Synthesis of Enantiopure *o*-Hydroxybenzylamines by Stereoselective Reduction of 2-Imidoylphenols: Application in the Catalytic Enantioselective Addition of Diethylzinc to Aldehydes

Gianni Palmieri[a]

Keywords: Aminophenols /Asymmetric synthesis / C–C coupling / Reductions / Conformation analysis

Enantiopure *o*-hydroxybenzylamines **2a–i** were synthesized by diastereoselective reduction of the 2-imidoylphenols (*R*)-**1a–i**. Conformational analysis enabled the assignment of the absolute configurations of compounds **2a–i**. The accessible *o*-hydroxybenzylamine (*R*,*R*)-**2h** serves as an effective catalyst precursor for highly enantioselective addition of diethylzinc to aliphatic and aromatic aldehydes. This pathway represents a practical and operationally very simple methodology for the enantioselective synthesis of both the enantiomers of secondary alcohols **7a–f**.

Catalytic asymmetric synthesis is an important subject in the field of organic synthesis. The development of efficient enantioselective catalysts applicable to a wide range of reactions represents an important challenge in synthetic organic chemistry. Among these catalysts, β-amino alcohols have been proved to be extremely efficient in catalytic reactions such as the synthesis of optically active secondary alcohols by enantioselective addition of diorganozinc compounds to aldehydes.[1]

In the course of developing the chemistry of 2-imidoylphenols **1**[2a] it has been found that they can be stereoselectively reduced to (*R*,*R*)-*o*-hydroxybenzylamine **2**. In addition, the presence of a catalytic amount of enantiopure (*R*,*R*)-*o*-hydroxybenzylamine **2** significantly enhances the rate of the reaction between diethylzinc and benzaldehyde to give stereoselectively and nearly quantitatively (*S*)-1-phenyl-1-propanol (**7a**) after hydrolysis. The *o*-hydroxybenzylamines **2a−i** were obtained with good to high *d.e.* and yields by two reductive methodologies applied to the imidoylphenols **1a−i**, which are accessible starting materials in both enantiomeric forms[2−4] (see Table 1).

Our methodology has been applied in Method A, and this has already been used in the diastereoselective reduction of the enamino esters.[5] The reaction of (*R*)-imidoylphenols **1a−i** with sodium borohydride in acetic acid/THF, occurs through an intramolecular diastereoselective hydride transfer in the aryloxyborohydride intermediate **4**. The asymmetric induction can be rationalized by examining the possible transition-state geometries depicted in Figure 1 for **4a**, **i**. The intramolecular hydride transfer occurs prevalently in the less hindered *si* face of the immonium function in the case of small R groups, as in **4a−h**, with formation of the (*R*)-*o*-hydroxybenzylamines (*R*)-**2a−h**. When R = *t*Bu the more stable conformation for **4i** is that depicted in Figure 1 and, therefore, only in this case does the consequent hydride transfer occur from the less hindered *re* face with formation of the (*S*)-*o*-hydroxybenzylamine (*S*)-**2i**.

In Method B the optimal conditions were determined for the stereoselective reduction of (*R*)-imidoylphenols **1a−i** using sodium borohydride in methanol, in the presence of cerium trichloride (Luche′s Reagent).[6] Cerium trichloride enhances the acidity of methanol (through complexation) and induces its reaction with $NaBH_4$ giving $BH_{(4-n)}(OCH_3)_n^-$ species. Alkoxy borohydrides are known to be more reactive[7] than BH_4^-, and should be at least in part responsible for the very high reduction rate. $CeCl_3$ meanwhile can coordinate with the phenolic hydroxy group, thus enhancing the reactivity of the imidoyl function towards nucleophiles. The hypothesis of phenol/methanol exchange with formation of an intermediate similar to **4** and a consequent intramolecular hydride transfer, as proposed for the mechanism of Method A, must be rejected for stereoelectronic reasons The proposed hypothetical push-pull type mechanism of the reduction with electrophilic assistance, probably provides the transition state for the hydride transfer as shown in Figure 2.

The reduction rate and stereoselectivity both increase with the amount of $CeCl_3$ added. Reaction is very fast and highly stereoselective in methanol at low temperature with 0.5 molar equiv. of $CeCl_3 \cdot 7\ H_2O$ (with respect to 2-imidoylphenol, as shown in Figure 2). Generally the hydride transfer occurs preferentially on the *si* face of the imidoyl function with formation of *o*-hydroxybenzylamine (*R*,*R*)-**2**. Only with bulky groups (R = *i*Pr, *t*Bu), as in **1g**, **i**, does the transition structure assume a different conformation, with a different orientation of the chiral group at the N atom (as in **4i**), inducing the hydride transfer to occur predominantly from the less hindered *re* face of the imidoyl function with formation of the *o*-hydroxybenzylamine (1*S*,1′*R*)-**2g**,**i**. In the case of a bulky substrate, as in compound **1h**, the reaction is very slow with low conversion yield. Generally method B leads to better yields and *d.e.*, although method A is sometimes preferable due to the different stereoselectivity and the convenience of the procedure and cheapness of the reagent used.

[a] Dipartimento di Scienze Chimiche,
v. S. Agostino 1, I-62032 Camerino, Italy
Fax: (internat.) +39-737/637345
E-mail: palmieri@camserv.unicam.it

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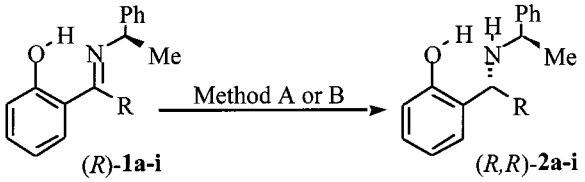
Table 1. Diastereoselective reduction of 2-imidoylphenols **1a−i** to *o*-hydroxybenzylamines **2a−i**

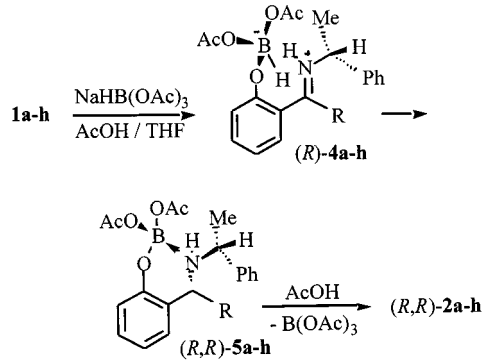


(*R*)-**1a-i** (*R,R*)-**2a-i**

Method A: $NaBH_4$/AcOH/THF, −70 to 20°C, 2 h; method B: $NaBH_4/CeCl_3 \cdot 7\ H_2O$/MeOH, −90 to 20°C, 2 h.

