Direct Organocatalytic Regioselective α-Hydroxyamination of α-Branched Aldehydes

Sung-Gon Kim,* Eun Ju Ahn, and Tae-Ho Park

Medicinal Science Division, Korea Research Institute of Chemical Technology, P.O. Box 107, Daejeon 305-600, Korea
**E-mail: sgkim@krict.re.kr*
Received July 3, 2007

A direct regioselective α-hydroxyamination of α-branched aldehydes with nitrosobenzene using *cis*-5-benzyl-proline as catalyst has been developed for the preparation of α-hydroxyamino aldehydes possessing a quaternary carbon center. Such compounds are versatile building blocks for the synthesis of quaternary α-amino acids, β-amino alcohols, and 1,2-diamines.

Key Words : Hydroxyamination, Amino acid, Amino alcohol, Organocatalysis

Introduction

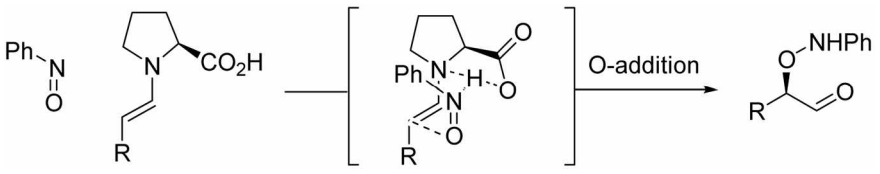
The class of compound with quaternary carbons bearing nitrogen has recently received considerable attention. In addition to many natural alkaloids such as lepadiformine, daphniphylline and (−)-adaline,[1] they include chiral α-quaternary amino acids which are not only useful molecular building blocks for the synthesis of peptides with specific properties,[2] but also have powerful biologically activities.[3] Optically active α-quaternary amino aldehydes have also been used in many synthetic applications.[4] The synthesis of quaternary nitrogen-bearing centers is therefore actively investigated recently because of the importance of corresponding compounds in molecular biology and synthetic chemistry.[5]

Results and Discussion

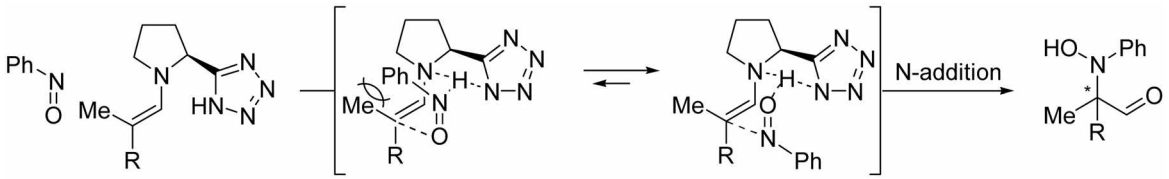
Very recently, we have developed enantioselective direct α-hydroxyamination reactions of α-branched aldehydes using a proline-derived tetrazole catalyst which provided direct access to α-quaternary amino aldehydes and alcohols.[6,7] However, the regioselectivity between α-hydroxyamination and α-aminooxylation was moderate in α-methyl-substituted aliphatic aldehydes. We have also interested in the development of an organocatalyst for the regioselective α-hydroxyamination of the α-branched aldehydes. Herein we report direct regioselective α-hydroxyamination of α-branched aldehydes with nitrosobenzene using *cis*-5-benzyl-proline catalyst.

In our previous report, we suggested that the enamine intermediate formed between an α-methyl aldehyde and proline-derived tetrazole might attack to the nitrogen of nitrosobenzene giving an α-hydroxyamino product due to the steric repulsion between the α-methyl group of enamine and the phenyl group of nitrosobenzene (Scheme 2).[6] In contrast, the enamine formed between a non-α-branched aldehyde and proline attacks to the oxygen of nitrosobenzene giving an α-aminoxy product (Scheme 1).[8] On the basis of previous results, we were prompted to consider a *cis*-5-substituted-proline as catalyst in the reaction of α-branched aldehydes with nitrosobenzene. In the transition state, the steric repulsion between the substituted group in the 5-position of proline and the phenyl group of nitrosobenzene might lead in which the enamine intermediate formed between an α-methyl aldehyde and proline attack to the nitrogen of nitrosobenzene giving an α-hydroxyamino product (Scheme 3).

