STEREOCONTROLLED ADDITION OF GRIGNARD REAGENTS TO CHIRAL 1,3-OXAZOLIDINES HAVING *N*-METHOXYBENZYL GROUPS : EFFECT OF *N*-SUBSTITUENT IN DIASTEREOSELECTIVITY

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Abstract -------- Chiral 1,3-oxazolidines having various *N*-methoxybenzyl groups were synthesized from (*R*)-phenylglycinol in three steps. The reactions of chiral 1,3-oxazolidines with Grignard reagents proceeded gently to give the corresponding chiral amines in quantitative yield and high diastereoselectivity. The best results regarding diastereoselectivity were achieved using a chiral 1,3-oxazolidine having *N*-2,4,6-trimethoxybenzyl moiety. These nitrogen functional groups could be easily removed from the chiral amines using TFA.

INTRODUCTION

The diastereoselective addition of organometallic reagents to the C=N bond of chiral imines and their derivatives is extremely useful for the asymmetric synthesis of chiral amines.[1] We previously described a synthetic method for the stereoselective preparation of both amine enantio- and diastereomers starting from a single enantiomeric source, (*R*)-phenylglycinol, using the diastereoselective addition of Grignard reagents to chiral imines and 1,3-oxazolidines.[2] The addition to chiral imines gives excellent diastereoselectivity (88-99% de). In contrast, that to 1,3-oxazolidines gives much lower diastereoselectivity (32-82% de). On the other hand, the stereospecificity of 1,3-oxazolidines using Grignard reagents has suggested that *N*-substitution of the 1,3-oxazolidine plays an important role in the appearance of diastereoselectivity.[3] Recently, we reported that diastereoselectivity can be improved by using chiral 1,3-oxazolidines having bulkier *N*-diphenylmethyl substituents.[4] Unfortunately, the diphenylmethyl substituent near the reactive site proved to be too bulky for the reaction to proceed energetically (5-19 d). To identify a more effective *N*-substitution, we examined diastereoselective addition to chiral 1,3-oxazolidines having various *N*-methoxybenzyl substituents using Grignard reagents. The methoxybenzyl moiety functions as a removable stereochemical controlling group.

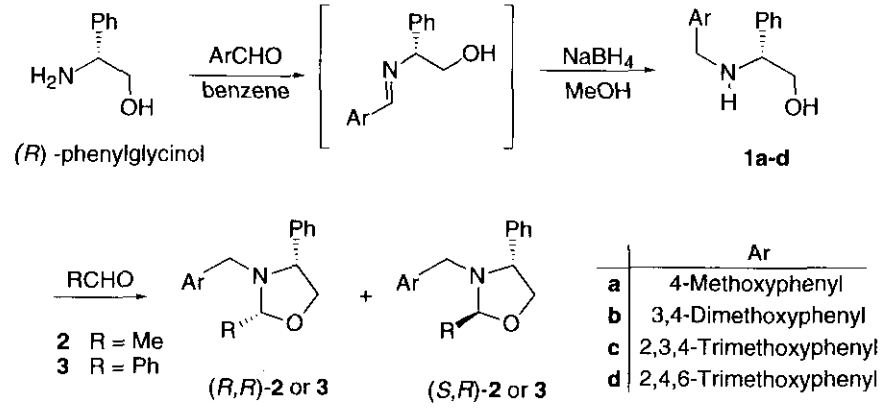
RESULTS AND DISCUSSION

Preparation of *N*-Methoxybenzyl-1,3-oxazolidines (2a-d, 3a-d) from (*R*)-Phenylglycinol

1,3-Oxazolidines were selected to develop this process in the expectation that they would be equivalent to

an imine and would give a structurally fascinating quaternary iminium-alkoxide salt intermediate. They were prepared by two condensations and one reduction as follows.

The dehydration condensation of (*R*)-phenylglycinol with some aromatic aldehydes (4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, 2,3,4-trimethoxybenzaldehyde, 2,4,6- trimethoxybenzaldehyde) in benzene with the azeotropic removal of water provided the anticipated imines. The products were considered to be an equilibrium mixture of the imine form and the 1,3-oxazolidine form in solution, as described previously.[2,4] The crude imines dissolved in methanol were reduced with $NaBH_4$ to give *N*-methoxybenzylphenylglycinols (**1a-d**) as crystals in quantitative yield.



Scheme 1

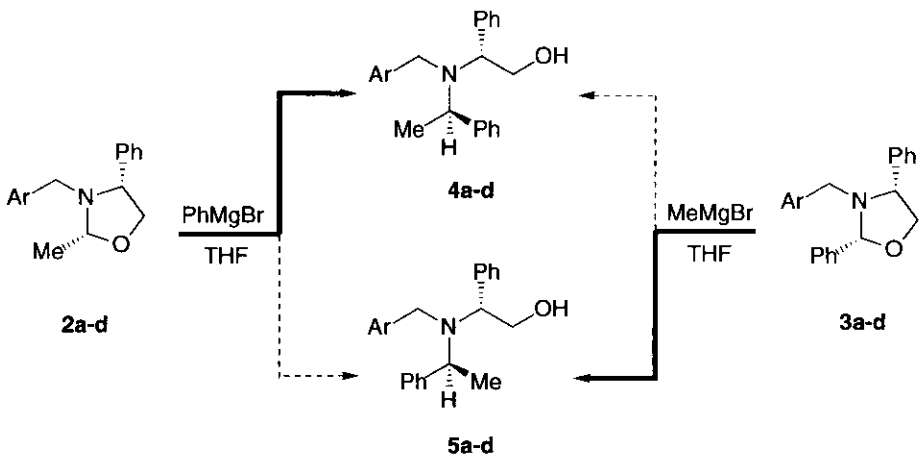
Table 1. Synthesis of Chiral 1,3-Oxazolidines (**2a-d**,**3a-d**)

