Diastereoselective Addition of Chiral Aliphatic Imines and 2-Alkyl-1,3-oxazolidines to Organometallic Reagents

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The reaction of organocerium reagents with chiral aliphatic imines derived from (*R*)-*O*-methylphenylglycinol afforded the corresponding amines with high diastereoselectivity. In contrast, the reaction of Grignard reagents with chiral 2-alkyl-1,3-oxazolidines derived from (*R*)-*N*-methylphenylglycinol afforded the amines with changeover in diastereoselectivity.

Key words diastereoselective reaction; chiral aliphatic imine; chiral 2-alkyl-1,3-oxazolidine; organocerium reagent; Grignard reagent

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 amines starting from the single enantiomeric source using the diastereoselective addition of organometallic reagents to the chiral aryl imines and 2-aryl-1,3-oxazolidines derived from (*R*)-phenylglycinol and aromatic carbaldehydes,[2] and we have also demonstrated its synthetic potential in the asymmetric syntheses of piperidine alkaloids, (−)-coniine and (−)-dihydropinidine,[3] and the indolizidine alkaloid, (+)-monomorine I.[4]

As part of a program aimed at expanding the generality of this method, we now report on the results of the diastereoselective addition of organometallic reagents to the chiral aliphatic imines (**2a—c**) and 2-alkyl-1,3-oxazolidines (**4a—c**) derived from (*R*)-phenylglycinol and aliphatic carbaldehydes. The desired starting chiral imines and 1,3-oxazolidines were readily prepared as follows. The condensation of (*R*)-*O*-methylphenylglycinol (**1**)[5] with several aliphatic carbaldehydes (acetaldehyde, propionaldehyde or isobutyraldehyde) in CH_2Cl_2 in the presence of anhydrous $MgSO_4$ gave the sensitive chiral imines (**2a—c**). Physical data for these chiral imines are given in Experimental. These products were assumed to be in the *E* configuration based upon the report by Hine and Yeh[6]

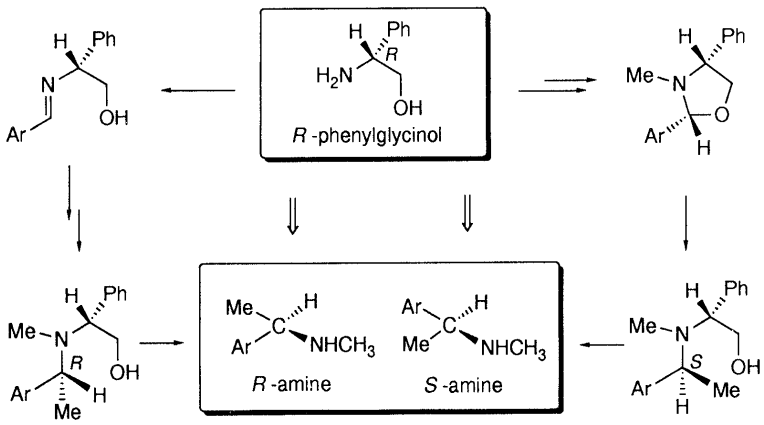

Chart 1

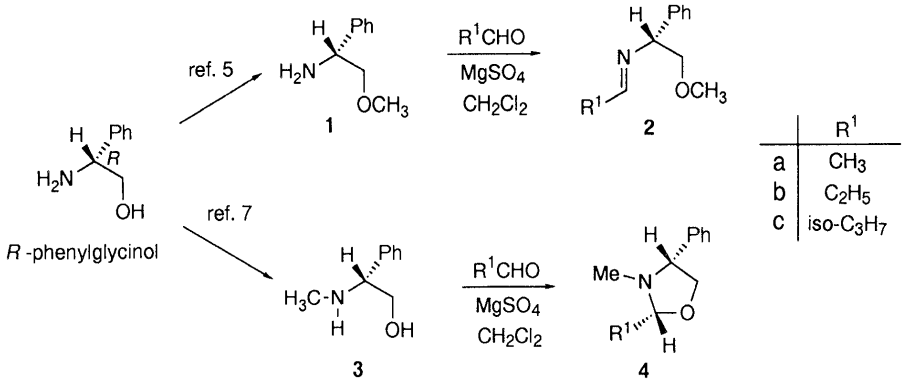

Chart 2

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and ^{1}H-NMR (270 MHz) studies which showed only a single resonance for the imine proton (7.61—7.82 ppm). A mixture of (*E*,*Z*)-imine would be expected to exhibit different chemical shifts. In a similar manner, chiral 1,3-oxazolidines (**4a—c**) were synthesized by the condensation of (*R*)-*N*-methylphenylglycinol (**3**)[7] with aliphatic carbaldehydes in quantitative yields. These products were confirmed to consist of a thermodynamic mixture,[8] depending on the asymmetric center at the 2-position of the 1,3-oxazolidine ring; the minor component amounted to less than 5% as judged from the ^{1}H-NMR (270 MHz) spectra.

With the requisite compound in hand, we next carried out diastereoselective addition of organometallic reagents to the chiral imines (**2a—c**) and 1,3-oxazolidines (**4a—c**). However, it is well known that the reaction of imines which contain α-hydrogen, such as **2a—c**, with most basic organometallic reagents (Grignard and organolithium reagents) results mainly in abstraction of α-hydrogen of the imines and consequently the desired addition products can not be obtained in satisfactory yields.[9] In order to circumvent this problem we choose the organocerium reagents, which are less basic than Grignard and organolithium reagents.[10]

Reaction of chiral aliphatic imines (**2a—c**) with an excess of organocerium reagents, which were readily prepared from the corresponding Grignard reagent and anhydrous $CeCl_3$ *in situ* according to Imamoto *et al.*,[11] afforded pairs of diastereomeric adducts (**5a—f**) in 60—93% yield with high diastereoselectivities. In the reaction of **2c** with $MeCeCl_2$ or $PhCeCl_2$, essentially complete diastereoselectivity was obtained with good yields, as evidenced by the ^{1}H-NMR (270 MHz) spectra of the crude product mixture. The isomer ratios were determined by analysis

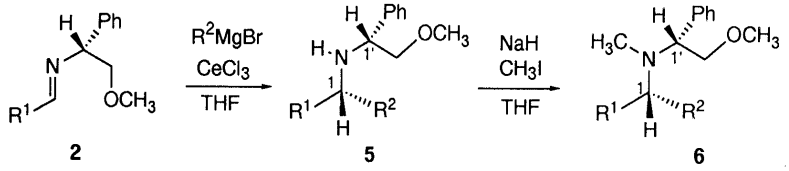

Chart 3

Table 1. Diastereoselective Reaction of Chiral Imines with Organocerium Reagents

Product	R^1	R^2	5		6	
			Yield[a] (%)	Ratio[b] (1*R*,1′*R*):(1*S*,1′*R*)	Yield[a] (%)	Ratio[b] (1*R*,1′*R*):(1*S*,1′*R*)
a	CH_3	C_6H_5	60	4: 96	89	4: 96
b	CH_3	C_2H_5	80	4: 96	92	5: 95
c	C_2H_5	CH_3	65	94: 6		
d	CH_3	iso-C_3H_7	74	2: 98	81	2: 98
e	iso-C_3H_7	CH_3	72	>99: 1		
f	iso-C_3H_7	C_6H_5	93	1: >99	77	1: >99

a) Isolated yield. *b*) Estimated from the ^{1}H-NMR (270 MHz) spectrum.