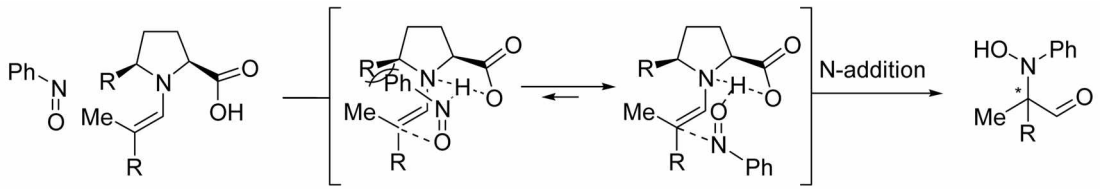
To test our assumption, we examined several *cis*-5-substitued proline derivatives (20 mol %) as catalyst in the



Scheme 1

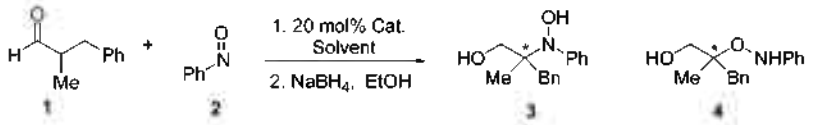


Scheme 2



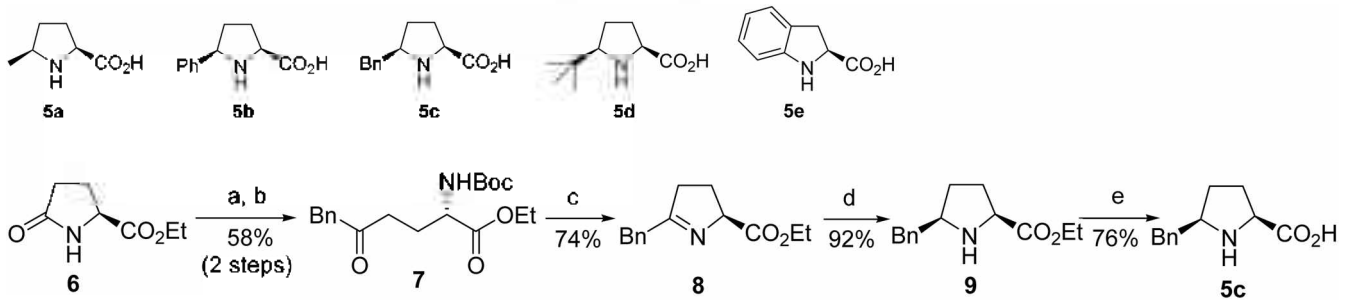
Scheme 3

Table 1. Regioselective *α*-*N*-hydroxyamination of 2-methyl-3-phenylpropionaldehyde with nitrosobenzene catalyzed by **5**



entry	Catalyst	solvent	temp (°C)	time (h)	yield[a] (%)	3/4[b]
1	**5a**	DMF	25	24	33	>99/1
2	**5b**	DMF	25	18	40	>99/1
3	**5c**	DMF	25	18	64	>99/1
4	**5d**	DMF	25	24	15	>99/1
5	**5e**	DMF	25	18	16[c]	>99/1
6	**5c**	DMSO	25	12	72	>99/1

[a]Yield of isolated product. [b]Determined by ^{1}H NMR analysis. [c]Conversion yield.