Entry	**1**	R	**2**	$\Delta\delta_H$ [a]	Method A Yield (%)[b]	d.e.[c]	config.[d]	Method B Yield (%)[b]	d.e.[c]	config.[d]
1	**1a**	Me	**2a**	0.37	34	83	*R*	88	86	*R*
2	**1b**	Et	**2b**	0.49	56	77	*R*	87	84	*R*
3	**1c**	Pr	**2c**	0.48	56	71	*R*	93	92	*R*
4	**1d**	$(CH_2)_2CH{=}CH_2$	**2d**	0.48	49	78	*R*	89	91	*R*
5	**1e**	*i*Bu	**2e**	0.50	54	72	*R*	78	71	*R*
6	**1f**	$(CH_2)_2Ph$	**2f**	0.44	53	82	*R*	93	93	*R*
7	**1g**	*i*Pr	**2g**	0.55	65	83	*R*	65	42	*S*
8	**1h**	Ph	**2h**	0.16	81	68	*R*	14 [e]	27	*R*
9	**1i**	*t*Bu	**2i**	0.59	44	20	*S*	88	95	*S*

[a] $\Delta\delta_H = \delta_{H(S)} - \delta_{H(R)}$ of the benzylic proton introduced by the reduction. − [b] Yields of the pure isolated major diastereomer. − [c] The *d.e.* values were determined by ^{1}H-NMR spectroscopy of the reaction mixture. − [d] Configuration of the new chiral center. − [e] 71% of starting material was recovered.



The absolute configuration of the *o*-hydroxybenzylamine (*R,R*)-**2a** was determined by chemical correlation with the (*R,R*)-*N*-(1′-methylbenzyl)-3,4-dihydro-2*H*-1,3-benzoxazine (*R,R*)-**3a**.[8] The absolute configuration of the *o*-hydroxybenzylamine (*R,R*)-**2h** was determined by analogy with (*R,R*)-**2a**. In fact, the ^{13}C-NMR spectra show γ effects[9] for (*R,R*)-**3a** and (*R,R*)-**3h** between C-2 (δ = 2.06 and 1.72) and Me-4 or Ph-4 (δ = 0.61 and 0.30, respectively). Moreover, γ effects for (4*S*,1′*R*)-**3a**, between C-4 (δ = 3.15) and Me-1′ (δ = 1.51), and for (4*S*,1′*R*)-**3h**, between C-4 (δ = 2.20) and C-1′ (δ = 1.13), are in agreement with the minimized structures (*R,R*)-**3a** and (4*S*,1′*R*)-**3a** (see Figure 3), obtained by conformational analysis.[10]

The conformations and the configurations of **3a**, **h** were confirmed by the ^{1}H-NMR shielding effect induced from the Ph-1′[11] on H-4eq, of 0.48 ppm for (*R,R*)-**3a**, **h** and the shielding effect on H-2eq of 0.59 and 0.69 ppm for (4*S*,1′*R*)-**3a** and (4*S*,1′*R*)-**3h**, respectively (see Figure 3). Analogous conformations were assumed for *o*-hydroxybenzylamines **2a−i**, stabilized by the intramolecular hydrogen bond[10] (see Figure 4). The configuration of all the *o*-hydroxyben-

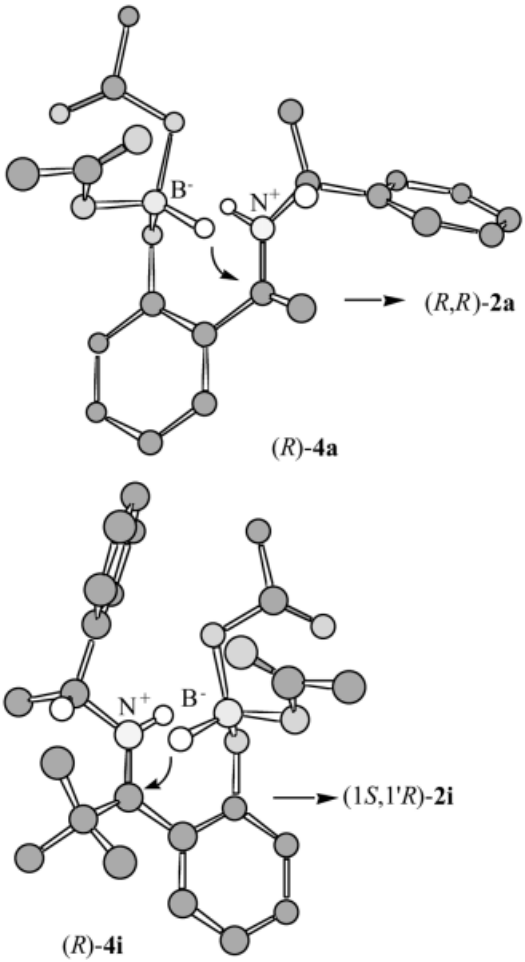


Figure 1. Method A: proposed mechanism and transition-state model geometries for intramolecular diastereoselective hydride transfer

