Modular Synthesis of Oxazolines and Their Derivatives

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Received June 26, 2008

A class of modular oxazolines and their derivatives **1**−**5** were synthesized with moderate to excellent yields using a simple one-pot method; 4 × 3 bis-oxazolines were obtained, as expected, from each of the three reactions of 1,4-dicyanobenzene, 1,3-dicyanobenzene, and 1,2-dicyanobenzene with optically active amino alcohols in chlorobenzene under dry, anaerobic conditions. $ZnCl_2$ was used as a Lewis acid catalyst. Direct condensation of 1, 2-bis(cyanomethyl) benzene or 2-cyanophenylacetonitrile did not yield the target products, but two series of novel compounds (**4** and **5**) were isolated and their structures were confirmed by X-Ray analysis. All products (**1**−**5**) were characterized by NMR, IR, and MS.

Introduction

Chiral oxazolines and their metal complexes are important catalysts in asymmetric catalysis,[1−3] because they are easily accessed and applicable in a wide range of metal-catalyzed transformations. For example, they have shown high activity in asymmetric Diels−Alder reactions, Henry reactions, cyclopropanation reactions, Aldol reaction, alkylation reaction, and cycloaddition reactions.[4,5] Diverse strategies for the synthesis of oxazolines have been reported, and the topic has been extensively reviewed.[6−21] However, there is limited information available about which specific structural features are advantageous in a wide range of asymmetric processes. This remains a major problem given the synthesis of increasing numbers of novel and highly active chiral oxazolines and their derivatives and the desired application of these compounds in the field of asymmetric catalysis.

The majority of the syntheses of chiral oxazoline ligands generally proceed by the reaction of carboxylic acid derivatives with β-amino alcohols, which are activated by Lewis acids.[22−24] These syntheses follow a general synthetic route in which oxalic acid or the substituted malonic acids are first condensed with the optically active amino alcohol to form the hydroamide derivatives, then the hydroxyl groups in the hydroxyamide are activated and cyclized to provide the oxazolines. The C. Bolm research group described this synthetic method using $ZnCl_2$ as a Lewis acid catalyst, starting from dicyanohydrocarbons and optically active amino alcohols.[25] Following this method, our research group has successfully synthesized two series of oxazolines from piperidine and pyrolidine.[26] In this paper, we report the modular synthesis of oxazolines and their derivatives by a simple and easy to perform method[27] (Figure 1). The crystal structures of oxazolines **1a**, **4c**, and **5a** are shown in Figures 2, 4, and 5, respectively. The synthetic routes can be seen in Scheme 1.

Results and Discussions

A series of oxazolines **1a**−**1d**, **2a**−**2d**, and **3a**−**3d** were obtained with moderate to excellent yields from the reactions of 1,4-dicyanobenzene, 1,3-dicyanobenzene and 1,2-dicyanobenzene, respectively, with optically active amino alcohols in chlorobenzene under dry, anaerobic conditions. $ZnCl_2$ was dried under vacuum and acted as a Lewis acid catalyst in this reaction. Scheme 1 summarizes the synthetic routes. All compounds were characterized by NMR, IR, and MS. The crystal structure of **2b** (Figure 2) was obtained after purification on a silica gel column. In addition, during the synthesis of **2d**, the byproduct **2d-1** was formed when the molar ratio of 1,3-dicyanobenzene and L-phenylalaninol was less than $^1/_2$. This compound was an oxazoline obtained by only one cyclization, and its crystal structure can be seen in Figure 3.

Direct condensation of 1,2-bis(cyanomethyl) benzene or 2-cyanophenyacetonitrile with optically active amino alcohols (synthesis routes 4 and 5) did not yield the desired target products. However, it produced the unexpected products **4a**−**4d** and **5a**−**5d.** In lieu of producing the anticipated bisoxazolines, the crystal strutures of **4c** and **5a** indicate that the reaction proceeded via mechanism shown in Schemes 3 and 4.

Scheme 3 can be explained by the fact that bis-oxazolines cannot be formed because of the steric hindrances. Following the nucleophilic attack on the C≡N bond and the electrophilic attack on the C═N bond, only the stable imidazol derivative can be obtained.

In the mechanism proposed in Scheme 4, the amino alcohol attacks the C≡N bond, but only one oxazoline ring can be formed by cyclic deamination. The other ring can not cyclize, once again because of steric effects, but it instead forms a stable 5-membered, 2-indanamine ring derivative.