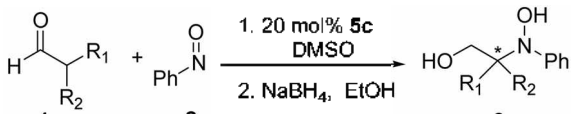


Scheme 4. Synthesis of (2*S*, 5*R*)-5-benzyl-pyrrolidine-2-carboxylic acid. Reagents and Conditions: (a) Boc_2O, CH_2Cl_2, r.t. (b) BnMgBr, THF, –40 °C (c) TFA, CH_2Cl_2 (d) H_2 (1 atm), cat. Pd/C, EtOH, r.t. (e) NaOH, MeOH/THF, r.t.

reaction of 2-methyl-3-phenylpropionaldehyde **1** (2 equiv.) with nitrosobenzene **2** (1 equiv.) in DMF at room temperature (Table 1). It was found that the reaction proceeded, as we anticipated, to give the *α*-hydroxyamino product **3** with a quaternary carbon center as the only product. The benzyl substituted-proline **5c** showed good activity, even though **5c** exhibited no enantioselectivity on this reaction (entry 3). On the other hand, the activities of the less or more bulky group substituted-prolines were diminished (entry 1 and 4). The best result was obtained using the *cis*-5-benzyl-proline **5c** as catalyst in DMSO (entry 5). The investigation prompted us to select *cis*-5-benzyl-proline **5c** as catalyst for the further examination of *α*-hydroxyamination reactions of *α*-branched aldehydes.

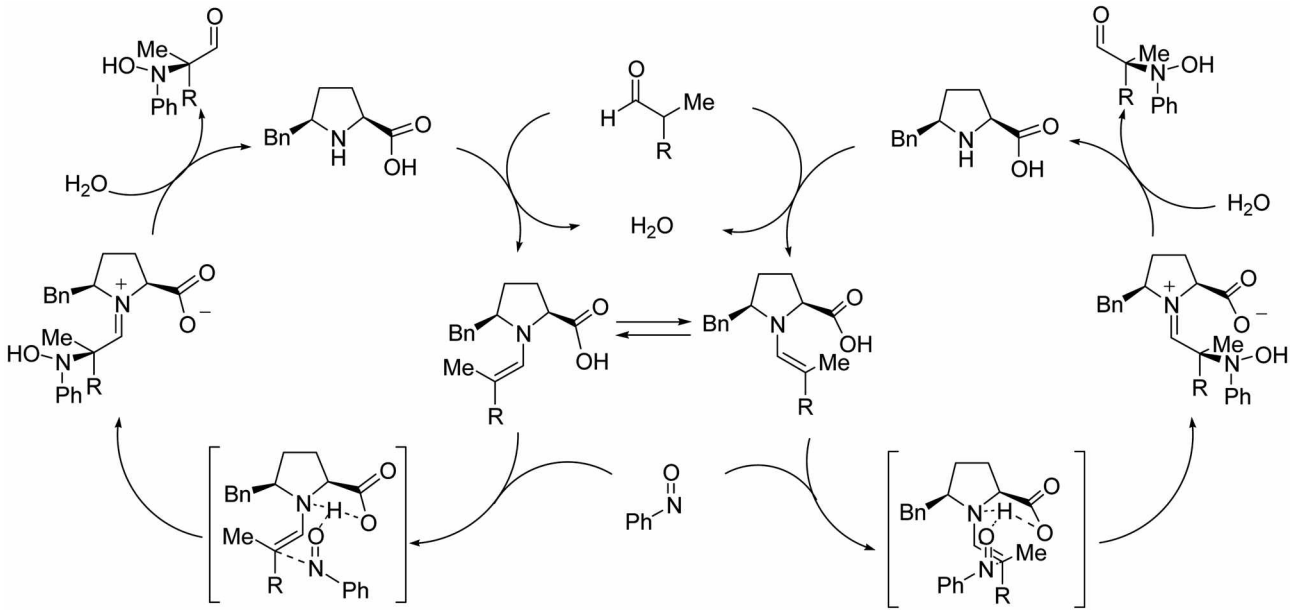
cis-5-Benzyl-proline **5c** was synthesized by modifications of Ezquerra's[9] and Rutjes' methods[10] (Scheme 4). Boc-protection of the nitrogen of ethyl (*S*)-2-pyroglutamate **6** followed by treatment of benzylmagnesium bromide gave dicarbonyl **7**. Removal of the Boc group with TFA afforded the corresponding imine **8** which was reduced by catalytic hydrogenation to yield *cis*-5-benzyl-proline ester **9**.[11] Finally, hydrolysis of the ester provided the *cis*-5-benzyl-proline **5c**.