		1a-d	**2a-d** R=Me		**3a-d** R=Ph	
	Ar	Yield (%)	Yield (%)	Ratio[a] (*R*,*R*) : (*S*,*R*)	Yield (%)	Ratio[a] (*R*,*R*) : (*S*,*R*)
a	4-Methoxyphenyl	99	97	89 : 11	81	92 : 8
b	3,4-Dimethoxyphenyl	75	90	91 : 9	99	95 : 5
c	2,3,4-Trimethoxyphenyl	98	86	94 : 6	82	94 : 6
d	2,4,6-Trimethoxyphenyl	99	99	97 : 3	81	>99 : 1

a) Estimated by ^{1}H-NMR(270 MHz) spectrum.

Condensation of **1a-d** with acetaldehyde in the presence of molecular sieves 3 Å (MS 3 Å) as a dehydrating agent gave chiral 2-methyl-1,3-oxazolidines (**2a-d**), while condensation of **1a-d** with benzaldehyde in benzene using a Dean-Stark tube gave chiral 2-phenyl-1,3-oxazolidines (**3a-d**). After purification by distillation with a tube oven or recrystallization with ether-hexane, these 1,3-oxazolidines

were obtained in yields ranging from 81 to 99%. The diastereomers were confirmed to be inseparable thermodynamic mixtures at the 2 position of the 1,3-oxazolidine ring, and their ratio in $CDCl_3$ was determined from the peak areas of 2-Me(**2a-d**) and 2-H(**3a-d**) of 1,3-oxazolidine in the ^{1}H-NMR spectrum. We previously reported that *cis*-(2*R*, 4*R*)-2-(*p*-bromophenyl)-*N*-methyl-4-phenyl-1,3-oxazolidine could be unambiguously assigned by X-Ray crystallographic analysis.[3] Thus, the absolute stereochemistry of the major products of the 1,3-oxazolidines(**2a-d, 3a-d**) was estimated to be (2*R*, 4*R*). (**Scheme 1, Table 1**)



Scheme 2

Table 2. Diastereoselective Reaction of **2a-d** and **3a-d** with Grignard Reagents

	Reaction of **2** with PhMgBr			Reaction of **3** with MeMgBr		
	Time (h)	Yield (%)	Ratio [a] **4** : **5**	Time (h)	Yield (%)	Ratio [a] **4** : **5**
a	2	86	73 : 27	4	99	12 : 88
b	2	99	71 : 29	3	94	12 : 88
c	20	87	89 : 11	37	78	8 : 92
d	40	99	93 : 7	40	92	5 : 95

a) Estimated by ^{1}H-NMR(270 MHz) spectrum.

Diastereoselective Addition of *N*-Methoxybenzyl-1,3-oxazolidines Using Grignard Reagents

Next, Grignard reagents were chosen as the nucleophilic reaction component. To examine both aliphatic and aromatic compounds, ordinary Grignard reagents were used in the following experiment.

The reaction of chiral 2-methyl-1,3-oxazolidines (**2a-d**) with PhMgBr in THF at room temperature gave

diastereomeric mixtures in yields of 86 to 99% and with diastereoselectivity of 71:29 to 93:7, while the similar reaction of chiral 2-phenyl-1,3-oxazolidines (**3a-d**) with MeMgBr gave diastereomeric mixtures in yields of 78 to 99% and with diastereoselectivity of 88:12 to 95:5. The isomer ratios were determined from the peak area of 2-Me in the ^{1}H-NMR spectrum. (**Scheme 2, Table 2**)

Based on the ^{1}H-NMR spectrum, **4a-d** were obtained as major products of the reaction of **2a-d** with PhMgBr, and **5a-d** were obtained as major products of the reaction of **3a-d** with MeMgBr. Therefore, **4a-d** and **5a-d** were diastereomers.

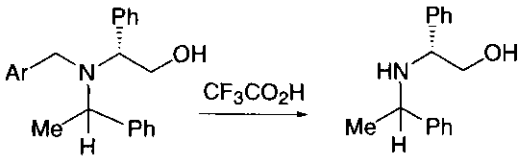
The mechanism of the ring-opening of chiral 1,3-oxazolidines has been described previously.[2b, 5] A similar diastereoselective additions of *N,O*-acetal to organometallic reagents have also been observed.[6] We also reported steric repulsion between phenyl and *N*-functional groups.[3] However, this diastereoselective process has not yet been completely elucidated. The best result regarding diastereoselectivity was obtained in additions of 1,3-oxazolidines having *N*-2,4,6-trimethoxybenzyl group. The stereoelectronic effect of methoxy at both *ortho* sites in the *N*-substituted group inevitably influenced diastereoselectivity.

It may be very useful to be able to obtained a preferable stereogenic center merely by using a different combination of Grignard reagents and aldehydes despite the use of the same chiral starting material, (*R*)-*N*-methoxybenzylphenylglycinol. The reaction times (2~40 h) were also drastically shorter than that (6~7 d) with *N*-diphenylmethylphenylglycinol, which we reported previously.[4]

Removal of the Methoxybenzyl Group and Determination of Absolute Configuration

As showed previously, the nitrogen functional group plays an important role in the expression of stereoselectivity, and a 2,4,6-trimethoxybenzyl group was particularly effective. However, cleavage of the *N*-substituted moiety is needed if this method is to enjoy a wider application. Therefore, we sought a method for effectively removing such functional groups and determined the absolute configuration of the newly formed chiral carbon as follows.