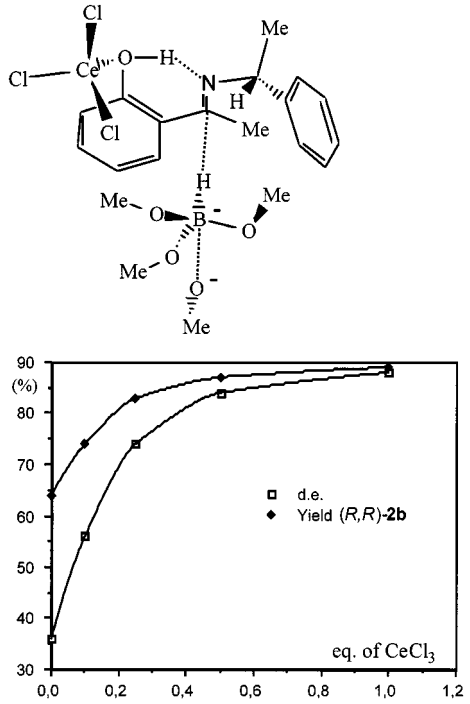


Figure 2. Method B: transition state model geometry proposed for the diastereoselective reduction of *o*-imidohylphenols **1a−i** with the catalysis of $CeCl_3 \cdot 7\ H_2O$

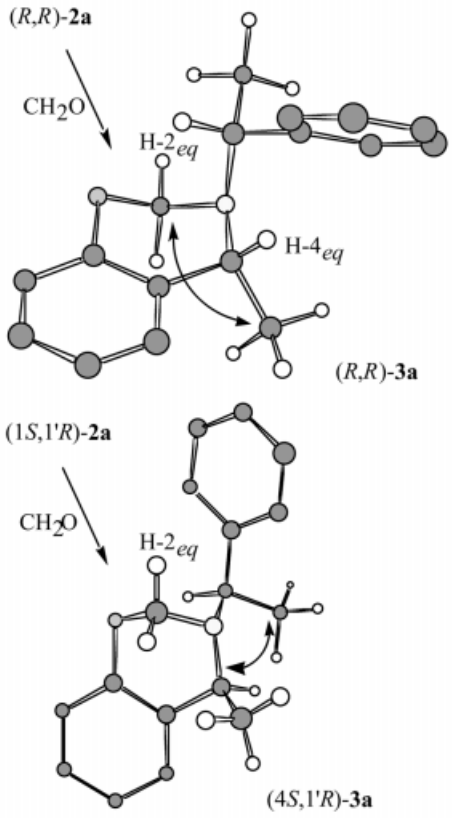


Figure 3. Minimized most stable conformations[10] for the 3,4-dihydro-2*H*-1,3-benzoxazines (*R,R*)-**3a** and (4*S*,1′*R*)-**3a**

zylamines (*R*,*R*)-**2a−i**, were attributed on the basis of the ^{1}H-NMR shielding effects $\Delta\delta_{H\text{-}1}$ = 0.16−0.59 ppm (see Table 1) caused by the Ph-1′[11] on the benzylic hydrogen (H-1_{eq}) introduced in the reduction.

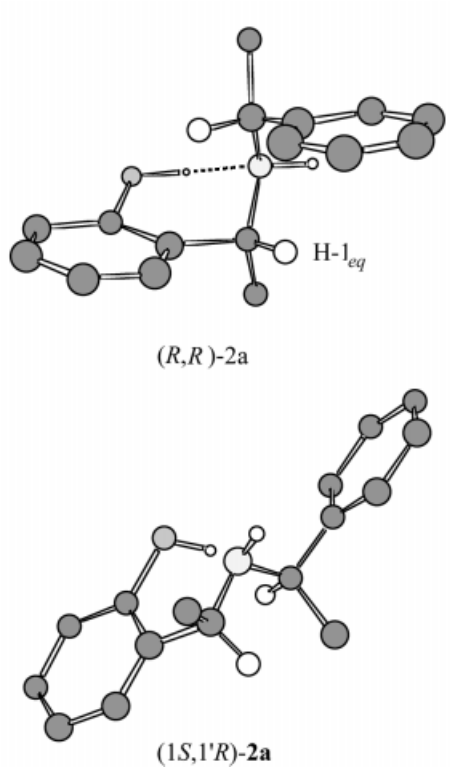


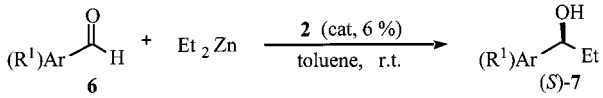
Figure 4. Minimized most stable conformations[10] for the *o*-hydroxybenzylamines (*R,R*)-**2a** and (1*S*,1′*R*)-**2a**

Application of the o-Hydroxybenzylamines 2a−i as Catalyst Precursors in the Asymmetric Addition of Diethylzinc to Aldehydes

In order to study the efficiency of the enantiopure *o*-hydroxybenzylamines **2** as catalyst precursors, the asymmetric addition of diethylzinc to aldehydes in toluene at 20°C was selected as a test reaction, using a 1:1.2:0.06 molar ratio for aldehydes/diethylzinc/catalyst precursor. The reaction is one of the most important asymmetric reactions and was used as model reaction.[1] The clean nucleophilic addition of diethylzinc to aldehydes is stereoselective and accelerated by the presence of optically active *o*-hydroxybenzylamines (*R*,*R*)-**2**. The enantiomeric ratio of the alcohols **7**, was determined by GC analysis on a chiral capillary column (DEX DMP).[12]

As reported in Table 2, the *o*-hydroxybenzylamines (*R*,*R*)-**2**, generally obtained as major diastereomers from the reduction of 2-imidoylphenols (*R*)-**1**, are the best catalysts and lead to asymmetric inductions with better *e.e.* and higher rates. In particular, the *o*-hydroxybenzylamine (*R*,*R*)-**2h** leads to the best results in the asymmetric addition of diethylzinc to benzaldehyde with formation of (*S*)-1-phenyl-1-propanol (*S*)-**7a**. It is worth noting that the preparation

Table 2. Enantioselective addition of diethylzinc to aldehydes in the presence of catalytic amount of *o*-hydroxybenzylamines **2**



