127.02d, 127.31d, 128.30d, 128.42d, 141.2s, 143.94s. HRMS calcd for $C_{33}H_{39}N_2O_2$: 495.3011. Found: 495.3040. IR (film): 3390, 2930 cm^{-1}.

3.5. General procedure for the preparation of chiral diamines by removal of auxiliary

To a solution of secondary amines **12**–**15** (1 mmol) in CH_2Cl_2 (10 mL) and MeOH (5 mL) was added $Pb(OAc)_4$ (3 equivalents) at 0°C. After being stirred for 5 min, the reaction mixture was alkalized with 1 mol/L NaOH solution, filtrated through Celite, extracted with CH_2Cl_2, and evaporated under reduced pressure. The residue was dissolved in ether (10 mL) and 6 mol/L HCl (10 mL). After vigorous stirring for 16 h, the ether was removed and the residue washed twice with CH_2Cl_2 (20 mL each). The acidic solution was evaporated in vacuo to give the expected crude product as salt **16**–**19**.

3.5.1. (2S,5S)-Hexane-2,5-diamine dihydrochloride ***16***

The crude title compound was prepared in 84% yield according to general procedures. ^{1}H NMR (D_2O) δ 0.97 (d, 6H, J = 6.6 Hz), 1.30–1.47 (m, 4H), 3.06 (m, 2H), 2.53 (br, 4H). ^{13}C NMR (D_2O include dioxane) δ 18.15q, 30.48t, 48.15d.

3.5.2. (1R,4R)-1,4-Diphenylbutane-1,4-diamine dihydrochloride ***17***

The crude title compound prepared in 81% yield according to general procedures was recrystallized with 2-propanol–AcOEt to give a hygroscopic solid **17**. $[\alpha]_D^{24}$ –19.06 (*c* 1.19, EtOH). MS *m*/*z*, (EI) 240 (M^+), 223 (base peak). ^{1}H NMR (D_2O) δ 1.55–1.68 (m, 2H), 1.90–2.00 (m, 2H), 4.22 (dd, 2H, J = 4.0, 10.2 Hz), 4.65 (br, 6H), 7.16–7.20 (m, 4H) 7.33–7.36 (m, 6H). ^{13}C NMR (D_2O) δ 30.27t, 55.56d, 128.13d, 130.28d, 130.49d, 135.90s. HRMS calcd for $C_{16}H_{20}N_2$: 240.1626. Found: 240.1603. IR (film): 2930 cm^{-1}.

3.5.3. (2S,6S)-Heptane-2,6-diamine dihydrochloride ***18***

The crude title compound was prepared in 99% yield according to general procedures. ^{1}H NMR (D_2O) δ 1.17 (d, 6H, $J=6.6$ Hz) 1.27–1.63 (m, 6H) 3.26 (m, 2H). ^{13}C NMR (D_2O include dioxane) δ 18.46q, 21.57t, 34.26t, 48.40d.

3.5.4. (1R,5R)-1,5-Diphenylpentane-1,5-diamine dihydrochloride ***19***

The crude title compound prepared in 83% yield according to general procedures was recrystallized with 2-propanol–AcOEt to give a hygroscopic solid **19**. $[\alpha]_D^{24}$ –25.6 (*c* 2.59, EtOH). MS *m*/*z*, (EI) 254 (M^+), 106 (base peak). ^{1}H NMR (D_2O) δ 0.84–0.98 (m, 2H), 1.84–1.96 (m, 4H), 4.09 (dd, 2H, $J=6.4$, 9.2 Hz), 4.65 (s, 6H), 7.16–7.32 (m, 10H). ^{13}C NMR (D_2O include dioxane) δ 21.97t, 33.01t, 55.77d, 128.16d, 130.15d, 130.23d, 136.30s. HRMS calcd for $C_{17}H_{22}N_2$: 254.1783. Found: 254.1760. IR (film): 2940 cm^{-1}.

3.6. General procedure for the benzamidations of chiral diamines

To a solution of primary amines **16** and **18** (1 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (20 equivalents) and benzoyl chloride (3 equivalents) at 0°C. After being stirred for 20 h at room temperature, the reaction mixture was washed with a saturated solution of NH_4Cl. The organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to give the dibenzoyl diamines **20** and **21** in purity.