Treatment of the diastereomeric mixture (**4a-b, 5c-d**) with TFA gave the best results for removing the methoxybenzyl group. The stereochemistry of **6a-d** was established by comparing ^{1}H-NMR spectra with published data.[3] The diastereomeric ratio of **6a-d** was almost the same as that of **4a-b, 5c-d**. (**Scheme 3, Table 3**)



4a-b, 5c-d **6**

Scheme 3

Table 3. Amino alcohol (**6**)

Substrate	Yield (%)	Ratio *R* : *S*
4a (73 : 27)	81	72 : 28
4b (71 : 29)	94	72 : 28
5c (8 : 92)	86	11 : 89
5d (5 : 95)	99	5 : 95

In conclusion, the reaction of chiral 1,3-oxazolidines having *N*-2,4,6-trimethoxylbenzyl group using Grignard reagents was achieved with good yield and high diastereoselectivity. Furthermore, the reaction time was less than that of chiral 1,3-oxazolidines having *N*-diphenylmethyl group. The methoxybenzyl group could be easily removed in the presence of TFA. Variations of this method may be useful for the

asymmetric synthesis of compounds with medical applications, including physiologically active natural products.

Experimental

General Procedures Melting points were measured with a Yanagimoto Micro melting Point apparatus without collection. IR spectra were recorded on a 215 Hitachi Grating IR spectrophotometer. ^{1}H-NMR spectra were obtained on a JEOL GSX 270 instrument, and chemical sifts are reported in ppm on the δ-scale from internal Me_4Si. MS spectra were measured with a JEOL JMS D-300 spectrometer by using the chemical ionization(CI) with isobutane and the electron impact(EI) methods. Elemental analyses were performed on a Perkin-Elmer 240-B instrument. Optical rotation were taken with a JASCO-DIP-370 polarimeter at rt. Sibata Glass Tube Oven GTO-350RD was used as distillation apparatus. Column chromatography was performed on silica gel (45~75μm, Wakogel C-300). The reaction solvents were prepared as the following. Tetrahydrofuran was distilled over potassium metal. Ether and toluene were distilled over sodium metal.

General Procedure for the Preparation of (*R*)-*N*-Methoxybenzylphenylglycinols (1a-d). A mixture of (*R*)-phenylglycinol (7.0 g, 51.03 mmol) and aryl aldehyde [4-methoxybenzaldehyde, 3,4-dimethoxybenzaldehyde, 2,3,4-trimethoxybenzaldehyde, or 2,4,6-trimethoxybenzaldehyde, (51.03 mmol)] in benzene (150 mL) was refluxed for 1 h with a Dean-Stark trap. After being cooled, the mixture was concentrated under reduced pressure, and the residue was dissolved in methanol (150 mL). To this solution was added portionwise $NaBH_4$ (4.82 g, 127.43 mmol) at rt. After the reaction mixture had been stirred for 40 min, it was quenched with water (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (2x 50 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was crystallized to afford the amino alcohol (**1a-d**).

(*R*)-*N*-(4-Methoxybenzyl)phenylglycinol (1a): Colorless needles, mp 45℃ (ether-hexane); yield 99%. $[\alpha]_D$ -76.17° (*c*=0.98, $CHCl_3$). MS *m/z*: CI, 258(M^++1, base peak); EI, 226(M^+-CH_2OH). ^{1}H-NMR($CDCl_3$)δ: 2.44(br s, 2H, OH and NH), 3.54(d, 1H, *J*=12.8 Hz, NCH_2), 3.57(dd, 1H, *J*=9.2, 10.2 Hz, C<u>H</u>$_2$OH), 3.69(dd, 1H, *J*=4.3, 10.2 Hz, C<u>H</u>$_2$OH), 3.71(d, 1H, *J*=12.8 Hz, NCH_2), 3.79(s, 3H, OCH_3), 3.82(dd, 1H, *J*=4.3, 9.2 Hz, PhC<u>H</u>N), 6.85(d, 2H, *J*=6.1 Hz, aromatic H), 7.20(d, 2H, *J*=6.1 Hz, aromatic H), 7.25-7.41 (m, 5H, aromatic H). IR($CHCl_3$): 3450(OH and NH) cm^{-1}. *Anal.* Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.85; H, 7.50; N, 5.37.

(*R*)-*N*-(3,4-Dimethoxybenzyl)phenylglycinol (1b): Colorless needles, mp 61℃ (hexane); yield 75%. $[\alpha]_D$ -70.69°(*c*=1.00, $CHCl_3$). MS *m/z*: CI, 288 (M^++1), 151(base peak); EI, 256(M^+-CH_2OH). ^{1}H-NMR($CDCl_3$)δ: 2.22(br s, 2H, OH and NH), 3.54(d, 1H, *J*=12.8 Hz, NCH_2), 3.56(dd, 1H, *J*=8.6, 11.0 Hz, C<u>H</u>$_2$OH), 3.70(dd, 1H, *J*=4.3, 11.0 Hz, C<u>H</u>$_2$OH), 3.70(d, 1H, *J*=12.8 Hz, NCH_2), 3.80(dd, 1H, *J*=4.3, 8.6 Hz, PhCHN), 3.86(s, 6H, 2x OCH_3), 6.80(s, 1H, aromatic H), 6.81(d, 2H, *J*=5.5 Hz, aromatic H), 7.29-7.37(m, 5H, aromatic H). IR($CHCl_3$): 3450(OH and NH) cm^{-1}. *Anal.* Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 70.86; H, 7.45; N, 4.69.