2 [a]	R	**7**	(R[1])Ar	reaction time [h]	Yield (%)[b]	*e.e.*[c]	config.[d]
(*R*,*R*)-**2a**	Me	**7a**	Ph	4	96	55	*S*[13a]
(*R*,*R*)-**2b**	Et	**7a**	Ph	4	93	57	*S*
(*R*,*R*)-**2f**	$(CH_2)_2Ph$	**7a**	Ph	4	97	45	*S*
(*R*,*R*)-**2g**	*i*Pr	**7a**	Ph	4	92	35	*S*
(1*S*,α*R*)-**2g**	*i*Pr	**7a**	Ph	15	89	10	*R*
(*R*,*R*)-**2h**	Ph	**7a**	Ph	4	93	89	*S*
(1*S*,α*R*)-**2h**	Ph	**7a**	Ph	12	84	60	*R*
(*R*,*R*)-**2i**	*t*Bu	**7a**	Ph	4	94	62	*S*
(1*S*,α*R*)-**2i**	*t*Bu	**7a**	Ph	15	88	8	*S*
(*R*,*R*)-**2h**	Ph	**7b**	4-MeOPh	4	92	94	*S*[13a]
(*R*,*R*)-**2h**	Ph	**7c**	4-ClPh	5	93	86	*S*[13a]
(*R*,*R*)-**2h**	Ph	**7d**	$Ph(CH_2)_2$	4	92	72	*S*[13a]
(*R*,*R*)-**2h**	Ph	**7e**	*i*Pr	4	86	98	*S*[13b]
(*R*,*R*)-**2h**	Ph	**7f**	Cyclohexyl	4	82	97	*S*[13c]

[a] Commercial (*R*)-(+)-α-methylbenzylamine (99% *e.e.*) was used. – [b] GC yield on the mixture of the two enantiomers. – [c] Determined by capillary chiral GC analysis using the chiral column MEGADEX DMP β.[12] – [d] Configuration determined by the sign of optical rotation.

of the enantiomer (*R*)-1-phenyl-1-propanol (*R*)-**7a** is as straightforward, by choosing the equally accessible (*S*)-phenylethylamine for the preparation of the catalyst precursor. The *o*-hydroxybenzylamine (*R*,*R*)-**2h**, which gave the better stereoselectivity in the case of benzaldehyde, was tested with different aromatic and aliphatic aldehydes. High enantioselectivities were observed with electron donating groups, such as in 4-methoxybenzaldehyde, or aliphatic aldehydes with branched alkyl chains (see Table 2).

Conclusion

In summary, enantiopure *o*-hydroxybenzylamines **2a–i** were synthesized by two simple new methodologies for diastereoselective reduction of the 2-imidoylphenols (*R*)-**1a–i**. The accessible *o*-hydroxybenzylamine (*R*,*R*)-**2h** serves as an effective catalyst precursor for the highly enantioselective addition of diethylzinc to aliphatic and aromatic aldehydes. This pathway represents a practical and operationally very simple methodology for the enantioselective synthesis of both enantiomers of the secondary alcohols **7a–f**. Further studies on the mechanism of the asymmetric induction, the modification of the ligand design and further applications to other catalytic asymmetric reactions are now under investigation.

Experimental Section

General Remarks: ^{1}H- and ^{13}C-NMR spectra were recorded with a Varian VXR 300 instrument. Chemical shifts are given in ppm downfield from Me_4Si in $CDCl_3$ solution. Coupling constants are given in Hertz. – IR spectra were recorded with a Perkin–Elmer 257 spectrometer. – GC-MS analyses were performed with an HP 59970 workstation consisting of an HP-5890 gas chromatograph equipped with a methyl silicone capillary column and an HP-5970 mass detector. – All melting points are uncorrected. – THF was dried by refluxing over sodium wire until the blue color of benzophenone ketyl persisted and then distilled into a dry receiver under a nitrogen atmosphere. All reagents and solvents were distilled prior to use or were of commercial quality from freshly opened containers. Commercial methyllithium and butyllithium solutions (Aldrich) were used under a dry atmosphere.

Preparation of Starting 2-Imidoylphenols 1a–i: The 2-imidoylphenols **1a**,**b**,**h**,**i** were prepared by direct condensation of the appropriate *o*-acylphenol[3] and (*R*)-(+)-α-methylbenzylamine (99% *e.e.*) according to a previously reported procedure.[4] The 2-imidoylphenols **1c–g** were prepared by alkylation of the 2-imidoylphenols **1a**,**b**.[2] The data for the characterization of a number of unknown 2-imidoylphenols follows.

2-[Phenyl{[(1′*R*)-1′-phenylethyl]imino}methyl]phenol [(*R*)-1h]: Mp 128–130°C (hexane). – $[\alpha]_D^{20} = -147.4$ (c = 3.1, $CHCl_3$). – IR (nujol): $\tilde{\nu}$ = 1595, 1440, 1290, 910 cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (d, 3 H, J = 6.6 Hz), 4.51 (q, 1 H, J = 6.6 Hz), 6.60–7.82 (m, 14 H), 15.84 (br s, 1 H). – $C_{21}H_{19}NO$ (301.4): calcd. C 83.69, H 6.35, N 4.65; found C 83.82, H 6.31, N 4.83.

2-{2,2-Dimethyl[(1′*R*)-1′-phenylethyl]propanimidoyl}phenol [(*R*)-1i]: Mp 168–170°C (hexane). – $[\alpha]_D^{20} = +91.5$ (c = 2.2, $CHCl_3$). – IR (nujol): $\tilde{\nu}$ = 1622, 1290, 1230, 1113, cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 9 H), 1.26 (d, 3 H, J = 6.5 Hz), 4.25 (q, 1 H, J = 6.5 Hz), 4.25 (br s, 1 H), 6.80–7.45 (m, 9 H). – $C_{19}H_{23}NO$ (281.4): calcd. C 81.10, H 8.24, N 4.98; found C 81.23, H 8.33, N 5.18.