Table 2. Regioselective *α*-*N*-hydroxyamination of *α*-branched aldehydes with nitrosobenzene catalyzed by **5c**



entry	R_1	R_2	3	time (h)	yield[a] (%)
1	Me	$C_6H_5CH_2$	**3a**	12	72
2	Me	*p*-$MeOC_6H_5CH_2$	**3b**	18	46
3	Me	*p*-$BrC_6H_5CH_2$	**3c**	18	55
4	Me	$C_6H_5CH_2OCH_2$	**3d**	12	88
5	Me	Et	**3e**	12	63
6	Me	Propyl	**3f**	12	78
7	Me	C_6H_5	**3g**	8	57
8	Me	*p*-$MeOC_6H_5$	**3h**	8	58
9	Et	$C_6H_5CH_2$	**3i**	24	41
10	Et	Butyl	**3j**	24	48
11	$(CH_2)_5$		**3k**	18	60
12	$(CH_2)_4$		**3l**	12	70

[a]Yield of isolated product



Scheme 5. Proposed mechanisim for the α-hydroxyamination of α-methyl aldehydes catalyzed by **5c**.

Using our optimized conditions, a variety of α-branched aldehydes were tested to investigate the scope of the present reaction, and the results are summarized in Table 2. Under these conditions it was found that selective α-hydroxyamino products **3** resulted exclusively for all α-branched aldehydes. For α-methyl aldehydes, the reaction generated α-hydroxyamino products within 18 hours in good yields (up to 88%) (entries 1-6). However, α-ethyl aldehydes required longer time in this reaction and the yields were moderate (entries 9-10). Though reaction preceeded rapidly in the case of α-methyl-α-aryl substituted aldehydes, the yields were moderate (entries 7-8). Interestingly, under these conditions, cyclohexane- and cyclopentanecarboxaldehyde gave the desired cyclic amino alcohol product in good yield (entries 11-12).[12]

The mechanism of the direct regioselective α-hydroxyamination catalyzed by *cis*-5-benzyl-proline **5c** is depicted in Scheme 5. Accordingly, the aldehyde donor reacts with catalyst **5c**, resulting in an enamine which react with nitosobenzene, affording an iminium ion intermediate. The α-hydroxyamino adduct is formed on hydrolysis and the catalytic cycle can be repeated. We deduce from experimental results that an enamine exists as *anti*- and *syn*-conformer which equilibrate fast and then react with nitrosobenzene to give racemic α-hydroxyamino adduct. Though we expected that *anti*-conformer prefer to *syn*-conformer due to the π-π interation between the benzyl group in catalyst and the duble bond in enamine, the steric repulsion between them might also be important factor in this catalytic system.[13]

In summary, we have developed regioselective α-hydroxyamination of α-branched aldehydes with nitrosobenzene using *cis*-5-benzyl-proline catalyst. Though *cis*-5-benzyl-proline exhibited no enantioselectivity, this method provides direct acess to α,α-disubstituted amino aldehydes and amino alcohols which are precursors to quaternary α-amino acids.