(*R*)-*N*-(2,3,4-Trimethoxybenzyl)phenylglycinol (1c): Colorless needles, mp 66℃ (ether-hexane); yield 98%. $[\alpha]_D$ -53.30° (*c*=1.02, $CHCl_3$). MS *m/z*: CI, 318(M^++1, base peak); EI, 286(M^+-

CH_2OH). ^{1}H-NMR($CDCl_3$)δ: 1.95 (br s, 2H, OH and NH), 3.51(d, 1H, *J*=12.8 Hz, NCH_2), 3.55(dd, 1H, *J*=8.6, 11.0 Hz, C<u>H</u>$_2$OH), 3.71(dd, 1H, *J*=4.3, 11.0 Hz, C<u>H</u>$_2$OH), 3.73(d, 1H, *J*=12.8 Hz, NCH_2), 3.80(dd, 1H, *J*=4.3, 8.6 Hz, PhC<u>H</u>N), 3.85(s, 6H, 2x OCH_3), 3.86(s, 3H, OCH_3), 6.59(d, 1H, *J*=8.6 Hz, aromatic H), 6.87(d, 1H, *J*=8.6 Hz, aromatic H), 7.28-7.36(m, 5H, aromatic H). IR($CHCl_3$): 3450(OH and NH) cm^{-1}. *Anal.* Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.34; H, 7.45; N, 4.34.

(*R*)-*N*-(2,4,6-Trimethoxybenzyl)phenylglycinol (1d): Colorless needles, mp 135℃ (ethyl acetate-hexane); yield 99%. [α]$_D$ -36.36°(*c*=0.99, $CHCl_3$). MS *m/z*: CI, 318(M^++1), 181(base peak); EI, 286(M^+-CH_2OH). ^{1}H-NMR($CDCl_3$)δ: 1.90(br s, 2H, OH and NH), 3.66-3.82(m, 5H, NCH_2, C<u>H</u>$_2$OH and PhCHN), 3.76(s, 6H, 2x OCH_3), 3.80(s, 3H, OCH_3), 6.08(s, 2H, aromatic H), 7.22-7.35(m, 5H, aromatic H). IR($CHCl_3$): 3400(OH and NH) cm^{-1}. *Anal.* Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.10; H, 7.34; N, 4.37.

General Procedure for the Preparation of (2*R*,4*R*)-*N*-Methoxybenzyl-2-methyl-4-phenyl-1,3-oxazolidines (2a-d). To a solution of (*R*)-*N*-methoxybenzylphenylglycinol (**1a-d**) (11.58 mmol) in dry CH_2Cl_2 (150 mL) in the presence of Molecular sieves 3Å (2.0 g) was added acetaldehyde (1.53 g, 34.73 mmol) at 0℃. After the reaction mixture had been stirred for 15 h at 0℃, it was filtered through a little Celite and the filtrate was concentrated under reduced pressure. The crude oxazolidines (**2a-d**) were obtained, which was purified by Kugelrohr distillation.

(2*R*,4*R*)-*N*-(4-Methoxybenzyl)-2-methyl-4-phenyl-1,3-oxazolidine (2a): Colorless oil, 190℃< (oven temperature, 5 mmHg); yield 97% (89:11 mixture). [α]$_D$ -49.19°(*c*=0.97, $CHCl_3$). MS *m/z*: CI, 284(M^++1, base peak); EI, 283(M^+), 268(M^+-CH_3). ^{1}H-NMR($CDCl_3$)δ: major component: 1.14 (d, 3H, *J*=4.9 Hz, CHC<u>H</u>$_3$), 3.44(d, 1H, *J*=13.4 Hz, NCH_2), 3.69(t, 1H, *J*= 7.3 Hz, PhC<u>H</u>N), 3.76(s, 3H, OCH_3), 3.80(d, 1H, *J*=13.4 Hz, NCH_2), 3.85(t, 1H, *J*=7.3 Hz, C<u>H</u>$_2$O), 4.10(t, 1H, *J*=7.3 Hz, C<u>H</u>$_2$O), 4.38(q, 1H, *J*=4.9 Hz, C<u>H</u>CH$_3$), 6.77(d, 2H, *J*=9.2 Hz, aromatic H), 7.11(d, 2H, *J*=9.2 Hz, aromatic H), 7.20-7.47(m, 5H, aromatic H). *Anal.* Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.48; H, 7.52; N, 4.92.

(2*R*,4*R*)-*N*-(3,4-Dimethoxybenzyl)-2-methyl-4-phenyl-1,3-oxazolidine (2b): Yellow oil, 160℃< (oven temperature, 4 mmHg); yield 90% (91:9 mixture). [α]$_D$ -48.05°(*c*=1.17, $CHCl_3$). MS *m/z*: CI, 314(M^++1), 151(base peak); EI, 313(M^+), 298(M^+-CH_3). ^{1}H-NMR($CDCl_3$)δ: major component: 1.19(d, 3H, *J*=4.9 Hz, CHC<u>H</u>$_3$), 3.48(d, 1H, *J*=14.1 Hz, NCH_2), 3.73(t, 1H, *J*=7.3 Hz, PhC<u>H</u>N), 3.78(s, 3H, OCH_3), 3.79(d, 1H, *J*=14.1 Hz, NCH_2), 3.83(s, 3H, OCH_3), 3.85(t, 1H, *J*=7.3 Hz, CH_2O), 4.12(t, 1H, *J*=7.3 Hz, CH_2O), 4.39(q, 1H, *J*=4.9 Hz, C<u>H</u>CH$_3$), 6.72(m, 3H, aromatic H), 7.23-7.45(m, 5H, aromatic H). *Anal.* Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.56; H, 7.45; N, 4.33.