General Procedure for the Stereoselective Reduction of 2-Imidoylphenols 1a–i to *o*-Hydroxybenzylamines 2a–i. – Method A: Reduction with $NaBH(OAc)_3$/AcOH/THF: $NaBH(OAc)_3$ was prepared by adding $NaBH_4$ (0.454 g, 12.0 mmol) to glacial acetic acid (7.0 mL) and THF (18 mL) while keeping the internal temperature between 10–20°C. After the evolution of H_2 had ceased (0.5 h) the mixture was cooled to –70°C. At this temperature the 2-imidoylphenol **1a–i** (4.0 mmol) was added in one portion and the temperature of the mixture allowed to rise slowly to room temperature (2 h). Evaporation of acetic acid and THF in vacuo at 50°C, followed

by dissolution of the residue in CH_2Cl_2 and washing with Na_2CO_3 (sat. aqueous solution), provided the *o*-hydroxybenzylamines **2a−i**, after evaporation of the solvent. The mixture was analysed by GC-MS or ^{1}H- and ^{13}C-NMR spectroscopy for the determination of the *d.e.* and the yields of all the diastereoisomeric *o*-hydroxybenzylamines obtained. Purification and separation of diastereoisomers separation was performed by flash chromatography or by preparative HPLC on silica gel (10−20% ethyl acetate in hexane as eluent). Yields are reported in Table 1.

Method B: Reduction with $NaBH_4/CeCl_3 \cdot 7\ H_2O$/MeOH: A mixture of 2-imidoylphenol **1a−i** (4.0 mmol) and $CeCl_3 \cdot 7\ H_2O$ (0.745 g, 2.0 mmol), dissolved in methanol (12 mL), was cooled to −90°C and $NaBH_4$ (0.302 g, 8.0 mmol) was added in one portion with stirring. The temperature of the mixture was allowed to rise slowly to room temperature (2 h). Dilution with CH_2Cl_2 (100 mL) was followed by water hydrolysis (20 mL saturated aq. NH_4Cl). The organic layer was dried with Na_2SO_4, and provided the *o*-hydroxybenzylamines **2a−i** after evaporation of the solvent. The mixture was analysed by GC-MS or ^{1}H- and ^{13}C-NMR spectroscopy for the determination of the yields of all the diastereoisomeric *o*-hydroxybenzylamines and the *d.e.* obtained. Purification and separation of diastereoisomers separation was performed by flash chromatography or by preparative HPLC on silica gel (10−20% ethyl acetate in hexane as eluent). Yields are reported in Table 1.

2-[(1*R*)-1-{[(1′*R*)-1′-Phenylethyl]amino}ethyl]phenol [(*R*,*R*)-2a]: Mp 56−57°C (AcOEt/hexane). − $[\alpha]_D^{20} = +142.1$ (*c* = 1.66, $CHCl_3$). − IR (nujol): $\tilde{\nu}$ = 3300, 2960, 1580, 1470, 1250 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, 3 H, *J* = 6.8 Hz), 1.42 (d, 3 H, *J* = 6.8 Hz), 2.10 (br s, 1 H), 3.64 (q, 1 H, *J* = 6.8 Hz), 3.70 (q, 1 H, *J* = 6.8 Hz), 6.60−7.33 (m, 9 H), 12.30 (br s, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5, 24.0, 55.9, 56.6, 117.3, 119.7, 126.8, 127.0, 128.0, 128.1, 128.8, 129.3, 144.0, 158.1. − MS; *m*/*z* (%): 241 [M$^+$] (58), 226 (100), 122 (98), 105 (100), 77 (88). − $C_{16}H_{19}NO$ (241.3): calcd. C 79.63, H 7.94, N 5.80; found C 79.76, H 7.91, N 5.62. − **2-[(1*S*)-1-{[(1′*R*)-1′-Phenylethyl]amino}ethyl]phenol [(1*S*,1′*R*)-2a]:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (d, 3 H, *J* = 6.7 Hz), 1.48 (d, 3 H, *J* = 6.7 Hz), 1.90 (br s, 1 H), 3.92 (q, 1 H, *J* = 6.7 Hz), 4.01 (q, 1 H, *J* = 6.7 Hz), 6.75−7.42 (m, 9 H), 11.77 (br s, 1 H).

2-[(1*R*)-1-{[(1′*R*)-1′-Phenylethyl]amino}propyl]phenol [(*R*,*R*)-2b]: Mp 124−125°C (AcOEt/hexane). − $[\alpha]_D^{20} = +80.0$ (*c* = 3.85, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77 (t, 3 H, *J* = 7.5 Hz), 1.43 (d, 3 H, *J* = 6.9 Hz), 1.50−1.90 (m, 2 H), 2.10 (br s, 1 H), 3.34 (t, 1 H, *J* = 7.1 Hz), 3.72 (q, 1 H, *J* = 6.9 Hz), 6.70−7.42 (m, 9 H), 11.70 (br s, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.7, 23.6, 29.0, 55.2, 62.5, 116.6, 118.8, 125.0, 126.3, 127.4, 128.3, 128.8, 129.3, 143.4, 157.7. − $C_{17}H_{21}NO$ (255.3): calcd. C 79.96, H 8.29, N 5.49; found C 79.77, H 8.13, N 5.62. − **2-[(1*S*)-1-{[(1′*R*)-1′-Phenylethyl]amino}propyl]phenol [(1*S*,1′*R*)-2b**]: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, 3 H, *J* = 7.3 Hz), 1.50 (d, 3 H, *J* = 6.6 Hz), 1.57−1.92 (m, 2 H), 2.10 (br s, 1 H), 3.83 (t, 1 H, *J* = 7.0 Hz), 3.88 (q, 1 H, *J* = 6.9 Hz), 6.70−7.42 (m, 9 H), 11.70 (br s, 1 H).