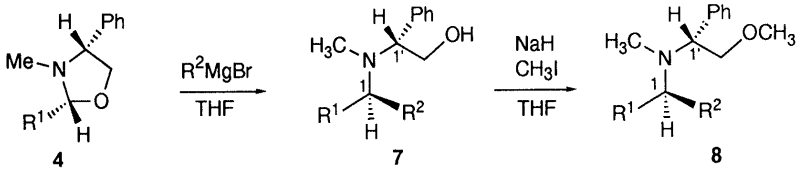

Chart 4

Table 2. Diastereoselective Reaction of Chiral 1,3-Oxazolidines with Grignard Reagents

Product	R^1	R^2	7		8	
			Yield[a] (%)	Ratio[b] (1*R*,1′*R*):(1*S*,1′*R*)	Yield[a] (%)	Ratio[b] (1*R*,1′*R*):(1*S*,1′*R*)
a	CH_3	C_6H_5	90	78:22	93	75:25
b	CH_3	C_2H_5	93	66:34		
c	C_2H_5	CH_3	89	15:85	90	15:85
d	CH_3	iso-C_3H_7	86	44:56		
e	iso-C_3H_7	CH_3	89	9:91	87	9:91
f	iso-C_3H_7	C_6H_5	93	93: 7	89	92: 8

a) Isolated yield. *b*) Estimated from the ^{1}H-NMR (270 MHz) spectrum.

of the ^{1}H-NMR (270 MHz) spectra. Further, in order to establish the sense of asymmetric induction, the adducts (**5a, b, d, f**) were converted into *N,O*-dimethyl compounds (**6**) by treatment with NaH and MeI in quantitative yields. The experimental results are summarized in Table 1. On the other hand, chiral 1,3-oxazolidines (**4a—c**) also reacted smoothly with Grignard reagents in tetrahydrofuran (THF) to give the diastereomeric adducts (**7a—f**) in 86—93% yields. The experimental results are summarized in Table 2.

It is of interest to note from Table 2 that the degree of diastereoselectivity of the addition is influenced by the size of the alkyl group at the 2-position of the 1,3-oxazolidine ring. Indeed, stereoselectivity in the addition of Grignard reagent to the chiral oxazolidine (**4c**) having a bulky isopropyl group is comparable to that shown in Table 1, but that in the addition of Grignard reagent to the chiral oxazolidine (**4a**) having a methyl group is surprisingly lower. More interestingly, the major products (**7a—f**) of these reactions were identical with the minor products obtained from the reaction of chiral imines (**2a—c**) by direct comparison of ^{1}H-NMR (270 MHz) spectra of the *O,N*-dimethyl compounds (**8**).

The absolute configuration of the newly formed chiral center in the adducts was determined as follows. The stereochemistry of **5a** and **7a** was established by ^{1}H-NMR (270 MHz) spectral comparisons with published data.[12] On the other hand, since **5b, c** and **7b, c** were unknown, the diastereomeric mixture of **7c** (ratio, 15 : 85) was submitted to catalytic hydrogenation to give the enantiomerically enriched *N*,1-dimethylpropylamine hydrochloride [(*S*)-**9**], and the specific rotation of this compound was $[\alpha]_D$ −5.8. Compound (*R*)-**9** was produced from (*R*)-1-methylpropylamine (the compound of $[\alpha]_D$ −7.5° was used) by formylation with ethyl formate followed by reduction with lithium aluminum hydride, and the specific rotation of its hydrochloride was $[\alpha]_D$ +6.2°. Consequently, the absolute configurations of **5b, c** and **7b, c** were determined. Similarly, hydrogenation of **5e** (from the reaction of **2c** with $MeCeCl_2$) gave the enantiomerically enriched amine (**10**) after removal of the chiral auxiliary and successive treatment with *p*-nitrobenzoyl

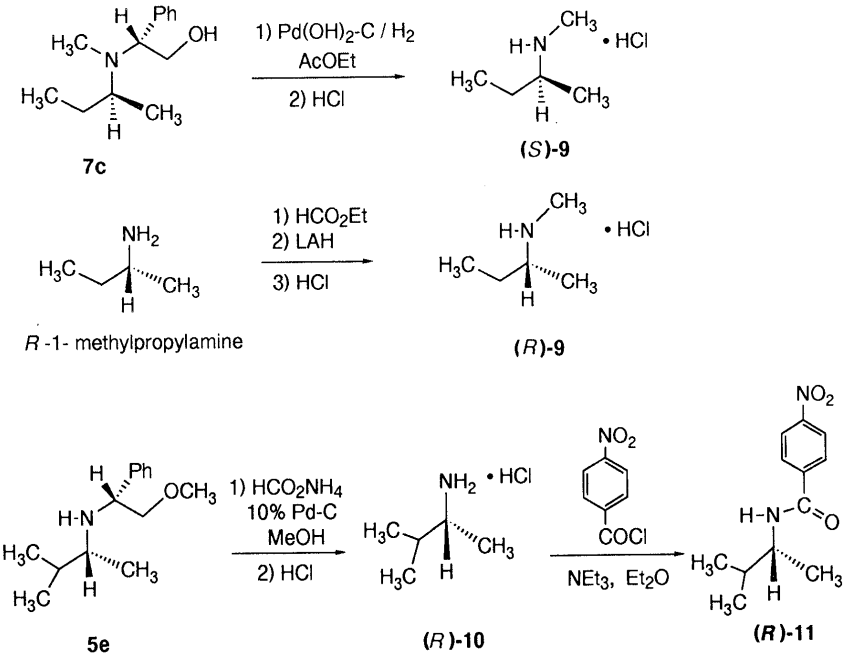

Chart 5

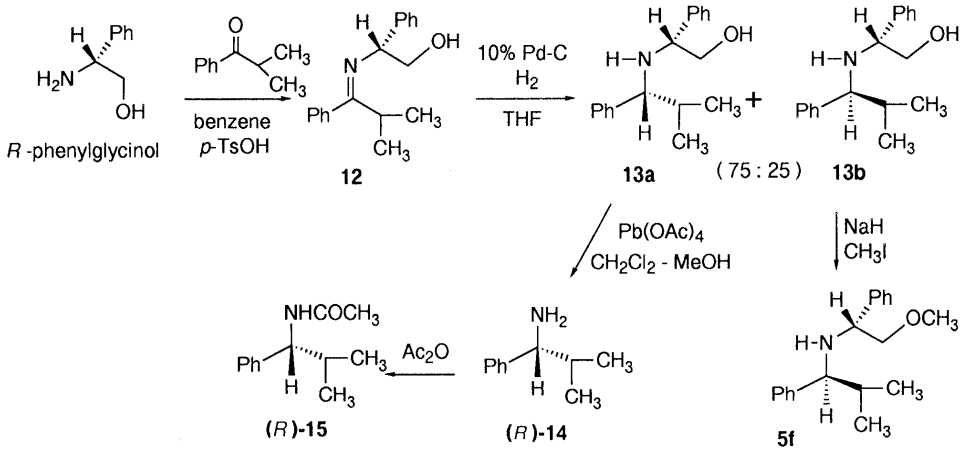

Chart 6

chloride afforded the optically active *p*-nitrobenzamide (**11**) ($[\alpha]_D$ −40.9°), which could be assigned as *R* form based on the reported specific rotation ($[\alpha]_D$ −55.8°).[13] Thus, the absolute configurations of **5d—e** and **7d—e** were determined.

In the case of **5f** and **7f**, we initially investigated the conversion of the amine (**5f**), obtained by the reaction of **2c** with $PhCeCl_2$, into the acetate derivative (**15**), whose absolute configuration was known, by removal of the chiral auxiliary and acetylation. However, the attempted conversion using a wide range of reductive cleavage or oxidative cleavage procedures failed to give the desired product, but yielded instead the decomposition products. Although the above conversions failed, compound **15** was readily prepared by an alternative route. Formation of the imine (**12**) from (*R*)-phenylglycinol and isobutyrophenone can conveniently be brought about by heating in benzene with azeotropic removal of water. The imine (**12**) does not need to be isolated, but can be reacted further without work-up, thus minimizing the risk of hydrolysis back to the starting materials. Hydrogenation of the crude imine (**12**) using palladium on carbon as a catalyst furnished the secondary amine (**13a, b**) in a quantitative yield as a separable diastereomeric mixture in a ratio of 75:25. After separation of the two isomers by silica gel column chromatography, the major diastereomer (**13a**) was submitted to oxidative cleavage with lead tetraacetate, and subsequent acetylation with acetic anhydride afforded the optically active acetate (**15**) ($[\alpha]_D$ +135°), which could be assigned as *R* form based on the reported specific rotation.[14] On the other hand, treatment of the minor diastereomer (**13b**) with NaH and MeI in THF yielded the *O*-methyl compound (**5f**), which was identical with the major product obtained from the reaction of the imine (**2c**) with $PhCeCl_2$ by ^{1}H-NMR (270 MHz) spectral comparison. Consequently, the absolute configurations of the newly formed chiral center in all the adducts (**5a—f** and **7a—f**) were determined.