(2*R*,4*R*)-*N*-(2,3,4-Trimethoxybenzyl)-2-methyl-4-phenyl-1,3-oxazolidine (2c): Yellow oil, 277℃< (oven temperature, 6 mmHg); yield 86% (94:6 mixture). [α]$_D$ -61.15°(*c*=1.02, $CHCl_3$). MS *m/z*: CI, 344(M^++1, base peak); EI, 343(M^+), 328(M^+-CH_3). ^{1}H-NMR($CDCl_3$)δ: major component: 1.23 (d, 3H, *J*=4.9 Hz, CHC<u>H</u>$_3$), 3.58(d, 1H, *J*=13.4 Hz, NCH_2), 3.69(t, 1H, *J*= 7.3 Hz, PhC<u>H</u>N), 3.75(d, 1H, *J*=13.4 Hz, NCH_2), 3.81(s, 3H, OCH_3), 3.82(s, 6H, 2x OCH_3), 3.88(t, 1H, *J*=7.3 Hz, CH_2O), 4.09(t, 1H, *J*=7.3 Hz, CH_2O), 4.39(q, 1H, *J*=4.9 Hz, C<u>H</u>CH$_3$), 6.53(d, 1H, *J*=8.6 Hz,

aromatic H), 6.85(d, 1H, *J*=8.6 Hz, aromatic H), 7.22-7.44(m, 5H, aromatic H). *Anal.* Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33; N, 4.08. Found: C, 70.00; H, 7.43; N, 3.98.

(2*R*,4*R*)-*N*-(2,4,6-Trimethoxybenzyl)-2-methyl-4-phenyl-1,3-oxazolidine (2d): Yellow oil, 200°< (oven temperature, 4 mmHg); yield 99% (97:3 mixture). $[\alpha]_D$ -77.12° (*c*=1.35, $CHCl_3$). MS *m/z*: CI, 344(M^++1), 181(base peak); EI, 343(M^+), 328(M^+-CH_3). ^{1}H-NMR($CDCl_3$)δ: major component: 1.33 (d, 3H, *J*=5.5 Hz, CHC<u>H</u>$_3$), 3.54(t, 1H, *J*=7.3 Hz, PhC<u>H</u>N), 3.66(s, 6H, 2x OCH_3), 3.75(s, 2H, NCH_2), 3.77(s, 3H, OCH_3), 3.89(t, 1H, *J*=7.3 Hz, CH_2O), 3.99(t, 1H, *J*=7.3 Hz, CH_2O), 4.41(q, 1H, *J*=5.5 Hz, C<u>H</u>CH_3), 6.00 (s, 2H, aromatic H), 7.18-7.40(m, 5H, aromatic H). *Anal.* Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33; N, 4.08. Found: C, 69.91; H, 7.43; N, 3.95.

General Procedure for the Preparation of (2*R*,4*R*)-*N*-Methoxybenzyl-2,4-diphenyl-1,3-oxazolidines (3a-d). A mixture of (*R*)-*N*-methoxybenzylphenylglycinols (**1a-d**) (12.07 mmol) and benzaldehyde (1.23 g, 12.44 mmol) in benzene (100 mL) was refluxed for 7-50 h using a Dean-Stark trap. After being cooled, the mixture was concentrated under reduced pressure to leave the crude oxazolidine (**3a-d**).

(2*R*,4*R*)-*N*-(4-Methoxybenzyl)-2,4-diphenyl-1,3-oxazolidine (3a): Colorless needles, mp 106℃ (ether-hexane); yield 81% (92:8 mixture). $[\alpha]_D$ -22.80° (*c*=1.03, $CHCl_3$). MS *m/z*: CI, 346(M^++1, base peak); EI, 345 (M^+), 268(M^+-C_6H_5). ^{1}H-NMR($CDCl_3$)δ: major component: 3.62(s, 2H, NCH_2), 3.74(s, 3H, OCH_3), 3.85(t, 1H, *J*=7.3 Hz, PhC<u>H</u>N), 4.01(t, 1H, *J*=7.3 Hz, CH_2O), 4.19(t, 1H, *J*=7.3 Hz, CH_2O), 5.13(s, 1H, NCHO), 6.67(d, 2H, *J*=9.2 Hz, aromatic H), 6.88(d, 2H, *J*=9.2 Hz, aromatic H), 7.28-7.64(m, 10H, aromatic H). *Anal.* Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 80.08; H, 6.76; N, 4.01.

(2*R*,4*R*)-*N*-(3,4-Dimethoxybenzyl)-2,4-diphenyl-1,3-oxazolidine (3b): Colorless needles, mp 108℃ (ether-hexane); yield 99% (95:5 mixture). $[\alpha]_D$ -15.11° (*c*=1.00, $CHCl_3$). MS *m/z*: CI, 376(M^++1), 151(base peak); EI, 375(M^+), 298(M^+-C_6H_5). ^{1}H-NMR($CDCl_3$)δ: major component: 3.64(s, 2H, NCH_2), 3.70(s, 3H, OCH_3), 3.81(s, 3H, OCH_3), 3.88(t, 1H, *J*=7.3 Hz, PhC<u>H</u>N), 4.03(t, 1H, *J*=7.3 Hz, CH_2O), 4.23(t, 1H, *J*=7.3 Hz, CH_2O), 5.14 (s, 1H, NCHO), 6.43(d, 1H, *J*=1.8 Hz, aromatic H), 6.51(dd, 1H, *J*=1.8, 7.9 Hz, aromatic H), 6.54(d, 1H, *J*=7.9 Hz, aromatic H), 7.27-7.62(m, 10H, aromatic H). *Anal.* Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.76; H, 6.75; N, 3.65.