Experimental Section

General procedure. All reactions were performed using flame- or oven-dried glassware under an atmosphere of dry nitrogen. Commercial reagents were purified prior to use according to the guidelines of Perrin and Armarego. Non-aqueous reagents were transferred under nitrogen by syringe. Organic solutions were concentrated under reduced pressure using a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or $KMnO_4$ stain. Melting points were determined on a Tomas Hoover capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual proton solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin-Elmer 1600 Series spectrometer using KBr salt plates, and reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the center for Chemical Analysis in Korea Research Institute of Chemical Technology. Optical rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm).

Synthesis of (2*S*, 5*R*)-5-Benzyl-pyrrolidine-2-carboxylic acid (5c). To a solution of (2*S*)-5-benzyl-3,4-dihydro-

2H-pyrrole-2-carboxylic acid ethyl ester **8** (3.4 g, 15.6 mmol) in EtOH (100 mL) was added 10% Pd/C (0.1 w/w, 340 mg). After stirring for 12 hours under 1 atm of H_2, the mixture was filtered through Celite and the reaction solvent was evaporated *in vacuo*. The mixture was diluted with MeOH (45 mL) and THF (45 mL). To a mixture was added aqueous 1 N NaOH (45 mL). After being stirred for 3 hours, the mixture was acidified with aqueous 1 N HCl solution and solvent was removed *in vacuo*. The residue was purified by flash column chromatography (5-20% MeOH in CH_2Cl_2, linear gradient) to afford the title compound **5c** (2.2 g, 70%) as a solid that could be recrystallized (Et_2O/MeOH). white needle; mp >250 °C (decomposed); $[\alpha]_D^{25}$ −94.5 (c = 1.00, CH_3OH); IR (KBr): 3435, 2947, 2935, 1649, 1311, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.20-7.34 (m, 5H), 3.73 (t, J = 6.9 Hz, 1H), 3.65 (tt, J = 6.9, 9.6 Hz, 1H), 3.10 (dd, J = 6.6, 13.5 Hz, 1H), 2.85 (dd, J = 8.1, 13.5 Hz, 1H), 2.00-2.50 (m, 2H), 1.84 (dt, J = 5.7, 12.3 Hz, 1H), 1.50 (ddd, J = 9.0, 12.3, 18.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 137.9, 129.6, 127.4, 61.6, 61.3, 38.3, 29.8, 28.6; MS (CI): m/z (%) = 206 (100) [M^+ + 1]; Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.58; H, 7.50; N, 6.89.

Typical α-Hydroxyamination procedure. To a solution of nitrosobenzene **2** (0.5 mmol) and (*S*)-*cis*-5-benzyl-proline **5c** (21 mg, 0.1 mmol) in DMSO (2 mL) was added α-branched aldehyde **1** (1.5 mmol). After stirring at room temperature until the starting material had disappeared (8-24 h), the reaction mixture was diluted with EtOH (3 mL), the solution was cooled to 0 °C, and excess $NaBH_4$ was added. After 20 minutes, the reaction was treated with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to afford products **3**. The regioselectivity of the product was determined by ^1H-NMR spectra.

2-(Hydroxy-phenyl-amino)-2-methyl-3-phenyl-propan-1-ol (3a). white power; mp 123-125 °C; IR (KBr): 3345, 2957, 2935, 1597, 1487, 1452, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.14-7.36 (m, 10H), 3.57 (d, J = 11.4 Hz, 1H), 3.50 (d, J = 11.4 Hz, 1H), 3.25 (d, J = 12.9 Hz, 1H), 2.57 (d, J = 12.9 Hz, 1H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.5, 137.6, 131.0, 128.3, 128.2, 126.5, 126.2, 125.2, 67.1, 65.5, 39.0, 17.8; HRMS (EI): m/z calcd for $C_{16}H_{19}NO_2$ 257.1416; found: 280.1414.