Thus, the proposed method seems to be of great potential value in the alkylation of aliphatic imines, since it can be applied to selective preparation of both asymmetric carbon atoms from a single enantiomeric source. Further studies on mechanistic and synthetic aspects of the stereoselective addition reaction are in progress.

Experimental

General Procedures Melting points were measured with a Yanagimoto micro melting point apparatus without correction. IR spectra were recorded on a 215 Hitachi grating IR spectrophotometer. ^{1}H-NMR spectra were obtained on a JEOL PMX 270 instrument, and chemical shifts 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) method. Optical rotations were taken with a JASCO-DIP-370 polarimeter at room temperature.

General Procedure for the Condensation of (*R*)-1 with Carbaldehydes A solution of *O*-methylphenylglycinol (**1**) (0.3 g, 2.0 mmol) in dry CH_2Cl_2 (20 ml) was prepared in the presence of anhydrous $MgSO_4$ (1.0 g). To this was added dropwise a solution of a carbaldehyde [acetaldehyde, propionaldehyde or isobutyraldehyde (2.4 mmol)] in dry CH_2Cl_2 (5 ml) over a 10 min period at 0 °C. The reaction mixture was stirred for 2 h, then filtered through a little Celite and the filtrate was concentrated at 30°C under 20 mmHg to give the corresponding imine (**2a—c**). These compounds were not stable enough to give a satisfactory microanalysis and were used for the next reaction.

(*R*)-*N*-Ethylidene-2-methoxy-1-phenylethylamine (**2a**): Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, d, J=4.9 Hz, $CHC\underline{H}_3$), 3.35 (3H, s, OCH_3), 3.59 (1H, dd, J=4.3, 9.2 Hz, CH_2O), 3.69 (1H, dd, J=8.5, 9.2 Hz, CH_2O), 4.30 (1H, dd, J=4.3, 8.5 Hz, PhCHN), 7.22—7.39 (5H, m, aromatic H), 7.82 (1H, q, J=4.6 Hz, N=CH). IR (film): 2800 (C–H), 1670 (C=N) cm^{-1}.

(*R*)-2-Methoxy-1-phenyl-*N*-propylideneethylamine (**2b**): Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 2.32 (2H, dq, J=4.9, 7.3 Hz, $C\underline{H}_2CH_3$), 3.35 (3H, s, OCH_3), 3.60 (1H, dd, J=4.9, 9.8 Hz, CH_2O), 3.66 (1H, dd, J=8.6, 9.8 Hz, CH_2O), 4.20 (1H, dd, J=4.9, 8.6 Hz, PhCHN), 7.22—7.40 (5H, m, aromatic H), 7.76 (1H, t, J=4.9 Hz, N=CH). IR (film): 2880 (C–H), 1670 (C=N) cm^{-1}.

(*R*)-2-Methoxy-*N*-(2-methylpropylidene)-1-phenylethylamine (**2c**): Pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.07 [3H, d, J=6.7 Hz, $CH(C\underline{H}_3)_2$], 1.10 [3H, d, J=6.7 Hz, $CH(C\underline{H}_3)_2$], 2.51 [1H, d septet, J=5.5, 6.7 Hz, $C\underline{H}(CH_3)_2$], 3.34 (3H, s, OCH_3), 3.61 (2H, d, J=6.1 Hz, CH_2O), 4.27 (1H, t, J=6.1 Hz, PhCHN), 7.21—7.40 (5H, m, aromatic H), 7.61 (1H, d, J=5.5 Hz, N=CH). IR (film): 2880 (C–H), 1670 (C=N) cm^{-1}.

General Procedure for the Condensation of (*R*)-3 with Carbaldehydes A solution of a carbaldehyde [acetaldehyde, propionaldehyde or isobutyraldehyde (50 mmol)] in dry CH_2Cl_2 (5 ml) was added dropwise to a solution of *N*-methylphenlglycinol (**3**) (5.0 g, 33 mmol) in dry CH_2Cl_2 (50 ml) in the presence of anhydrous $MgSO_4$ (3.0 g) over a 10 min period at 0 °C. The reaction mixture was stirred for 2 h at room temperature, then filtered through a little Celite and the filtrate was concentrated under reduced pressure. The corresponding crude oxazolidine (**4b, c**) was obtained, and purified by bulb-to-bulb distillation.

(2*R*,4*R*)-*N*,2-Dimethyl-4-phenyl-1,3-oxazolidine (**4a**): Colorless oil, oven temperature 63 °C (0.6 mmHg), yield (82%), $[\alpha]_D$ −164° (c=1.10, *n*-hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=5.1 Hz, $CH_2C\underline{H}_3$), 2.16 (3H, s, NCH_3), 3.51 (1H, dd, J=7.1, 8.8 Hz, CH_2O), 3.70 (1H, dd, J=7.1, 8.8 Hz, CH_2O), 4.06 (1H, q, J=5.1 Hz, NCHO), 4.14 (1H, t, J=7.1 Hz, PhCHN), 7.21—7.43 (5H, m, aromatic H). IR (film): 2950 (C–H) cm^{-1}. MS *m/z*: CI, 178 (M^++1); EI, 162 (M^+−CH_3). It was identical with an authentic sample.[15]

(2*R*,4*R*)-2-Ethyl-*N*-methyl-4-phenyl-1,3-oxazolidine (**4b**): Colorless oil, oven temperature 80 °C (2.3 mmHg), yield (95%), $[\alpha]_D$ −166° (c=6.67, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.54—1.86 (2H, m, $C\underline{H}_2CH_3$), 2.17 (3H, s, NCH_3), 3.56 (1H, dd, J=7.3, 9.2 Hz, CH_2O), 3.66 (1H, dd, J=7.3, 9.2 Hz, CH_2O), 3.99 (1H, dd, J=2.4, 6.1 Hz, NCHO), 4.15 (1H, t, J=7.3, PhCHN), 7.24—7.42 (5H, m, aromatic H). IR (film): 2950 (C–H) cm^{-1}. MS *m/z*: CI, 192 (M^++1); EI, 162 (M^+−CH_2CH_3). It was identical with an authentic sample.[15]

(2*R*,4*R*)-*N*-Methyl-2-(1-methyl)ethyl-4-phenyl-1,3-oxazolidine (**4c**): Colorless oil, oven temperature 98 °C (4.2 mmHg), yield (84%), $[\alpha]_D$ −98.2° (c=5.38, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 1.03 [3H, d, J=6.7 Hz, $CH(C\underline{H}_3)_2$], 1.05 [3H, d, J=6.7 Hz, $CH(C\underline{H}_3)_2$], 1.88 [1H, d septet, J=2.4, 6.7 Hz, $C\underline{H}(CH_3)_2$], 2.18 (3H, s, NCH_3), 3.54—3.64 (2H, m, CH_2O), 3.93 (1H, d, J=2.4 Hz, NCHO), 4.08—4.19 (1H, m, PhCHN), 7.22—7.43 (5H, m, aromatic H). IR (film): 2950 (C–H) cm^{-1}. MS *m/z*: CI, 206 (M^++1); EI, 162 [M^+−$CH(C\underline{H}_3)_2$]. *Anal.* Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 75.83; H, 9.51; N, 7.00.