[(1*R*)-1-{[(1′*R*)-1′-Phenylethyl]amino}butyl]phenol [(*R*,*R*)-2c]: Mp 64−65°C (AcOEt/hexane). − $[\alpha]_D^{20} = +63.1$ (*c* = 1.3, $CHCl_3$). − IR (nujol): $\tilde{\nu}$ = 3300, 1585, 1255, 1100 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77 (t, 3 H, *J* = 7.2 Hz), 1.05−1.32 (m, 2 H), 1.41 (d, 3 H, *J* = 7.0 Hz), 1.55−1.74 (m, 2 H), 1.97 (br s, 1 H), 3.42 (t, 1 H, *J* = 7.2 Hz), 3.68 (m, 1 H), 6.70−7.40 (m, 9 H), 11.72 (br s, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 19.8, 24.1, 38.8, 55.7, 61.2, 117.1, 119.3, 126.0, 126.8, 128.0, 128.7, 129.2, 129.5, 143.9, 158.2. − $C_{18}H_{23}NO$ (269.4): calcd. C 80.26, H 8.61, N 5.20; found C 80.41, H 8.48, N 5.03. − **2-[(1*S*)-1-{[(1′*R*)-1′-Phenylethyl]amino}butyl]phenol [(1*S*,1′*R*)-2c]:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, *J* = 7.3 Hz), 1.00−1.35 (m, 2 H), 1.45 (d, 3 H, *J* = 6.7 Hz), 1.54−1.74 (m, 2 H), 1.97 (br s, 1 H), 3.85 (q, 1 H, *J* = 6.4 Hz), 3.90 (t, 1 H, *J* = 7.0 Hz), 6.70−7.40 (m, 9 H), 11.72 (br s, 1 H).

2-[(1*R*)-1-{[(1′*R*)-1′-Phenylethyl]amino}pent-4-enyl]phenol [(*R*,*R*)-2d]: Colorless oil; $[\alpha]_D^{20} = +33.8$ (*c* = 3.2, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 3420, 3300, 1585, 1485, 1250 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (d, 3 H, *J* = 7.0 Hz), 1.62−2.10 (m, 5 H), 3.46 (t, 1 H, *J* = 6.7 Hz), 3.70 (q, 1 H, *J* = 6.7 Hz), 4.85−4.95 (m, 2 H), 5.59−5.73 (m, 1 H), 6.70−7.45 (m, 9 H), 11.70 (br s, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5, 30.3, 35.1, 55.2, 60.5, 115.2, 116.7, 118.9, 125.1, 126.3, 127.5, 128.4, 128.7, 129.1, 137.5, 143.3, 157.7. − $C_{19}H_{23}NO$ (281.4): calcd. C 81.10, H 8.24, N 4.98; found C 80.94, H 8.36, N 4.81. − **2-[(1*S*)-1-{[(1′*R*)-1′-Phenylethyl]amino}pent-4-enyl]phenol [(1*S*,1′*R*)-2d]:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (d, 3 H, *J* = 6.4 Hz), 1.62−2.10 (m, 5 H), 3.86 (q, 1 H, *J* = 6.7 Hz), 3.94 (t, 1 H, *J* = 6.7 Hz), 4.97−5.10 (m, 2 H), 5.73−5.85 (m, 1 H), 6.70−7.45 (m, 9 H), 11.70 (br s, 1 H).

2-[(1*R*)-3-Methyl-1-{[(1′*R*)-1′-Phenylethyl]amino}butyl]phenol [(*R*,*R*)-2e]: Colorless oil, $[\alpha]_D^{20} = +64.3$ (*c* = 2.7, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.62 (d, 3 H, *J* = 6.0 Hz), 0.82 (d, 3 H, *J* = 6.1 Hz), 1.43 (d, 3 H, *J* = 6.9 Hz), 1.35−1.70 (m, 3 H), 1.95 (br s, 1 H), 3.50 (dd, 1 H, *J* = 7.9, 5.9 Hz), 3.70 (q, 1 H, *J* = 6.9 Hz), 6.70−7.45 (m, 9 H), 11.75 (br s, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 23.5, 23.9, 25.1, 45.7, 55.7, 59.1, 117.2, 119.5, 126.5, 126.8, 128.0, 128.7, 129.1, 129.2, 143.8, 158.2. − $C_{19}H_{25}NO$ (283.4): calcd. C 80.52, H 8.89, N 4.94; found C 80.33, H 8.74, N 5.18. − **2-[(1*S*)-3-Methyl-1-{[(1′*R*)-1′-phenylethyl]-amino}butyl]phenol [(1*S*,1′*R*)-2e]:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, 3 H, *J* = 6.4 Hz), 0.93 (d, 3 H, *J* = 6.4 Hz), 1.40−1.60 (m, 1 H), 1.49 (d, 3 H, *J* = 6.6 Hz), 1.64 (t, 2 H, *J* = 7.0 Hz), 2.00 (br s, 1 H), 3.85 (q, 1 H, *J* = 6.6 Hz), 4.00 (t, 1 H, *J* = 7.1 Hz), 6.70−7.40 (m, 9 H), 11.75 (br s, 1 H).

2-[(1*R*)-3-Phenyl-1-{[(1′*R*)-1′-phenylethyl]amino}propyl]phenol [(*R*,*R*)-2f]: Mp 101−102°C (CH_2Cl_2-hexane). − $[\alpha]_D^{20} = -5.97$ (*c* = 1.4, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (d, 3 H, *J* = 6.7 Hz), 1.90−2.20 (m, 3 H), 2.35−2.60 (m, 2 H), 3.50 (t, 1 H, *J* = 6.9 Hz), 3.70 (br q, 1 H, *J* = 6.7 Hz), 6.70−7.40 (m, 14 H), 11.65 (br s, 1H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.4, 32.4, 37.5, 55.2, 60.7, 116.8, 119.0, 125.1, 125.9, 126.3, 127.5, 128.2, 128.3, 128.4, 128.8, 129.1, 141.1, 143.3, 157.7. − $C_{23}H_{25}NO$ (331.4): calcd. C 83.34, H 7.60, N 4.23; found C 83.26, H 7.74, N 4.04. − **2-[(1*S*)-3-Phenyl-1-{[(1′*R*)-1′-phenylethyl]amino}propyl]-phenol [(1*S*,1′*R*)-2f]:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (d, 3 H, *J* = 6.7 Hz), 1.90−2.20 (m, 3 H), 2.35−2.60 (m, 2 H), 3.84 (q, 1 H, *J* = 6.7 Hz), 3.94 (t, 1 H, *J* = 6.9 Hz), 6.70−7.40 (m, 14 H), 11.65 (br s, 1H);