(2*R*, 4*R*)-*N*-(2,3,4-Trimethoxybenzyl)-2,4-diphenyl-1,3-oxazolidine (3c):
Colorless solid, mp 66℃ (ether-hexane); yield 82% (94:6 mixture). $[\alpha]_D$ -16.56° (*c*=1.00, $CHCl_3$). MS *m/z*: CI, 406(M^++1, base peak); EI, 405(M^+), 328(M^+-C_6H_5). ^{1}H-NMR($CDCl_3$)δ: major component: 3.61(s, 3H, OCH_3), 3.62(d, 1H, *J*=13.4 Hz, NCH_2), 3.68(d, 1H, *J*=13.4 Hz, NCH_2), 3.74(s, 6H, 2x OCH_3), 3.83(t, 1H, *J*=7.3 Hz, PhC<u>H</u>N), 4.05(t, 1H, *J*=7.3 Hz, CH_2O), 4.21(t, 1H, *J*=7.3 Hz, CH_2O), 5.18(s, 1H, NCHO), 6.37(d, 1H, *J*=8.5 Hz, aromatic H), 6.60(d, 1H, *J*=8.5 Hz, aromatic H), 7.20-7.62(m, 10H, aromatic H). *Anal.* Calcd for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 74.26; H, 6.76; N, 3.41.

(2*R*, 4*R*)-*N*-(2,4,6-Trimethoxybenzyl)-2,4-diphenyl-1,3-oxazolidine (3d):
Colorless viscous oil, 260°< (oven temperature, 4 mmHg); yield 81% (>99:1 mixture). $[\alpha]_D$ -16.48° (*c*=1.06, $CHCl_3$). MS *m/z*: CI, 406(M^++1), 181(base peak); EI, 405(M^+), 328(M^+-C_6H_5). ^{1}H-

NMR($CDCl_3$)δ: major component: 3.55(s, 6H, 2x OCH_3), 3.68(t, 1H, *J*=6.1 Hz, PhC<u>H</u>N), 3.70(s, 3H, OCH_3), 3.71(d, 1H, *J*=14.0 Hz, NCH_2), 3.76(d, 1H, *J*=14.0 Hz, NCH_2), 4.08(t, 1H, *J*=6.1 Hz, CH_2O), 4.13(t, 1H, *J*=6.1 Hz, CH_2O), 5.23(s, 1H, NCHO), 5.84(s, 2H, aromatic H), 7.19-7.61 (m, 10H, aromatic H). *Anal.* Calcd for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 74.22; H, 6.79; N, 3.39.

General Procedure for the Reaction of (2*R*,4*R*)-2a-d with Phenylmagnesium Bromide. Phenylmagnesium bromide (14.18 ml, 28.35 mmol, 2 M solution in ether) was added dropwise to a stirred solution of oxazolidine (**2a-d**) (9.45 mmol) in dry THF (80 mL) at rt under argon over a 10 min period. After the reaction mixture had been stirred at rt for 2-40 h, it was quenched with a small amount of water and diluted with ether (100 mL). The resulting white precipitate was filtered off, and filtrate was washed with saturated aqueous NH_4Cl (50 mL). The aqueous phase was extracted with ether (2x 50 mL). The combined organic extract was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to leave a oily residue, which was subjected to column chromatography on silica gel with ethyl acetate-hexane (1:3) to give a diastereomeric mixture of amine (**4a-d**).

(1*R*,1'*R*)-*N*-(2'-Hydroxy-1'-phenylethyl)-*N*-(4-methoxybenzyl)-1-phenylethylamine (4a): Colorless viscous oil, yield 86% (73:27 mixture). MS *m/z*: CI, 362(M^++1, base peak); EI, 330(M^+-CH_2OH). ^{1}H-NMR($CDCl_3$)δ: major component: 1.05(d, 3H, *J*=6.7 Hz, CHC<u>H</u>$_3$), 2.40(br s, 1H, OH), 3.56(d, 1H, *J*=13.4 Hz, NCH_2), 3.75(s, 3H, OCH_3), 3.91(d, 1H, *J*=13.4 Hz, NCH_2), 4.14 (q, 1H, *J*=6.7 Hz, C<u>H</u>CH_3), 3.33-4.17(m, 3H, C<u>H</u>C<u>H</u>$_2$OH), 6.83(d, 2H, *J*=8.5 Hz, aromatic H), 7.15(d, 2H, *J*=8.5 Hz, aromatic H), 7.17-7.35(m, 10H, aromatic H). IR($CHCl_3$): 3470(OH) cm^{-1}. *Anal.* Calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.88. Found: C, 79.95; H, 7.74; N, 3.73.

(1*R*,1'*R*)-*N*-(2'-Hydroxy-1'-phenylethyl)-*N*-(3,4-dimethoxybenzyl)-1-phenylethylamine (4b): Yellow viscous oil, yield 99% (71:29 mixture). MS *m/z*: CI, 392(M^++1), 151(base peak); EI, 360(M^+-CH_2OH). ^{1}H-NMR($CDCl_3$)δ: major component: 1.07(d, 3H, *J*=6.7 Hz, CHC<u>H</u>$_3$), 2.25(br s, 1H, OH), 3.54(d, 1H, *J*=14.7 Hz, NCH_2), 3.78(s, 3H, OCH_3), 3.84(s, 3H, OCH_3), 3.89(d, 1H, *J*= 14.7 Hz, NCH_2), 4.16(q, 1H, *J*=6.7 Hz, C<u>H</u>CH_3), 3.37-4.13(m, 3H, C<u>H</u>C<u>H</u>$_2$OH), 6.62-6.90(m, 3H, aromatic H), 7.19-7.41(m, 10H, aromatic H). IR($CHCl_3$): 3450(OH) cm^{-1}. *Anal.* Calcd for $C_{25}H_{29}NO_3$: C, 76.69; H, 7.47; N, 3.58. Found: C, 76.80; H, 7.51; N, 3.51.

