# Direct Organocatalytic Regioselective α-Hydroxyamination of α-Branched Aldehydes

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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

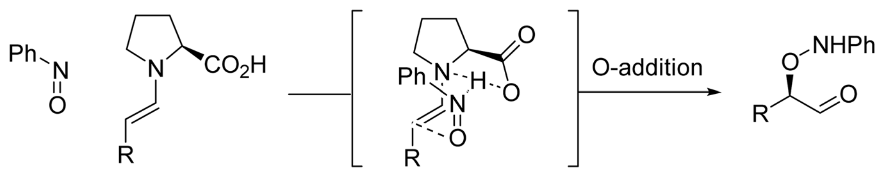
The class of compound with quaternary carbons bearing nitrogen has recently received considerable attention. In addition to many natural alkaloids such as lepadiformine, daphniphylline and (–)-adaline,[1] they include chiral α-quaternary amino acids which are not only useful molecular building blocks 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

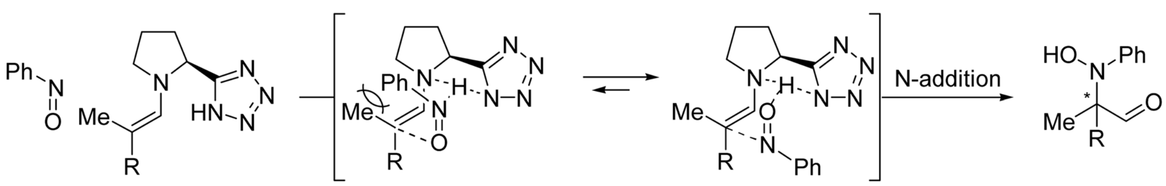
Very recently, we have developed enantioselective direct α-hydroxyamination reactions of α-branched aldehydes using a proline-derived tetrazole catalyst which provided direct access to α-quaternary amino aldehydes and alcohols.[6,7] However, the regioselectivity between α-hydroxyamination and α-aminooxylation 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).

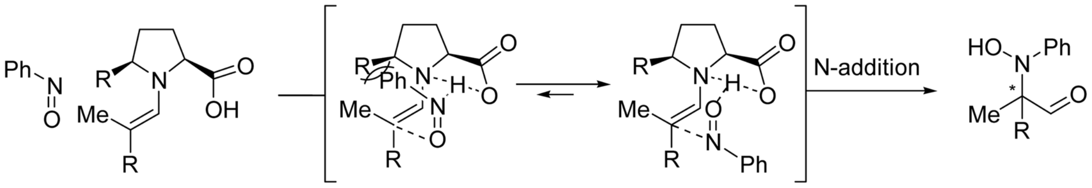
To test our assumption, we examined several *cis*-5-substitued proline derivatives (20 mol %) as catalyst in the




**Scheme 1**

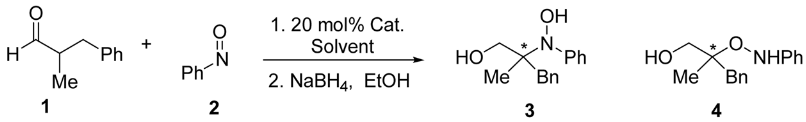



**Scheme 2**



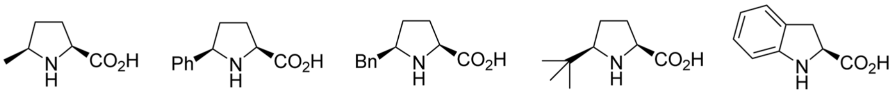
Scheme 3

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

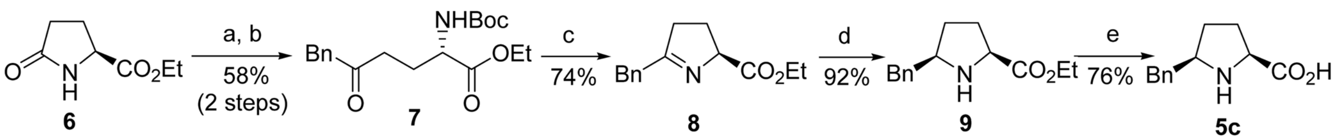


| entry | Catalyst | solvent | temp (°C) | time (h) | yield[a] (%) | 3/4[b] |
|---|---|---|---|---|---|---|
| 1 | **5a** | DMF | 25 | 24 | 33 | >99/1 |
| 2 | **5b** | DMF | 25 | 18 | 40 | >99/1 |
| 3 | **5c** | DMF | 25 | 18 | 64 | >99/1 |
| 4 | **5d** | DMF | 25 | 24 | 15 | >99/1 |
| 5 | **5e** | DMF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



5a 5b 5c 5d 5e

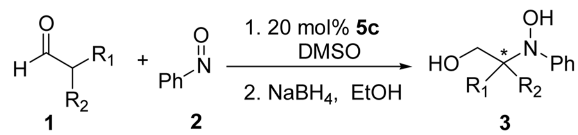


**Scheme 4**. Synthesis of (2*S*, 5*R*)-5-benzyl-pyrrolidine-2-carboxylic acid. Reagents and Conditions: (a) $Boc_2O$, $CH_2Cl_2$, r.t. (b) BnMgBr, THF, −40 °C (c) TFA, $CH_2Cl_2$ (d) $H_2$ (1 atm), cat. Pd/C, EtOH, r.t. (e) NaOH, MeOH/THF, r.t.