2-(Hydroxy-phenyl-amino)-3-(4-methoxy-phenyl)-2-methyl-propan-1-ol (3b). IR (KBr): 3311, 2934, 2935, 1596, 1487, 1463, 1246, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.14-7.34 (m, 5H), 7.02 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 3.74 (s, 2H), 3.56 (d, J = 11.1 Hz, 1H), 3.46 (d, J = 11.1 Hz, 1H), 3.28 (d, J = 13.2 Hz, 1H), 2.37 (d, J = 12.6 Hz, 1H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.3, 148.6, 131.9, 129.6, 128.2, 126.0, 125.2, 113.7, 67.1, 65.4, 55.4, 38.1, 17.6; HRMS (EI): m/z calcd for $C_{17}H_{21}NO_3$ 287.1521; found: 287.1517.

3-(4-Bromo-phenyl)-2-(hydroxy-phenyl-amino)-2-methyl-propan-1-ol (3c). IR (KBr): 3339, 2956, 2930, 2874, 1549, 1460, 1404, 1204, 1071, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.17-7.41 (m, 9H), 3.56 (d, J = 11.4 Hz, 2H), 3.20 (d, J = 12.6 Hz, 1H), 2.42 (d, J = 12.6 Hz, 1H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.5, 136.7, 131.3, 128.3, 126.2, 125.1, 120.5, 119.9, 66.8, 65.4, 38.4, 17.7; HRMS (EI): m/z calcd for $C_{16}H_{18}BrNO_2$ 335.0521; found: 335.0521.

3-Benzyloxy-2-(hydroxy-phenyl-amino)-2-methyl-propan-1-ol (3d). IR(KBr): 3339, 2934, 2874, 1596, 1487, 1453, 1366, 1208, 1097, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.06-7.37 (m, 10H), 4.44 (d, J = 12.0 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 3.76 (s, 3H), 3.56 (d, J = 12.3 Hz, 1H), 3.34 (d, J = 12.3 Hz, 1H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.6, 137.9, 128.7, 128.1, 128.0, 127.9, 125.6, 124.4, 74.2, 73.7, 67.3, 66.2, 14.9; HRMS (EI): m/z calcd for $C_{17}H_{21}NO_3$ 287.1521; found: 287.1519.

2-(Hydroxy-phenyl-amino)-2-methyl-butan-1-ol (3e). IR (KBr): 3313, 2972, 2940, 2882, 1569, 1487, 1463, 1221, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.10-7.26 (m, 5H), 3.69 (d, J = 11.7 Hz, 1H), 3.57 (d, J = 11.7 Hz, 1H), 1.73 (dq, J = 7.5, 13.8 Hz, 1H), 1.26 (dq, J = 7.5, 9.6 Hz, 1H), 0.94 (s, 3H), 0.81 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.7, 128.1, 125.9, 125.0, 66.8, 66.0, 26.2, 17.0, 8.8; HRMS (EI): m/z calcd for $C_{11}H_{17}NO_2$ 195.1259; found: 209.1277.

2-(Hydroxy-phenyl-amino)-2-methyl-pentan-1-ol (3f). IR (KBr): 3306, 2955, 2872, 1596, 1488, 1452, 1377, 1053, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.11-7.31 (m, 5H), 3.67 (d, J = 11.4 Hz, 1H), 3.57 (d, J = 11.4 Hz, 1H), 1.63 (dt, J = 11.4, 15.0 Hz, 1H), 1.12-1.27 (m, 3H), 0.95 (s, 3H), 0.82 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.6, 128.1, 125.9, 1245.0, 66.6, 66.5, 35.9, 17.8, 17.6, 15.0; HRMS (EI): m/z calcd for $C_{12}H_{19}NO_2$ 209.1416; found: 209.1423.

2-(Hydroxy-phenyl-amino)-2-phenyl-propan-1-ol (3g). IR (KBr): 3371, 3060, 2985, 2936, 1599, 1477, 1447, 1393, 1228, 1046 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ = 7.16-7.52 (m, 5H), 6.85-7.05 (m, 5H), 3.97 (d, J = 11.1 Hz, 2H), 3.87 (d, J = 11.1 Hz, 2H) 1.43 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ = 150.7, 143.3, 127.8, 127.4, 126.9, 123.1, 122.0, 69.3, 68.8, 16.5; HRMS (EI): m/z calcd for $C_{15}H_{17}NO_2$ 243.1259; found: 243.1255.