(1*R*,1'*R*)-*N*-(2'-Hydroxy-1'-phenylethyl)-*N*-(2,3,4-trimethoxybenzyl)-1-phenylethylamine (4c): Colorless needles, mp 101℃ (ether-hexane); yield 87% (89:11 mixture). MS *m/z*: CI, 422(M^++1), 181(base peak); EI, 390(M^+-CH_2OH). ^{1}H-NMR($CDCl_3$)δ: major component: 0.98(d, 3H, *J*=6.7 Hz, CHC<u>H</u>$_3$), 1.68(br s, 1H, OH), 3.39(dd, 1H, *J*=4.3, 11.0 Hz, C<u>H</u>C<u>H</u>$_2$OH), 3.72(d, 1H, *J*=14.7 Hz, NCH_2), 3.80(s, 3H, OCH_3), 3.83(s, 3H, OCH_3), 3.87(s, 3H, OCH_3), 4.02(d, 1H, *J*=14.7 Hz, NCH_2), 3.97-4.12(m, 3H, CHC<u>H</u>$_2$OH and C<u>H</u>CH_3), 6.66(d, 1H, *J*=8.5 Hz, aromatic H), 6.86(d, 1H, *J*=8.5 Hz, aromatic H), 7.12-7.36(m, 10H, aromatic H). IR($CHCl_3$): 3460(OH) cm^{-1}. *Anal.* Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 74.23; H, 7.47; N, 3.31.

(1*R*,1'*R*)-*N*-(2'-Hydroxy-1'-phenylethyl)-*N*-(2,4,6-trimethoxybenzyl)-1-phenylethylamine (4d): Yellow viscous oil, yield 99% (93:7 mixture). MS *m/z*: CI, 422(M^++1), 181(base peak); EI, 390(M^+-CH_2OH). ^{1}H-NMR($CDCl_3$)δ: major component: 0.97(d, 3H, *J*=6.7 Hz, CHC<u>H</u>$_3$), 1.74(br s, 1H, OH), 3.33(dd, 1H, *J*=4.3, 10.4 Hz, C<u>H</u>CH_2OH), 3.72(s, 6H, 2x OCH_3),

3.79(s, 3H, OCH_3), 3.83(d, 1H, *J*=12.8 Hz, NCH_2), 4.05(d, 1H, *J*=12.8 Hz, NCH_2), 3.83-4.13(m, 3H, $CHCH_2OH$ and $CHCH_3$), 6.12(s, 2H, aromatic H), 7.19-7.43(m, 10H, aromatic H). IR($CHCl_3$): 3470(OH) cm^{-1}. *Anal.* Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 74.15; H, 7.54; N, 3.22.

General Procedure for the Reaction of (2*R*,4*R*)-3a-d with Methylmagnesium Bromide. Methylmagnesium bromide(15.10 ml, 45.30 mmol, 3M solution in ether) was added dropwise to a stirred solution of oxazolidine (**3a-d**) (9.06 mmol) in dry THF (80 mL) at rt under argon over a 10 min period. After the reaction mixture had been stirred at rt for 3-40 h, it was worked up as previously described for compounds (**4a-d**), gave an oily product which was subjected to column chromatography on silica gel with ethyl acetate-hexane (1:3) to give a diastereomeric mixture of amine (**5a-d**).

(1*S*,1'*R*)-*N*-(2'-Hydroxy-1'-phenylethyl)-*N*-(4-methoxybenzyl)-1-phenylethylamine (5a): Yellow viscous oil, yield 99% (12:88 mixture). MS *m/z*: CI, 362(M^++1, base peak); EI, 330(M^+-CH_2OH). ^{1}H-NMR($CDCl_3$)δ: major component: 1.29(d, 3H, *J*=6.7 Hz, $CHCH_3$), 2.25(br s, 1H, OH), 3.37(d, 1H, *J*=15.3 Hz, NCH_2), 3.59(dd, 1H, *J*=6.1, 11.0 Hz, $CHCH_2OH$), 3.78(s, 3H, OCH_3), 4.01(d, 1H, *J*=15.3 Hz, NCH_2), 3.76-4.20(m, 3H, $CHCH_2OH$ and $CHCH_3$), 6.85(d, 2H, *J*=8.6 Hz, aromatic H), 7.13-7.35(m, 12H, aromatic H). IR($CHCl_3$): 3470(OH) cm^{-1}. *Anal.* Calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.88. Found: C, 79.54; H, 7.68; N, 3.75.

(1*S*,1'*R*)-*N*-(2'-Hydroxy-1'-phenylethyl)-*N*-(3,4-dimethoxybenzyl)-1-phenylethylamine (5b): Colorless needles, mp 94℃ (ether-hexane); yield 94% (12:88 mixture). MS *m/z*: CI, 392(M^++1), 151(base peak); EI, 360(M^+-CH_2OH). ^{1}H-NMR($CDCl_3$)δ: major component: 1.33(d, 3H, *J*=6.7 Hz, $CHCH_3$), 2.56(br s, 1H, OH), 3.40(d, 1H, *J*=15.9 Hz, NCH_2), 3.64(dd, 1H, *J*=6.1, 11.0 Hz, $CHCH_2OH$), 3.85(s, 3H, OCH_3), 3.87(s, 3H, OCH_3), 4.00(d, 1H, *J*=15.9 Hz, NCH_2), 3.89-4.18(m, 3H, $CHCH_2OH$ and $CHCH_3$), 6.88(d, 1H, *J*=8.5 Hz, aromatic H), 6.82(d, 1H, *J*=1.8 Hz, aromatic H), 6.81(dd, 1H, *J*=1.8, 8.5 Hz, aromatic H), 7.20-7.41(m, 10H, aromatic H). IR($CHCl_3$): 3550(OH) cm^{-1}. *Anal.* Calcd for $C_{25}H_{29}NO_3$: C, 76.69; H, 7.47; N, 3.58. Found: C, 76.51; H, 7.55; N, 3.46.