2-[(1*R*)-2-Methyl-1-{[(1′*R*)-1′-phenylethyl]amino}propyl]phenol [(*R*,*R*)-2g]: Mp 119−121°C (AcOEt-hexane). − $[\alpha]_D^{20} = +92.1$ (*c* = 1.6, $CHCl_3$). − IR (nujol) $\tilde{\nu}$ = 3305, 2750, 1590, 1255 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.71 (d, 3 H, *J* = 7.0 Hz), 0.90 (d, 3 H, *J* = 6.7 Hz), 1.42 (d, 3 H, *J* = 6.7 Hz), 1.94 (octet, 1 H, *J* = 6.7 Hz), 2.10 (br d, 1 H, *J* = 11.6 Hz), 3.12 (d, 1 H, *J* = 7.0), 3.67 (dq, 1 H, *J* = 11.6, 7.0 Hz), 6.67−7.39 (m, 9 H), 11.80 (br s, 1 H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 19.2, 19.8, 23.6, 33.1, 55.3, 67.1, 116.5, 118.5, 123.9, 126.3, 127.4, 128.2, 128.7, 130.1, 143.4, 158.0. − $C_{18}H_{23}NO$ (269.4): calcd. C 80.26, H 8.61, N 5.20; found: C 80.12, H 8.69, N 5.13. − **2-[(1*S*)-2-Methyl-1-{[(1′*R*)-1′-phenylethyl]amino}propyl]phenol [(1*S*,1′*R*)-2g]:** Colorless oil. − $[\alpha]_D^{20} = +54.1$ (*c* = 1.2, $CHCl_3$). − ^{1}H NMR (300 MHz,

$CDCl_3$): δ = 0.83 (d, 3 H, *J* = 6.8 Hz), 1.01 (d, 3 H, *J* = 6.7 Hz), 1.47 (d, 3 H, *J* = 6.7 Hz), 2.02 (octet, 1 H, *J* = 6.8 Hz), 3.67 (d, 1 H, *J* = 7.0 Hz), 3.80 (q, 1 H, *J* = 6.6 Hz), 6.68−7.43 (m, 9 H), 11.60 (br s, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.0, 20.1, 20.4, 33.4, 54.7, 68.0, 117.3, 118.9, 124.4, 127.0, 127.8, 128.7, 129.1, 130.5, 144.4, 158.2.

2-[(*R*)-Phenyl-{[(1′*R*)-1′-phenylethyl]amino}methyl]phenol [(*R*,*R*)-2h]: Colorless oil; $[\alpha]_D^{20}$ = −120.8 (*c* = 1.96, $CHCl_3$); IR (neat): ṽ = 3300, 1585, 1480, 1250, 1095 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (d, 3 H, *J* = 6.7 Hz), 2.26 (br s, 1 H), 3.83 (br q, 1 H, *J* = 6.7 Hz), 4.65 (s, 1 H), 6.42−7.45 (m, 14 H), 12.20 (br s, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.7, 56.4, 65.3, 117.6, 119.9, 124.5, 127.0, 127.8, 128.2, 128.3, 129.3, 129.4, 129.5, 129.8, 142.6, 143.7, 158.6. − $C_{21}H_{21}NO$ (303.4): calcd. C 83.13, H 6.98, N 4.62; found: C 83.38, H 7.13, N 4.46. − **2-[(*S*)-Phenyl-{[(1′*R*)-1′-phenylethyl]amino}methyl[phenol [(1*S*,1′*R*)-2h]:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (d, 3 H, *J* = 6.7 Hz), 2.26 (br s, 1 H), 3.70 (br q, 1 H, *J* = 6.7 Hz), 4.81 (s, 1 H), 6.42−7.45 (m, 14 H), 12.20 (br s, 1 H).

2-[(1*R*)-2,2-Dimethyl-1-{[(1′*R*)-1′-phenylethyl]amino-[propyl}phenol [(*R*,*R*)-2i]: Mp 110−112°C (hexane). − $[\alpha]_D^{20}$ = +104.3 (*c* = 2.2, $CHCl_3$). − IR (nujol): ṽ = 3400, 1713, 1461, 1377 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (s, 9 H), 1.47 (d, 3 H, *J* = 6.8 Hz), 2.43 (br s, 1 H), 3.11 (s, 1 H), 3.59 (q, 1 H, *J* = 6.8 Hz), 6.65−7.40 (m, 9 H), 12.20 (br s, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.67, 27.29, 35.92, 55.64, 70.48, 116.92, 118.18, 122.01, 126.68, 127.69, 128.48, 128.85, 131.80, 143.34, 158.79. − $C_{19}H_{25}NO$ (283.4): calcd. C 80.52, H 8.89, N 4.94; found C 80.39, H 8.97, N 4.71. − **2-[(1*S*)-2,2-Dimethyl-1-{[(1′*R*)-1′-phenylethyl]amino}propyl]phenol [(1*S*,1′*R*)-2i]:** Mp 76−78°C (hexane). − $[\alpha]_D^{20}$ = +73.2 (*c* = 1.8, $CHCl_3$). − IR (nujol): ṽ = 3430, 1587, 1463, 1257 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (s, 9 H), 1.47 (d, 3 H, *J* = 6.6 Hz), 1.90 (br s, 1 H), 3.70 (s, 1 H), 3.79 (q, 1 H, *J* = 6.6 Hz), 6.65−7.40 (m, 9 H), 11.70 (br s, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.14, 27.29, 36.08, 54.37, 70.69, 116.99, 117.88, 121.86, 126.57, 127.33, 128.38, 128.59, 131.46, 143.91, 158.34. − $C_{19}H_{25}NO$ (283.4): calcd. C 80.52, H 8.89, N 4.94; found C 80.42, H 8.91, N 5.13.