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 $\alpha$-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 $\alpha$-hydroxyamination reactions of $\alpha$-branched aldehydes.

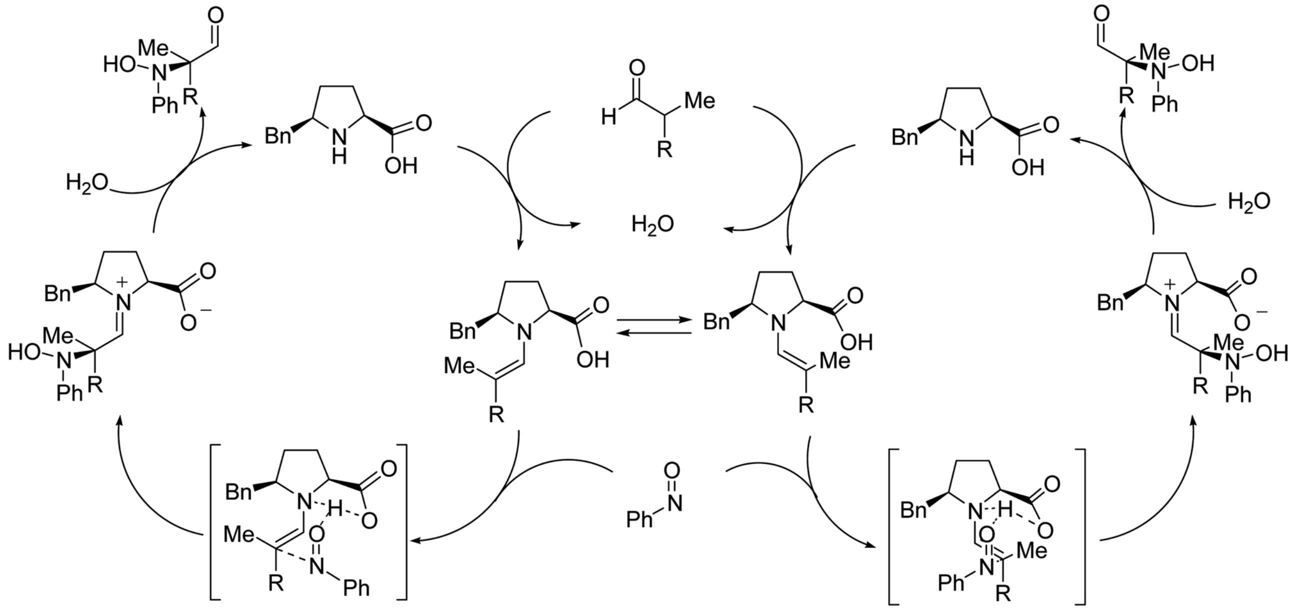
*cis*-5-Benzyl-proline **5c** was synthesized by modifications of Ezquerra's[9] and Rutjes' methods[10] (Scheme 4). Boc-protection of the nitrogen of ethyl (*S*)-2-pyroglutamate **6** followed by treatment of benzylmagnesium bromide gave dicarbonyl **7**. Removal of the Boc group with TFA afforded the 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 $\alpha$-*N*-hydroxyamination of $\alpha$-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 $\alpha$-hydroxyamination of $\alpha$-methyl aldehydes catalyzed by **5c**.

Using our optimized conditions, a variety of $\alpha$-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 $\alpha$-hydroxyamino products **3** resulted exclusively for all $\alpha$-branched aldehydes. For $\alpha$-methyl aldehydes, the reaction generated $\alpha$-hydroxyamino products within 18 hours in good yields (up to 88%) (entries 1-6). However, $\alpha$-ethyl aldehydes required longer time in this reaction and the yields were moderate (entries 9-10). Though reaction preceeded rapidly in the case of $\alpha$-methyl-$\alpha$-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 $\alpha$-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 $\alpha$-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 $\alpha$-hydroxyamino adduct. Though we expected that *anti*-conformer prefer to *syn*-conformer due to the $\pi$-$\pi$ 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 $\alpha$-hydroxyamination of $\alpha$-branched aldehydes with nitrosobenzene using *cis*-5-benzyl-proline catalyst. Though *cis*-5-benzyl-proline exhibited no enantioselectivity, this method provides direct acess to $\alpha,\alpha$-disubstituted amino aldehydes and amino alcohols which are precursors to quaternary $\alpha$-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 ($\delta$ 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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 $\alpha$-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 $\alpha$-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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CD_3OD$): $\delta$ = 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, $CD_3OD$): $\delta$ = 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, $CD_3OD$): $\delta$ = 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, $CD_3OD$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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.

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## References and Notes

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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.