(1*S*,1'*R*)-*N*-(2'-Hydroxy-1'-phenylethyl)-*N*-(2,3,4-trimethoxybenzyl)-1-phenylethylamine (5c): Yellow viscous oil, yield 78% (8:92 mixture). MS *m/z*: CI, 422(M^++1), 181(base peak); EI, 390(M^+-CH_2OH). ^{1}H-NMR($CDCl_3$)δ: major component: 1.29(d, 3H, *J*=6.7 Hz, $CHCH_3$), 1.57(br s, 1H, OH), 3.47 (d, 1H, *J*=15.3 Hz, NCH_2), 3.57(dd, 1H, *J*=4.3, 10.4 Hz, $CHCH_2OH$), 3.83 (s, 3H, OCH_3), 3.84(s, 3H, OCH_3), 3.88(s, 3H, OCH_3), 4.04(d, 1H, *J*=15.3 Hz, NCH_2), 3.91-4.03(m, 3H, $CHCH_2OH$ and $CHCH_3$), 6.63(d, 1H, *J*=8.6 Hz, aromatic H), 7.17(d, 1H, *J*=8.6 Hz, aromatic H), 7.09-7.32(m, 10H, aromatic H). IR($CHCl_3$): 3450(OH) cm^{-1}. *Anal.* Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 74.04; H, 7.49; N, 3.26.

(1*S*,1'*R*)-*N*-(2'-Hydroxy-1'-phenylethyl)-*N*-(2,4,6-trimethoxybenzyl)-1-phenylethylamine (5d): Colorless viscous oil, yield 92% (5:95 mixture). MS *m/z*: CI, 422(M^++1), 181(base peak); EI, 390(M^+-CH_2OH). ^{1}H-NMR($CDCl_3$)δ: major component: 1.32(d, 3H, *J*=6.7 Hz, $CHCH_3$), 1.84(br s, 1H, OH), 3.50 (dd, 1H, *J*=3.7, 9.2 Hz, $CHCH_2OH$), 3.80(s, 3H, OCH_3), 3.81(s, 6H, 2x OCH_3), 3.85(s, 2H, NCH_2), 3.71-4.09(m, 3H, $CHCH_2OH$ and $CHCH_3$), 6.10(s, 2H, aromatic H), 6.98-7.18(m, 10H, aromatic H). IR($CHCl_3$): 3440(OH) cm^{-1}. *Anal.* Calcd for $C_{26}H_{31}NO_4$: C,

74.08; H, 7.41; N, 3.32. Found: C, 74.09; H, 7.51; N, 3.23.

General Procedure for the Removal of the *N*-Methoxybenzyl Groups from 4a-b and 5c-d. A diastereomeric mixture of **4a-b** or **5c-d** (0.45 mmol) and trifluoroacetic acid (6 mL) was stirred at 50℃ for 20 h, and then diluted with water (20 mL). The resulting aqueous phase was basified with 10% NaOH solution and extracted with CH_2Cl_2 (3x 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to leave a oily residue, which was subjected to column chromatography on silica gel with ethyl acetate-hexane (1:3) to give a diastereomeric mixture of amine (**6**).

(1*R*,1'*R*)-*N*-(2'-Hydroxy-1'-phenylethyl)-1-phenylethylamine (*R*, *R*-6):
This compound was prepared by removal of the *N*-methoxybenzyl groups from **4a** (73:27 mixture) or **4b** (71:29 mixture) according to the general procedure. Pale yellow oil, yield 81% (72:28 mixture) from **4a** and yield 94% (72:28 mixture) from **4b**. ^{1}H-NMR($CDCl_3$)δ: major component: 1.36(d, 3H, *J*=6.7 Hz, $CHC\underline{H}_3$), 2.48(br s, 2H, OH and NH), 3.51(dd, 1H, *J*=7.9, 11.0 Hz, $CHC\underline{H}_2OH$), 3.72(dd, 1H, *J*=4.3, 11.0 Hz, $CHC\underline{H}_2OH$), 3.76(q, 1H, *J*=6.7 Hz, $C\underline{H}CH_3$), 3.88(dd, 1H, *J*=7.9, 4.3 Hz, $C\underline{H}CH_2OH$), 7.19-7.35(m, 10H, aromatic H). This ^{1}H-NMR spectral data of major component were identical with those of an authentic specimen.

(1*S*,1'*R*)-*N*-(2'-Hydroxy-1'-phenylethyl)-1-phenylethylamine (*S*,*R*-6):
This compound was prepared by removal of the *N*-methoxybenzyl groups from **5c** (8:92 mixture) or **5d** (5:95 mixture) according to the general procedure. Colorless oil, yield 86% (11:89 mixture) from **5c** and yield 99% (5:95 mixture) from **5d**. ^{1}H-NMR($CDCl_3$)δ: major component: 1.33(d, 3H, *J*=6.7 Hz, $CHC\underline{H}_3$), 2.25(br s, 2H, OH and NH), 3.52-3.58(m, 3H, $C\underline{H}C\underline{H}_2OH$), 3.64(q, 1H, *J*=6.7 Hz, $C\underline{H}CH_3$), 7.18-7.39(m, 10H, aromatic H). This ^{1}H-NMR spectral data of major component were identical with those of an authentic specimen.

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