General Procedure for the Reaction of (*R*)-2a—c with Organocerium Reagent Anhydrous cerium chloride (1.0 g, 4.0 mmol) was placed in a 50 ml two-necked flask and heated at 140 °C under 0.1 mmHg for 2 h. While the flask was still hot, nitrogen gas was introduced and the flask was cooled in an ice-bath. Dry THF (30 ml) was then added with stirring and stirring was continued for 2 h at room temperature. The resulting suspension was again cooled to 0 °C and Grignard reagent [C_6H_5MgBr, C_2H_5MgBr, iso-C_3H_7MgBr or CH_3MgBr (4.0 mmol)] was added. The mixture was stirred for 1.5 h at 0 °C, then a solution of crude imine (**2a—c**) (2.0 mmol) in dry THF (5 ml) was added dropwise over a 10 min period and the mixture was warmed to room temperature. It was stirred for 20 h, then the reaction was quenched with a small amount of saturated K_2CO_3 solution. The resulting white precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

(1*S*,1′*R*)-*N*-(2′-Methoxy-1′-phenylethyl)-1-phenylethylamine (**5a**): Prepared by adding the imine (**2a**) to phenylcerium dichloride using the general procedure to give a diastereomeric mixture of **5a** (96:4 mixture) as a pale yellow oil (flash chromatography 0.5% MeOH in CH_2Cl_2). Yield 60% from **1**. ^{1}H-NMR ($CDCl_3$) δ: major component: 1.32 (3H, d, J=6.7 Hz, $NCHC\underline{H}_3$), 2.07 (1H, br s, NH), 3.27 (3H, s, OCH_3), 3.32 (1H, dd, J=4.3, 9.2 Hz, CH_2O), 3.40 (1H, t, J=9.2 Hz, CH_2O), 3.53

(1H, q, J=6.7 Hz, NC<u>H</u>CH_3), 3.63 (1H, dd, J=4.3, 9.2 Hz, PhCHN), 7.14—7.36 (10H, m, aromatic H). IR (film): 3350 (NH), 2880 (C–H) cm^{-1}. MS m/z: CI, 256 (M^++1); EI, 210 ($M^+ - CH_2OCH_3$). *Anal.* Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 80.03; H, 8.32; N, 5.46.

(1*S*,1′*R*)-*N*-(2′-Methoxy-1′-phenylethyl)-1-methylpropylamine (**5b**): Prepared by adding the imine (**2a**) to ethylcerium dichloride using the general procedure to give a diastereomeric mixture of **5b** (96 : 4 mixture) as a colorless oil (flash chromatography 1.0% MeOH in CH_2Cl_2). An analytical sample was purified by bulb-to-bulb distrillation; oven temperature 100 °C (4.2 mmHg). Yield 80% from **1**. ^{1}H-NMR ($CDCl_3$) δ: major component: 0.88 (3H, t, J=6.7 Hz, $NCH_2C\underline{H}_3$), 0.96 (3H, d, J=6.7 Hz, $NCHC\underline{H}_3$), 1.35 (1H, m, $NCHC\underline{H}_2CH_3$), 1.57 (1H, m, $NCHC\underline{H}_2CH_3$), 1.81 (1H, br s, NH), 2.52 (1H, m, $NC\underline{H}CH_2CH_3$), 3.39 (3H, s, OCH_3), 3.41 (1H, dd, J=8.6, 9.2 Hz, CH_2O), 3.46 (1H, dd, J=4.3, 9.2 Hz, CH_2O), 4.03 (1H, dd, J=4.3, 8.6 Hz, PhCHN), 7.27—7.43 (5H, m, aromatic H). IR (film): 3360 (NH), 2960 (C–H) cm^{-1}. MS m/z: CI, 208 (M^++1); EI, 162 ($M^+ - CH_2OCH_3$). *Anal.* Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.38; H, 10.43; N, 6.74.

(1*R*,1′*R*)-*N*-(2′-Methoxy-1′-phenylethyl)-1-methylpropylamine (**5c**): Prepared by adding the imine (**2b**) to methylcerium dichloride using the general procedure to give a diastereomeric mixture of **5c** (94 : 6 mixture) as a colorless oil (flash chromatography 1.0% MeOH in CH_2Cl_2). An analytical sample was purified by bulb-to-bulb distillation; oven temperature 75 °C (4.2 mmHg). Yield 65% from **1**. ^{1}H-NMR ($CDCl_3$) δ: major component: 0.84 (3H, t, J=7.3 Hz, $NCH_2C\underline{H}_3$), 1.01 (3H, d, J=6.1 Hz, $NCHC\underline{H}_3$), 1.20—1.45 (2H, m, $NCHC\underline{H}_2CH_3$), 1.61 (1H, br s, NH), 2.35 (1H, m, $NC\underline{H}CH_2CH_3$), 3.35 (3H, s, OCH_3), 3.39 (1H, dd, J=8.5, 9.2 Hz, CH_2O), 3.44 (1H, dd, J=4.3, 9.2 Hz, CH_2O), 4.04 (1H, dd, J=4.3, 8.5 Hz, PhCHN), 7.22—7.39 (5H, m, aromatic H). IR (film): 3360 (NH), 2970 (C–H) cm^{-1}. MS m/z: CI, 208 (M^++1); EI, 162 ($M^+ - CH_2OCH_3$). *Anal.* Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.31; H, 10.45; N, 6.71.

(1*S*,1′*R*)-*N*-(2′-Methoxy-1′-phenylethyl)-1,2-dimethylpropylamine (**5d**): Prepared by adding the imine (**2a**) to isopropylcerium dichloride using the general procedure to give a diastereomeric mixture of **5d** (98 : 2 mixture) as a colorless oil (flash chromatography 35% Et_2O in hexane). An analytical sample was purified by bulb-to-bulb distillation; oven temperature 75 °C (4.2 mmHg). Yield 74% from **1**. ^{1}H-NMR ($CDCl_3$) δ: major component: 0.82 (3H, d, J=6.7 Hz, $NCHC\underline{H}_3$), 0.83 [3H, d, J=6.7 Hz, $CH(C\underline{H}_3)_2$], 0.86 [3H, d, J=6.7 Hz, $CH(C\underline{H}_3)_2$], 1.73 (1H, br s, NH), 1.85 [1H, d septet, J=4.3, 6.7 Hz, $C\underline{H}(CH_3)_2$], 2.44 (1H, dq, J=4.3, 6.7 Hz, $NC\underline{H}CH_3$), 3.35 (3H, s, OCH_3), 3.37 (1H, dd, J=8.1, 9.5 Hz, CH_2O), 3.42 (1H, dd, J=4.9, 9.5 Hz, CH_2O), 3.98 (1H, dd, J=4.9, 8.1 Hz, PhCHN), 7.21—7.39 (5H, m, aromatic H). IR (film): 3360 (NH), 2960 (C–H) cm^{-1}. MS m/z: CI, 222 (M^++1); EI, 176 ($M^+ - CH_2OCH_3$). *Anal.* Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.67; H, 10.62; N, 6.31.

(1*R*,1′*R*)-*N*-(2′-Methoxy-1′-phenylethyl)-1,2-dimethylpropylamine (**5e**): Prepared by adding the imine (**2c**) to methylcerium dichloride using the general procedure to give a diastereomeric dimixture of **5e** (>99 : 1 mixture) as a colorless oil (flash chromatography 28% Et_2O in hexane). An analytical sample was purified by bulb-to-bulb distillation; oven temperature 72 °C (2.3 mmHg). Yield 72% from **1**. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, d, J=6.7 Hz, $NCHC\underline{H}_3$), 0.83 [3H, d, J=6.7 Hz, $CH(C\underline{H}_3)_2$], 0.96 [3H, d, J=6.7 Hz, $CH(C\underline{H}_3)_2$], 1.54 [1H, d septet, J=4.9, 6.7 Hz, $C\underline{H}(CH_3)_2$], 1.60 (1H, br s, NH), 2.22 (1H, dq, J=4.9, 6.7 Hz, $NC\underline{H}CH_3$), 3.35 (3H, s, OCH_3), 3.38 (1H, dd, J=7.9, 9.2 Hz, CH_2O), 3.41 (1H, dd, J=4.9, 9.2 Hz, CH_2O), 4.03 (1H, dd, J=4.9, 7.9 Hz, PhCHN), 7.21—7.39 (5H, m, aromatic H). IR (film): 3350 (NH), 2950 (C–H) cm^{-1}. MS m/z: CI, 222 (M^++1); EI, 176 ($M^+ - CH_2OCH_3$). *Anal.* Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.95; H, 10.60; N, 6.31.