3.6.1. (2S,5S)-N,N′-Dibenzoylhexane-2,5-diamine ***20***

The reaction was performed as described in general procedures. Column chromatography on silica gel with CH_2Cl_2:MeOH, 30:1, gave the title compound in 86% yield as colorless needles. Mp 216°C (CH_2Cl_2). $[\alpha]_D^{24}$ +5.4 (*c* 0.36, $CHCl_3$). MS *m*/*z*: EI, 324 (M^+), 148 (base peak). ^{1}H NMR ($CDCl_3$) δ 1.27 (d, 6H, $J=6.6$ Hz), 1.66 (d, 4H), 4.22 (m, 2H), 5.99 (d, 2H, $J=8.4$ Hz), 7.38–7.51 (m, 6H), 7.74 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 21.13q, 33.80t, 45.79d, 126.82d, 128.53d, 131.36d, 134.73s, 166.73s. IR (KBr): 3310, 3070, 2960, 1630, 1530 cm^{-1}. Anal. calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.84; H, 7.46; N, 8.66.

3.6.2. (2S,6S)-N,N′-Dibenzoylheptane-2,6-diamine ***21***

The reaction was performed as described in general procedures. Column chromatography on silica gel with CH_2Cl_2:MeOH, 40:1, gave in 54% yield of the title compound as colorless needles. Mp 191°C (AcOEt). $[\alpha]_D^{25}$ +67.3 (*c* 0.98, $CHCl_3$). MS *m*/*z*: EI, 338 (M^+), 105 (base peak). ^{1}H NMR ($CDCl_3$) δ 1.26 (d, 6H, $J=6.6$ Hz), 1.43–1.76 (m, 6H), 4.22 (m, 2H), 6.21 (d, 2H, $J=7.9$ Hz), 7.28 (m, 4H), 7.42 (m, 2H), 7.65 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 21.81q, 22.53t, 36.52t, 45.08d, 126.90d, 128.36d, 131.10d, 134.76s, 167.49s. IR (KBr): 3310, 2940, 1630, 1530 cm^{-1}. Anal. calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.24; H, 7.70; N, 7.98.

3.7. X-Ray crystal structure determinations

3.7.1. (1R,4R)-Bis[(R)-N-(2-hydroxy-1-phenylethyl)-N-(2,4,6-trimethoxybenzyl)]-1,4-diphenylbutane-1,4-diamine ***9***

A colorless prismatic single crystal, having approximate dimensions of 0.30×0.30×0.40 mm, grown from AcOEt–hexane was used for the data collections of a Rigaku AFC7R diffractometer

with graphite monochromated Cu-Kα radiation ($\lambda = 1.54178$ Å) and a rotating anode generator. Crystal data of **9**: $C_{26}H_{30}NO_4$; $M = 420.53$; trigonal space group $P3_121$ (#152), $Z = 6$ with $a = 11.0415(5)$ Å, $c = 31.6140(7)$ Å, $V = 3337.8(3)$ Å^3, and $D_{calc} = 1.255$ g/cm^3. All calculations were performed using the teXsan program.[17] The structure was solved by direct methods[18] and expanded using Fourier techniques.[19] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final R- and R_w-factors after full-matrix least-squares refinement were 0.047 and 0.052, respectively, based on 1716 observed reflections ($I > 3.00\sigma(I)$).

3.7.2. (2S,5S)-Bis[(R)-N-2-hydroxy-1-phenylethylhexane-2,5-diamine ***12*** *monohydrochloride*

A colorless prismatic single crystal, having approximate dimensions of 0.10×0.10×0.20 mm, grown from EtOH–acetone was used for the data collections of a Rigaku AFC7R diffractometer with graphite monochromated Cu-Kα radiation ($\lambda = 1.54178$ Å) and a rotating anode generator. Crystal data of **10a** monohydrochloride: $C_{22}H_{33}N_2O_2Cl$; $M = 392.97$; orthorhombic space group $P2_12_12_1$ (#19), $Z = 4$ with $a = 11.3949(9)$ Å, $b = 17.7701(7)$ Å, $c = 11.2061(9)$ Å, $V = 2269.1(2)$ Å^3, and $D_{calc} = 1.150$ g/cm^3. All calculations were performed using the teXsan program.[17] The structure was solved by heavy-atom Patterson methods[20] and expanded using Fourier techniques.[19] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final R- and R_w-factors after full-matrix least-squares refinement were 0.074 and 0.042, respectively, based on 997 observed reflections ($I > 3.00\sigma(I)$).

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