General Procedure for the Preparation of 3,4-Dihydro-2*H*-1,3-Benzoxazines 3a, h: To a solution of **2** (2 mmol) in THF (3 mL) was added 35% aqueous formaldehyde (2.2 mmol). The solution was stirred for 15 h at room temperature. Solvent was removed and the residue dried under reduced pressure. The crude material was purified by filtration through an SiO_2 pad eluting with CH_2Cl_2.[9]

(4*R*)-4-Methyl-3-[(1′*R*)-1′-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine [(*R*,*R*)-3a]: Yield 86%, colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, 3 H, *J* = 7.0 Hz), 1.46 (d, 3 H, *J* = 6.4 Hz), 3.63 (q, 1 H, *J* = 6.9 Hz), 3.91 (q, 1 H, *J* = 6.6 Hz), 5.03 (d, 1 H, *J* = 11.1 Hz), 5.18 (dd, 1 H, *J* = 11.1, 2.1 Hz), 6.80−7.45 (m, 9 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8, 24.6, 52.6, 59.4, 74.7, 117.0, 120.8, 126.2, 127.5, 127.8, 128.8, 129.0, 129.1, 146.3, 155.0. − $C_{17}H_{19}NO$ (253.3): calcd. C 80.60, H 7.56, N 5.53; found C 80.81, H 7.74, N 5.32. **(4*S*)-4-Methyl-3-[(1′*R*)-1′-phenylethyl]-3,4-dihydro-2*H*-1,3-benzoxazine [(4*S*,1′*R*)-3a]:** Yield 83%, colorless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (d, 3 H, *J* = 6.5 Hz), 1.50 (d, 3 H, *J* = 7.0 Hz), 4.06 (q, 1 H, *J* = 6.6 Hz), 4.11 (q, 1 H, *J* = 6.7 Hz), 4.58 (dd, 1 H, *J* = 10.7, 1.7 Hz), 4.91 (d, 1 H, *J* = 10.7 Hz), 6.80−7.45 (m, 9 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 25.2, 49.4, 59.2, 76.7, 117.2, 120.7, 126.6, 127.7, 127.9, 128.2, 128.5, 128.9, 144.5, 154.9.

(4*R*)-4-Phenyl-3-[(1′*R*)-1′-phenylethyl]-3,4-dihydro-2*H*-1,3-benz oxazine [(*R*,*R*)-3h]: Yield 91%, colorless crystals, mp 98−100°C (hexane). − $[\alpha]_D^{20}$ = −36.1 (*c* = 1.6, $CHCl_3$). − IR (nujol): ṽ = 1608, 1491, 1227, 940 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (d, 3 H, *J* = 6.6 Hz), 3.98 (q, 1 H, *J* = 6.6 Hz), 4.72 (br s, 1 H), 4.83 (d, 1 H, *J* = 10.9 Hz), 5.07 (dd, 1 H, *J* = 10.9, 2.0 Hz), 6.80−7.50 (m, 14 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 58.8, 59.3, 74.4, 116.5, 120.1, 120.3, 127.1, 127.5, 127.7, 128.0, 128.2, 128.6, 128.9, 130.2, 143.8, 145.2, 155.0. − $C_{22}H_{21}NO$ (315.4): calcd. C 83.78, H 6.71, N 4.44; found C 83.92, H 6.81, N 4.27. − **(4*S*)-4-Phenyl-3-[(1′*R*)-1′-phenylethyl]-3,4-dihydro-2H-1,3-benzoxazine [(4*S*,1′*R*)-3h]:** Yield 87%, colorless crystals, mp 117−119°C (hexane). − $[\alpha]_D^{20}$ = +63.1 (*c* = 1.9, $CHCl_3$). − IR (nujol): ṽ = 1608, 1230, 1128, 935 cm^{-1}. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.58 (d, 3 H, *J* = 6.6 Hz), 4.12 (q, 1 H, *J* = 6.6 Hz), 4.38 (dd, 1 H, *J* = 10.5, 2.0 Hz), 4.58 (d, 1 H, *J* = 10.5 Hz), 5.21 (br s, 1 H), 6.80−7.50 (m, 14 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 57.1, 57.9, 76.1, 116.8, 120.0, 120.4, 127.0, 127.4, 127.8, 128.1, 128.3, 128.5, 128.9, 129.8, 143.8, 144.1, 154.8. − $C_{22}H_{21}NO$ (315.4): calcd. C 83.78, H 6.71, N 4.44; found C 83.97, H 6.65, N 4.36.

General Procedure for the Enantioselective Addition of Diethylzinc to Benzaldehyde by Using Catalytic *o*-Hydroxybenzylamines: Under a nitrogen atmosphere, a toluene solution of Et_2Zn (6.0 mmol, 1.1 M) was added to a mixture of benzaldehyde (5.0 mmol) and *o*-hydroxybenzylamine **2** (0.30 mmol) at 0°C and the mixture was stirred at room temperature for 5−15 h. The progress of the reaction was monitored by GC analysis of an aliquot of the reaction mixture, before quenching. Aqueous hydrochloric acid (2 N) was added to quench the reaction under cooling with ice-water. The resulting mixture was extracted with CH_2Cl_2, and the extract was dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt) followed by bulb-to-bulb distillation. The product was identified by spectroscopic methods and the optical rotation was measured. Optical purities (% e.e.) were determined by GC analyses of the resulting alcohols on a chiral capillary column MEGADEX DMP β (30% dimethylpentyl-β-cyclodextrin on OV1701, 25 m, 0.25 mm ID, 0.25 μm film).[12]

Acknowledgments

Financial support from Ministero dell′Università e della Ricerca Scientifica e Tecnologica, Rome, and the University of Camerino (National Project "Stereoselezione in Sintesi Organica. Metodologie ed applicazioni") is gratefully acknowledged.

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Received November 3, 1998
[O98482]