(1*S*,1′*R*)-*N*-(2′-Methoxy-1′-phenylethyl)-2-methyl-1-phenylpropylamine (**5f**): Prepared by adding the imine (**2c**) to phenylcerium dichloride using the general procedure to give a diastereomeric mixture of **5f** (>99 : 1 mixture) as a pale yellow oil (flash chromatography 15% Et_2O in hexane). Yield 93% from **1**. ^{1}H-NMR ($CDCl_3$) δ: 0.66 [3H, d, J=6.7 Hz, $CH(C\underline{H}_3)_2$], 1.02 [3H, d, J=6.7 Hz, $CH(C\underline{H}_3)_2$], 1.80 [1H, octet, J=4.9, 6.7 Hz, $C\underline{H}(CH_3)_2$], 2.18 (1H, br s, NH), 2.99 (1H, d, J=6.7 Hz, $NC\underline{H}CHCH_3$), 3.24 (3H, s, OCH_3), 3.28 (1H, dd, J=4.3, 9.2 Hz, CH_2O), 3.40 (1H, t, J=9.2 Hz, CH_2O), 3.58 (1H, dd, J=4.3, 9.2 Hz, PhCHN), 7.06—7.34 (10H, m, aromatic H). IR (film): 3350 (NH), 2870 (C–H) cm^{-1}. MS m/z: CI, 284 (M^++1); EI, 240 [$M^+ - CH(CH_3)_2$], 238 ($M^+ - CH_2OCH_3$). *Anal.* Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.65; H, 8.92; N, 4.91.

General Procedure for the Preparation of *N,O*-Dimethylamine (6a, b, d, f) A solution of an amine (**5a, b, d, f**) (1.3 mmol) in dry THF (5 ml) was added dropwise to a stirred suspension of 60% NaH (2.6 mmol) in dry THF (10 ml) at room temperature under a nitrogen atmosphere. The resulting pale yellow mixture was stirred for 3 h and then a solution of methyl iodide (3.9 mmol) in dry THF (10 ml) was added dropwise over a 10 min period. The mixture was stirred for 40 h, the mixture was poured into water and extracted with ether (3 × 10 ml). The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to leave the residue, which was subjected to column chromatography on silica gel to give the corresponding *N,O*-dimethylamine (**7a, b, d, f**) as an oil.

(1*S*,1′*R*)-*N*-(2′-Methoxy-1′-phenylethyl)-*N*-methyl-1-phenylethylamine (**6a**): This compound was prepared by *N*-methylation of amine **5a** (4 : 96 mixture) according to the general procedure. Pale yellow oil. Yield: 89% (96 : 4 mixture) (flash chromatography $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: major component: 1.33 (3H, d, J=6.7 Hz, $NCHC\underline{H}_3$), 2.13 (3H, s, NCH_3), 3.26 (3H, s, OCH_3), 3.62 (1H, dd, J=6.1, 9.8 Hz, CH_2O), 3.75 (1H, dd, J=6.1, 9.8 Hz, CH_2O), 3.79 (1H, q, J=6.7 Hz, $NC\underline{H}CH_3$), 3.89 (1H, t, J=6.1 Hz, PhCHN), 7.16—7.42 (10H, m, aromatic H).

(1*S*,1′*R*)-*N*-(2′-Methoxy-1′-phenylethyl)-*N*,1-dimethylpropylamine (**6b**): This compound was prepared by *N*-methylation of amine **5b** (4 : 96 mixture) according to the general procedure. Pale yellow oil. Yield: 92% (95 : 5 mixture) (flash chromatography 30% ether in hexane). ^{1}H-NMR ($CDCl_3$) δ: major component: 0.83 (3H, t, J=7.3 Hz, $NCH_2C\underline{H}_3$), 0.93 (3H, d, J=6.7 Hz, $NCHC\underline{H}_3$), 1.14—1.31 (1H, m, $NCHC\underline{H}_2CH_3$), 1.43—1.62 (1H, m, $NCHC\underline{H}_2CH_3$), 2.10 (3H, s, NCH_3), 2.72 (1H, sextet, J=6.7 Hz, $NC\underline{H}CH_2CH_3$), 3.28 (3H, s, OCH_3), 3.55 (1H, dd, J=4.9, 9.2 Hz, CH_2O), 3.68—3.78 (2H, m, $PhC\underline{H}C\underline{H}_2O$), 7.19—7.36 (5H, m, aromatic H). MS m/z: CI, 222 (M^++1); EI, 176 ($M^+ - CH_2OCH_3$).

(1*S*,1′*R*)-*N*-(2′-Methoxy-1′-phenylethyl)-*N*,1,2-trimethylpropylamine (**6d**): This compound was prepared by *N*-methylation of amine **5d** (98 : 2 mixture) according to the general procedure. Pale yellow oil. Yield: 81% (98 : 2 mixture) (flash chromatography 9% ether in hexane). ^{1}H-NMR ($CDCl_3$) δ: major component: 0.88 (3H, d, J=6.7 Hz, $NCHC\underline{H}_3$), 0.89 [3H, d, J=6.7 Hz, $CH(C\underline{H}_3)_2$], 1.00 [3H, d, J=6.7 Hz, $CH(C\underline{H}_3)_2$], 1.65 [1H, d septet, J=6.7, 9.2 Hz, $C\underline{H}(CH_3)_2$], 1.95 (3H, s, NCH_3), 2.54 (1H, dq, J=6.7, 9.2 Hz, $NC\underline{H}CH_3$), 3.27 (3H, s, OCH_3), 3.45—3.53 (1H, m, CH_2O), 3.68—3.75 (2H, m, $PhC\underline{H}C\underline{H}_2O$), 7.19—7.35 (5H, m, aromatic H). MS m/z: CI, 236 (M^++1); EI, 192 [$M^+ - CH(CH_3)_2$], 190 ($M^+ - CH_2OCH_3$).

(1*S*,1′*R*)-*N*-(2′-Methoxy-1′-phenylethyl)-*N*,2-dimethyl-1-phenylpropylamine (**6f**): This compound was prepared by *N*-methylation of **5f** (>99 : 1 mixture) according to the general procedure. Pale yellow oil. Yield: 77% (1 : >99 mixture) (flash chromatography 6% ether in hexane). ^{1}H-NMR ($CDCl_3$) δ: 0.56 [3H, d, J=6.1 Hz, $CH(C\underline{H}_3)_2$], 0.99 [3H, d, J=6.1 Hz, $CH(C\underline{H}_3)_2$], 2.18—2.31 [1H, m, $C\underline{H}(CH_3)_2$], 2.25 (3H, s, NCH_3), 3.08 (1H, d, J=9.2 Hz, $NC\underline{H}CHCH_3$), 3.15 (3H, s, OCH_3), 3.44—3.55 (3H, m, $PhC\underline{H}C\underline{H}_2O$), 7.07—7.41 (10H, m, aromatic H). MS m/z: CI, 298 (M^++1); EI, 254 [$M^+ - CH(CH_3)_2$], 252 ($M^+ - CH_2OCH_3$).

General Procedure for the reaction of (*R*)-4a—c with Grignard Reagents A Grignard reagent [C_6H_5MgBr, C_2H_5MgBr, iso-C_3H_7MgBr or CH_3MgBr (5.1 mmol)] was added dropwise to a stirred solution of (2*R*,4*R*)-**4a—c** (1.7 mmol) in THF (30 ml) at 0 °C under nitrogen atmosphere over a period of 15 min. The mixture was stirred at room temperature for 20 h, then the reaction was quenched with saturated ammonium chloride (20 ml), the organic layer was separated and the aqueous layer was extracted with ether (2 × 20 ml). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give an oily residue, which was subjected to column chromatography on silica gel with ether–hexane to give a diastereomeric mixture of the corresponding amine (**7a—f**).