2-(Hydroxy-phenyl-amino)-2-(4-methoxy-phenyl)-propan-1-ol (3h). IR (KBr): 3368, 2935, 2836, 1609, 1488, 1460, 1375, 1220, 1182, 1030 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ = 7.37 (d, J = 8.1 Hz, 2H), 6.83-7.05 (m, 7H), 3.99 (d, J = 11.1 Hz, 2H), 3.83 (d, J = 11.1 Hz, 2H) 3.77 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ = 159.0, 150.7, 134.9, 129.0, 127.2, 123.2, 122.3, 113.0, 69.4, 68.3, 54.6, 16.5; HRMS (EI): m/z calcd for $C_{16}H_{19}NO_2$ 273.1365; found: 209.1373.

2-Benzyl-2-(hydroxy-phenyl-amino)-butan-1-ol (3i). IR (KBr): 3360, 2960, 2932, 2877, 1597, 1453, 1379, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.16-7.36 (m, 10H), 3.78 (d, J = 11.7 Hz, 1H), 3.55 (s, 2H), 3.18 (d, J = 11.7 Hz, 1H), 1.71 (t, J = 7.2 Hz, 2H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$): δ = 148.3, 138.1, 131.0, 128.5, 128.3, 126.4, 125.8, 124.5, 69.3, 65.4, 37.0, 25.4, 11.6; HRMS (EI): m/z calcd for $C_{17}H_{21}NO_2$ 271.1572; found: 271.1570.

2-Ethyl-2-(hydroxy-phenyl-amino)-hexan-1-ol (3j). IR (KBr): 3318, 2966, 2872, 1596, 1487, 1463, 1379, 1218, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.10-7.27 (m, 5H), 3.62 (s, 2H), 1.40-1.55 (m, 4H), 1.23-1.34 (m, 4H), 0.88 (t, J = 6.3 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.0, 128.2, 125.8, 124.4, 68.5, 65.8, 31.0, 25.9, 24.2, 23.6, 14.3, 8.5; HRMS (EI): m/z calcd for $C_{14}H_{23}NO_2$ 237.1729; found: 237.1737.

[1-(Hydroxy-phenyl-amino)-cyclohexyl]-methanol (3k). IR (KBr): 3314, 2955, 2863, 1595, 1486, 1450, 1349, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.12-7.29 (m, 5H), 3.75 (s, 2H), 1.51-1.76 (m, 5H), 1.01-1.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.2, 128.1, 125.8, 125.0, 65.8, 63.3, 29.4, 25.8, 22.5; HRMS (EI): m/z calcd for $C_{13}H_{19}NO_2$ 221.1416; found: 221.1458.

[1-(Hydroxy-phenyl-amino)-cyclopentyl]-methanol (3l). IR (KBr): 3338, 2953, 2872, 1596, 1486, 1451, 1324, 1052, 1005 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.10-7.28 (m, 5H), 3.58 (s, 2H), 1.83-1.88 (m, 2H), 1.45-1.63 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.2, 128.3, 125.8, 124.1, 76.1, 66.4, 31.9, 24.2; HRMS (EI): m/z calcd for $C_{12}H_{17}NO_2$ 207.1259; found: 207.1253.

Acknowledgements. This work was financially supported by Ministry of Science & Technology (KN-0642) and Korea Research Institute of Chemical Technology (KRICT).

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13. In the reaction of 2-methyl-3-phenylpropionaldehyde **1** with nitrosobenzene **2**, though benzyl substituted-proline **5c** exhibited no enantioselectivity, phenyl substituted-proline **5b** showed 30% enatiomeric excess.