(1*R*,1′*R*)-*N*-(2′-Hydroxy-1′-phenylethyl)-*N*-methyl-1-phenylethylamine (**7a**): Prepared by adding C_6H_5MgBr to the oxazolidine (**4a**) using the general procedure to give a diastereomeric mixture of **7a** (78 : 22 mixture) as a pale yellow oil (flash chromatography 35% hexane in ether). Yield 90% ^{1}H-NMR ($CDCl_3$) δ: major component: 1.40 (3H, d, J=6.7 Hz, $NCHC\underline{H}_3$), 2.03 (3H, s, NCH_3), 3.69 (1H, q, J=6.7 Hz, $NC\underline{H}CH_3$), 3.72 (1H, dd, J=5.4, 10.4 Hz, CH_2O), 3.97 (1H, dd, J=8.6, 10.4 Hz, CH_2O), 4.16 (1H, dd, J=5.4, 8.6 Hz, $NC\underline{H}CH_2O$), 7.22—7.36

(5H, m, aromatic H). IR (film): 3430 (OH), 2900 (C–H) cm^{-1}. MS *m/z*: CI, 256 ($M^+ + 1$); EI, 224 ($M^+ - CH_2OH$). It was identical with an authentic sample.[12a)]

(1*R*,1′*R*)-*N*-(2′-Hydroxy-1′-phenylethyl)-*N*,1-dimethylpropylamine (**7b**): Prepared by adding C_2H_5MgBr to the oxazolidine (**4a**) using the general procedure to give a diastereomeric mixture of **7b** (66 : 34 mixture) as a pale yellow oil (flash chromatography, 35% hexane in ether), yield 93%. ^{1}H-NMR ($CDCl_3$) δ: major component: 0.78 (3H, d, J=6.7 Hz, $NCHCH_3$), 0.85 (3H, t, J=7.3 Hz, $NCHCH_2CH_3$), 1.21—1.51 (2H, m, $NCHCH_2CH_3$), 2.25 (3H, s, NCH_3), 2.65 (1H, sextet, J=6.7 Hz, $NCHCH_3$), 3.86 (1H, dd, J=4.3, 8.5 Hz, CH_2O), 3.74—3.84 (2H, m, $NCHCH_2O$), 7.25—7.36 (5H, m, aromatic H). IR (film): 3430 (OH), 2900 (C–H) cm^{-1}. MS *m/z*: CI, 208 ($M^+ + 1$); EI, 176 ($M^+ - CH_2OH$). *Anal.* Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.05; H, 10.34; N, 6.65.

(1*S*,1′*R*)-*N*-(2′-Hydroxy-1′-phenylethyl)-*N*,1-dimethylpropylamine (**7c**): Prepared by adding CH_3MgBr to the oxazolidine (**4b**) using the general procedure to give a diastereomeric mixture of **6c** (15 : 85 mixture) as a pale yellow oil (flash chromatography 35% hexane in ether), yield 89%. ^{1}H-NMR ($CDCl_3$) δ: major component: 0.82 (3H, d, J=6.7 Hz, $NCHCH_3$), 0.88 (3H, t, J=7.3 Hz, $NCHCH_2CH_3$), 1.19—1.36 (1H, m, $NCHCH_2CH_3$), 1.37—1.53 (1H, m, $NCHCH_2CH_3$), 2.12 (3H, s, NCH_3), 2.76 (1H, sextet, J=6.7 Hz, $NCHCH_3$), 3.53—3.89 (3H, m, $NCHCH_2O$), 7.23—7.35 (5H, m, aromatic H). IR (film): 3450 (OH), 2960 (C–H) cm^{-1}. MS *m/z*: CI, 208 ($M^+ + 1$); EI, 207 (M^+), 176 ($M^+ - CH_2OH$). *Anal.* Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.21; H, 10.37; N, 6.62.

(1*R*,1′*R*)-*N*-(2′-Hydroxy-1′-phenylethyl)-*N*,1,2-trimethylpropylamine (**7d**): Prepared by adding iso-C_3H_7MgBr to the oxazolidine (**4a**) using the general procedure to give a diastereomeric mixture of **7d** (44 : 56 mixture) as a pale yellow oil (flash chromatography, 35% ether in hexane), yield 86%. ^{1}H-NMR ($CDCl_3$) δ: minor component: 0.70 (3H, d, J=6.7 Hz, $NCHCH_3$), 0.78 [3H, d, J=6.7 Hz, $CH(CH_3)_2$], 0.95 [3H, d, J=6.7 Hz, $CH(CH_3)_2$], 1.67—1.76 [1H, m, $CH(CH_3)_2$], 2.21—2.32 (1H, m, $NCHCH_3$), 2.28 (3H, s, NCH_3), 2.69 (1H, br s, OH), 3.68—3.83 (3H, m, $PhNCHCH_2O$), 7.26—7.31 (5H, m, aromatic H). IR (film): 3440 (OH), 2950 (C–H) cm^{-1}. MS *m/z*: CI, 222 ($M^+ + 1$); EI, 190 ($M^+ - CH_2OH$), 178 [$M^+ - CH(CH_3)_2$]. *Anal.* Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 76.09; H, 10.68; N, 6.34.

(1*S*,1′*R*)-*N*-(2′-Hydroxy-1′-phenylethyl)-*N*,1,2-trimethylpropylamine (**7e**): Prepared by adding CH_3MgBr to the oxazolidine (**4c**) using the general procedure to give a diastereomeric mixture of **7e** (9 : 91 mixture) as a pale yellow oil (flash chromatography, 35% ether in hexane). An analytical sample was purified by bulb-to-bulb distillation; oven temperature 100 °C (2.3 mmHg), yield 89%. ^{1}H-NMR ($CDCl_3$) δ: major component: 0.74 (3H, d, J=6.7 Hz, $NCHCH_3$), 0.89 [3H, d, J=6.7 Hz, $CH(CH_3)_2$], 1.02 [3H, d, J=6.7 Hz, $CH(CH_3)_2$], 1.70 [1H, d septet, J=6.7, 8.6 Hz, $CH(CH_3)_2$], 2.06 (3H, s, NCH_3), 2.49 (1H, dq, J=6.7, 8.6 Hz, $NCHCH_3$), 3.57 (1H, dd, J=3.7, 9.2 Hz, CH_2O), 3.78—3.92 (2H, m, $PhNCHCH_2O$), 7.23—7.37 (5H, m, aromatic H). IR (film): 3340 (OH), 2960 (C–H) cm^{-1}. MS *m/z*: CI, 222 ($M^+ + 1$); EI, 190 ($M^+ - CH_2OH$), 178 [$M^+ - CH(CH_3)_2$]. *Anal.* Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 76.15; H, 10.69; N, 6.33.

(1*R*,1′*R*)-*N*-(2′-Hydroxy-1′-phenylethyl)-*N*,2-dimethyl-1-phenylethylamine (**7f**): Prepared by adding C_6H_5MgBr to the oxazolidine (**4c**) using the general procedure to give a diastereomeric mixture of **7f** (93 : 7 mixture) as a pale yellow oil (flash chromatography, 15% ether in hexane). An analytical sample was purified by bulb-to-bulb distillation; oven temperature 170 °C (2.3 mmHg), yield 93%. ^{1}H-NMR ($CDCl_3$) δ: major component: 0.76 [3H, d, J=6.7 Hz, $CH(CH_3)_2$], 1.05 [3H, d, J=6.7 Hz, $CH(CH_3)_2$], 1.59 (1H, br s, OH), 2.07 (3H, s, NCH_3), 2.41 [1H, m, $CH(CH_3)_2$], 3.37 [1H, d, J=8.6 Hz, $NCHCH(CH_3)_2$], 3.47—3.96 (3H, m, $PhNCHCH_2O$), 7.03—7.37 (10H, m, aromatic H). IR (film): 3350 (OH), 2960 (C–H) cm^{-1}. MS *m/z*: CI, 284 ($M^+ + 1$); EI, 252 ($M^+ - CH_2OH$), 240 [$M^+ - CH(CH_3)_2$]. *Anal.* Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.73; H, 8.99; N, 4.93.

General Procedure for the Preparation of *N,O*-Dimethylamines (8a,c,e,f) The same procedure as for **6a,b,d,f** was used on a 1.0 mmol scale.

(1*R*,1′*R*)-*N*-(2′-Methoxy-1′-phenylethyl)-*N*-methyl-1-phenylethylamine (**8a**): This compound was prepared by *O*-methylation of amine **7a** (78 : 22 mixture) according to the general procedure. Pale yellow oil. Yield: 93% (75 : 25 mixture) (flash chromatography with $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: major component: 1.30 (3H, d, J=6.7 Hz, $NCHCH_3$), 2.18 (3H, s, NCH_3), 3.30 (3H, s, OCH_3), 3.67 (1H, dd, J=6.1, 9.8 Hz, CH_2O), 3.81 (1H, dd, J=5.5, 9.8 Hz, CH_2O), 3.84 (1H, q, J=6.7 Hz, $NCHCH_3$), 3.92 (1H, dd, J=5.5, 6.1 Hz, PhCHN), 7.16—7.41 (10H, m, aromatic H).

(1*S*,1′*R*)-*N*-(2′-Methoxy-1′-phenylethyl)-*N*,1-dimethylpropylamine (**8c**): This compound was prepared by *O*-methylation of **7c** (15 : 85 mixture) according to the general procedure. Pale yellow oil. Yield: 90% (14 : 86 mixture) (flash chromatography with 30% ether in hexane). This major product was identical with the major product obtained by the *N*-methylation of **5b** (4 : 96 mixture).

(1*S*,1′*R*)-*N*-(2′-Methoxy-1′-phenylethyl)-*N*,1,2-trimethylpropylamine (**8e**): This compound was prepared by *O*-methylation of **7e** (9 : 91 mixture) according to the general procedure. pale yellow oil. Yield: 87% (9 : 91 mixture) (flash chromatography with 9% ether in hexane). This major product was identical with the major product obtained by the *N*-methylation of **5d** (2 : 98 mixture).

(1*R*,1′*R*)-*N*-(2′-Methoxy-1′-phenylethyl)-*N*,2-dimethyl-1-phenylpropylamine (**8f**): This compound was prepared by *O*-methylation of **7f** (93 : 7 mixture) according to the general procedure. Pale yellow oil. Yield: 89% (92 : 8 mixture) (flash chromatography 6% with ether in hexane). ^{1}H-NMR ($CDCl_3$) δ: major component: 0.75 [3H, d, J=6.7 Hz, $CH(CH_3)_2$], 0.98 [3H, d, J=6.7 Hz, $CH(CH_3)_2$], 2.06 (3H, s, NCH_3), 2.32—2.37 [1H, m, $CH(CH_3)_2$], 3.27 (3H, s, OCH_3), 3.56 (1H, d, J=7.9 Hz, $NCHCHCH_3$), 3.64 (1H, dd, J=6.7, 9.2 Hz, $PhCHCH_2O$), 3.73—3.83 (2H, m, $PhCHCH_2O$), 7.08—7.41 (10H, m, aromatic H). MS *m/z*: CI, 298 ($M^+ + 1$); EI, 254 [$M^+ - CH(CH_3)_2$], 252 ($M^+ - CH_2OCH_3$).

(*S*)-*N*,1-Dimethylpropylamine Hydrochloride [(*S*)-9] A solution of **7c** (15 : 85 mixture) (0.14 g, 20 mmol) in ethyl acetate was hydrogenated over palladium hydroxide on carbon (20 mg) under 3.5 kg/cm^2 of hydrogen for 70 h at room temperature. The reaction mixture was filtered through a little Celite, and a solution of saturated HCl in EtOH (1 ml) was added dropwise to the filtrate. The mixture was concentrated under reduced pressure to leave a crystalline residue, which was purified by recrystallization to give the (*S*)-**9**·HCl salt as colorless needles, yield 95%, mp 119 °C (from CH_2Cl_2–hexane), $[\alpha]_D$ −5.8° (c=4.8, EtOH). For the HCl salt, ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, t, J=7.3 Hz, CH_2CH_3), 1.41 (3H, d, J=6.1 Hz, $NCHCH_3$), 1.63—1.79 (1H, m, CH_2CH_3), 1.91—2.06 (1H, m, CH_2CH_3), 2.64 (3H, s, NCH_3), 3.01—3.07 (1H, m, $NCHCH_3$), 9.40 (2H, br s, N^+H_2). For the free amine, IR (film): 2950 (C–H) cm^{-1}. MS *m/z*: CI, 88 ($M^+ + 1$); EI, 58 ($M^+ - CH_2CH_3$).

(*R*)-*N*,1-Dimethylpropylamine Hydrochloride [(*R*)-9] A solution of (*R*)-1-methylpropylamine (1.0 g, 13 mmol) in ethyl formate (10 ml) was refluxed for 9 h, then the solvent was evaporated off under reduced pressure. The oily residue was added dropwise to a stirred suspension of $LiAlH_4$ (1.1 g, 28 mmol) in dry THF (50 ml) and the mixture was refluxed for 4 h, after which the excess hydride was decomposed by slow addition of water (2 ml). The mixture was filtered through a little Celite, then a solution of saturated HCl in EtOH (1 ml) was added dropwise to this filtrate and the whole was concentrated under reduced pressure to leave a crystalline residue, which was purified by recrystallization to give the (*R*)-**9**·HCl salt as colorless needles, yield 95%, mp 120 °C (from CH_2Cl_2–hexane), $[\alpha]_D$ +6.4° (c=5.2, EtOH). The spectral data were identical with those of (*S*)-**9**·HCl salt.

(*R*)-1,2-Dimethylpropylamine Hydrochloride [(*R*)-10] A mixture of (1*R*,1′*R*)-**5e** (>99 : 1) (0.30 g, 1.4 mmol), ammonium formate (1.3 g, 20 mmol) and 10% palladium on carbon (50 mg) in methanol (30 ml) was refluxed for 24 h. The mixture was filtered through a little Celite, then a solution of saturated HCl in ethanol (3 ml) was added dropwise to the filtrate and the mixture was concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (10 ml) and the solution was filtered then evaporated. The residue was dissolved in ether and 5% hydrochloric acid (1 : 1, v/v, 20 ml), and the aqueous layer was separated. Concentration of the aqueous layer afford a crystalline residue, which was purified by recrystallization to give (*R*)-**10**·HCl as a colorless solid, yield 95%, mp 205 °C (from acetone), $[\alpha]_D$ +2.15° (c=1.07, EtOH). [lit.,[13)] (*R*)-**10**·HCl: $[\alpha]_{546}$ +3.5° (c=6.54, water)]. For the HCl salt, ^{1}H-NMR ($CDCl_3$) δ: 1.01 [3H, d, J=6.7 Hz, $CH(CH_3)_2$], 1.07 [3H, d, J=6.7 Hz, $CH(CH_3)_2$], 1.36 (3H, d, J=6.7 Hz, $NCHCH_3$), 1.92—2.10 [1H, m, $CH(CH_3)_2$], 2.13—2.87 (1H, m, $NCHCH_3$), 8.36 (3H, br s, N^+H_3). For the free amine, MS *m/z*: CI, 88 ($M^+ + 1$); EI, 44 [$M^+ - CH(CH_3)_2$].

(*R*)-*p*-Nitro-*N*-(1,2-dimethylpropyl)benzamide [(*R*)-11] A solution of 4-nitrobenzoyl chloride (0.11 g, 0.58 mmol) in dry ether (5 ml) was added dropwise to a stirred solution of (*R*)-**10** (60 mg, 0.48 mmol) and

triethylamine (0.14 g, 1.4 mmol) in dry ether (10 ml) over a 5 min period at 0 °C. The reaction mixture was stirred for 2 h at room temperature, then it was filtered through a little Celite and the filtrate was concentrated under reduced pressure to leave a residue, which was subjected to column chromatography on silica gel with CH_2Cl_2–ether (20 : 1) to give (*R*)-**11** as colorless needles, yield, 44%, mp 115 °C (from hexane), $[\alpha]_{546}$ −40.9° (*c* = 1.63, pyridine) [lit.,[13] (*R*)-**11**: $[\alpha]_{546}$ −55.8° (*c* = 4.84, pyridine)]. ^{1}H-NMR ($CDCl_3$) δ: 0.98 [3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)_2$], 0.99 [3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)_2$], 1.21 (3H, d, *J* = 6.7 Hz, $NCHC\underline{H}_3$), 1.84 [1H, octet, *J* = 6.7 Hz, $C\underline{H}(CH_3)_2$], 4.10 (1H, d quintet, *J* = 8.9, 6.7 Hz, $NC\underline{H}CH_3$), 5.95 (1H, br s, NH), 7.88—7.94 (2H, m, aromatic H), 8.25—8.31 (2H, m, aromatic H). MS *m/z*: CI, 237 ($M^+ + 1$); EI, 193 [$M^+ - CH(CH_3)_2$].

(1*R*,1′*R*)-*N*-(2′-Hydroxy-1′-phenylethyl)-2-methyl-1-phenylpropylamine (13) A mixture of (*R*)-phenylglycinol (2.0 g, 14.6 mmol), isobutyrophenone (2.3 g, 15.5 mmol) and a catalytic amount of *p*-toluenesulfonic acid in toluene (30 ml) was refluxed for 20 h using a Dean–Stark trap. After cooling, the reaction mixture was washed with saturated Na_2CO_3 and brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the imine (**12**) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 0.95 [3H, d, *J* = 7.3 Hz, $CH(C\underline{H}_3)_2$], 1.00 [3H, d, *J* = 7.3 Hz, $CH(C\underline{H}_3)_2$], 2.22 [1H, septet, *J* = 7.3 Hz, $C\underline{H}(CH_3)_2$], 3.73 (1H, t, *J* = 7.3 Hz, CH_2O), 4.06 (1H, t, *J* = 7.3 Hz, CH_2O), 4.10 (1H, t, *J* = 7.3 Hz, $NC\underline{H}CH_2O$), 7.20—7.40 (8H, m, aromatic H), 7.63 (2H, dd, *J* = 8.3, 1.5 Hz, aromatic H). This, without further purification, was used for the next reaction.

A solution of the aldimine (**12**) (2.0 g, 7.5 mmol) in THF (30 ml) was hydrogenated over 10% palladium on carbon (20 mg) at atmospheric pressure for 72 h at room temperature. The reaction mixture was filtered through a little Celite, and the filtrate was evaporated under reduced pressure to give a diastereomeric amine mixture (**13a, b**) (75 : 25 mixture), which was separated by column chromatography on silica gel with CH_2Cl_2–ether (20 : 1) as the eluent. The first fraction gave the major product (**13a**) as a colorless oil, yield 74%, $[\alpha]_D$ −16.1° (*c* = 0.47, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.78 [3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)_2$], 1.00 [3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)_2$], 1.94 [1H, octet, *J* = 6.7 Hz, $C\underline{H}(CH_3)_2$], 3.40 [1H, d, *J* = 6.7 Hz, $NC\underline{H}CH(CH_3)_2$], 3.53 (1H, dd, *J* = 5.5, 10.4 Hz, CH_2O), 3.69 (1H, dd, *J* = 4.9, 5.5 Hz, $NC\underline{H}CH_2O$), 3.78 (1H, dd, *J* = 4.9, 10.4 Hz, CH_2O), 7.09—7.29 (10H, m, aromatic H). IR (film): 3370 (NH), 2950 (C–H) cm^{-1}. MS *m/z*: CI, 270 ($M^+ + 1$); EI, 220 [$M^+ - CH(CH_3)_2$]. *Anal.* Calcd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.20. Found: C, 80.26; H, 8.81; N, 5.23. The second fraction gave the minor product (**13b**) as a colorless oil, yield, 23%. ^{1}H-NMR ($CDCl_3$) δ: 0.67 [3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)_2$], 0.97 [3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)_2$], 1.74—1.87 [1H, m, $C\underline{H}(CH_3)_2$], 3.12 [1H, d, *J* = 7.9 Hz, $NC\underline{H}CH(CH_3)_2$], 3.44—3.57 (3H, m, $NC\underline{H}C\underline{H}_2O$), 7.09—7.38 (10H, m, aromatic H).

(*R*)-2-Methyl-1-phenylpropylamine [(*R*)-14] Lead tetraacetate (2.6 g, 5.8 mmol) was added in one portion to a stirred solution of the amine (**13a**) (1.3 g, 5.3 mmol) in CH_2Cl_2–methanol (2 : 1, v/v, 40 ml) at 0 °C. The reaction mixture was stirred for 2 min, basified with 15% NaOH solution and extracted with CH_2Cl_2 (3 × 30 ml). The combined extracts were washed with brine and concentrated under reduced pressure to leave the residue, which was dissolved in ether–3 N HCl (1 : 2, v/v, 20 ml). This solution was stirred for 20 h at room temperature. The layers were separated, and the aqueous layer was basified with Na_2CO_3 and extracted with ether (3 × 30 ml). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to leave the viscous oil, which was purified by bulb-to-bulb distillation to give the amine (**14**) as a colorless oil, yield 67%, oven temperature 110 °C (17 mmHg), $[\alpha]_D$ +3.84° (*c* = 3.21, EtOH). ^{1}H-NMR ($CDCl_3$) δ: 0.77 [3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)_2$], 0.98 [3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)_2$], 1.56 (2H, br s, NH_2), 1.77—1.94 [1H, m, $C\underline{H}(CH_3)_2$], 3.60 [1H, d, *J* = 7.3 Hz, $NC\underline{H}CH(CH_3)_2$], 7.20—7.35 (5H, m, aromatic H). MS *m/z*: CI, 150 ($M^+ + 1$); EI, 106 [$M^+ - CH(CH_3)_2$]. (*R*)-**14**·HCl: ^{1}H-NMR ($CDCl_3$) δ: 0.97 [3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)_2$], 1.06 [3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)_2$], 2.23—2.35 [1H, m, $C\underline{H}(CH_3)_2$], 3.74—3.92 [1H, m, $NC\underline{H}CH(CH_3)_2$], 7.32—7.38 (5H, m, aromatic H), 8.82 (3H, br s, $N^+\underline{H}_3$).

(*R*)-*N*-(2-Methyl-1-phenylpropyl)acetamide [(*R*)-15] A solution of the amine (*R*)-**14** (0.48 g, 3.2 mmol) in acetic anhydride (20 ml) was stirred under a nitrogen atmosphere at room temperature. After the mixture had been stirred for 3 h, the mixture was poured into water (50 ml) and extracted with ether (3 × 30 ml). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to leave the residue, which was subjected to column chromatography on aluminum oxide with CH_2Cl_2–hexane (9 : 1) to give the acetate (**15**) as colorless needles, yield 72%, mp 120 °C (from CH_2Cl_2–hexane), $[\alpha]_D$ +135° (*c* = 3.83, MeOH) [lit.,[14] (*R*)-**15**: $[\alpha]_D$ +72.3° (*c* = 3.8, MeOH)]. ^{1}H-NMR ($CDCl_3$) δ: 0.83 [3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)_2$], 0.97 [3H, d, *J* = 6.7 Hz, $CH(C\underline{H}_3)_2$], 1.96—2.12 [1H, m, $C\underline{H}(CH_3)_2$], 2.01 (3H, s, $COC\underline{H}_3$), 4.77 [1H, d, *J* = 8.6 Hz, $NC\underline{H}CH(CH_3)_2$], 5.79 (1H, br s, NH), 7.22—7.37 (5H, m, aromatic H). MS *m/z*: CI, 192 ($M^+ + 1$); EI, 148 [$M^+ - CH(CH_3)_2$].

***O*-Methylation of (*R*)-13b** A solution of the amine (**13b**, 0.24 g, 0.90 mmol) in dry THF (5 ml) was added dropwise to a stirred suspension of 60% NaH (60 mg, 1.5 mmol) in dry THF (10 ml) at room temperature under a nitrogen atmosphere. The resulting pale yellow mixture was stirred for 3 h and then a solution of methyl iodide (0.22 g, 1.5 mmol) in dry THF (10 ml) was added dropwise. The mixture was refluxed for 40 h, poured into water and extracted with ether (3 × 10 ml). The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to leave the residue, which was subjected to column chromatography on silica gel with hexane–ether (6 : 1) to give the *O*-methylamine (**5f**) as an oil, yield 86%. This compound was identical with the major product obtained from the reaction of imine the **2c** with $PhCeCl_2$ on the basis of ^{1}H-NMR (270 MHz) spectral comparison.

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