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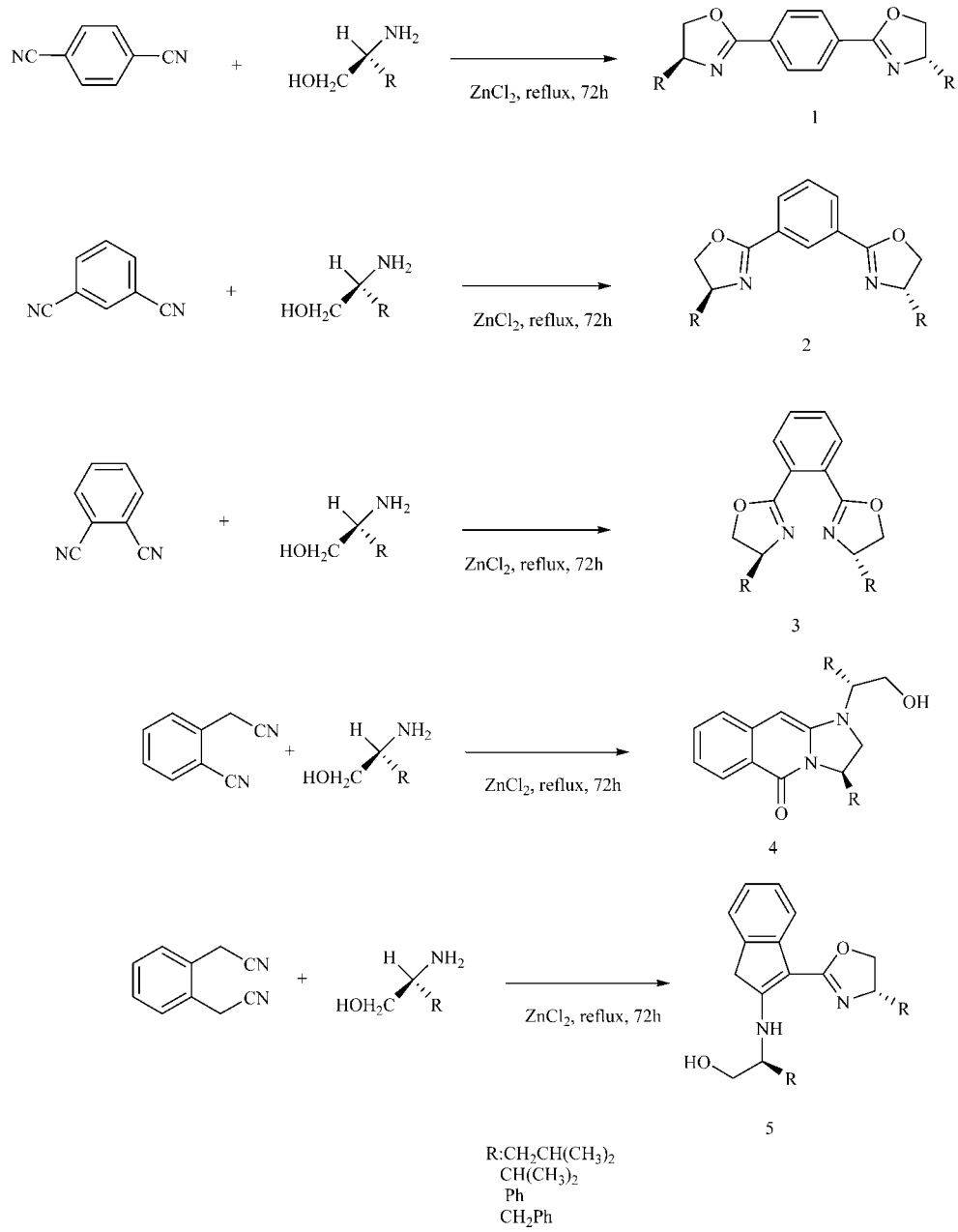
10.1021/cc8001537 CCC: $40.75
Published on Web 01/12/2009

Scheme 1. Synthetic Routes to the Oxazolines and Derivatives



The yields of the products ranged from moderate to excellent range. The yields were closely correlated with the amount of the amino alcohol present. When the molar ratio of nitrile to amino alcohol was 1:3, a large improvement in yield was seen increasing from low or moderate (30−50%) to high or excellent yields(80−90%).

Conclusions

In conclusion, we have synthesized 4 × 4 oxazolines, some of their derivatives (1 × 4) and a byproduct in moderate to excellent yields using a simple one-pot method. In addition, we isolated two series of novel compounds, **4** and **5**, which heretofore had not been reported. Our results indicate that $ZnCl_2$ acts as a good Lewis acid catalyst for the preparation of libraries of diverse oxazolines, and the commerically availability of this catalyst makes it the reagent of choice. Finally, the crystal structures of several of the synthesized compounds were unambiguously demonstrated, and will help to explain the proposed mechanism.

Experimental Section

General Information. 1,4-Dicyanobenzene, 1,3-dicyanobenzene, 1,2-dicyanobenzene, 1,2-bis(cyanomethyl)benzene, 2-cyanophenyacetonitrile, and amino alcohol were purchased from Acros, Aldrich, and Fluka. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.02−0.03 mm); ^1H and ^{13}C NMR spectra were obtained using Bruker AM-300 and Bruker AM-400 spectrometer. Proton chemical shifts are reported in ppm (δ) with the solvent relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$, δ 7.26 ppm). The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, m = multiplet. Infrared spectra were recorded on a Mattson

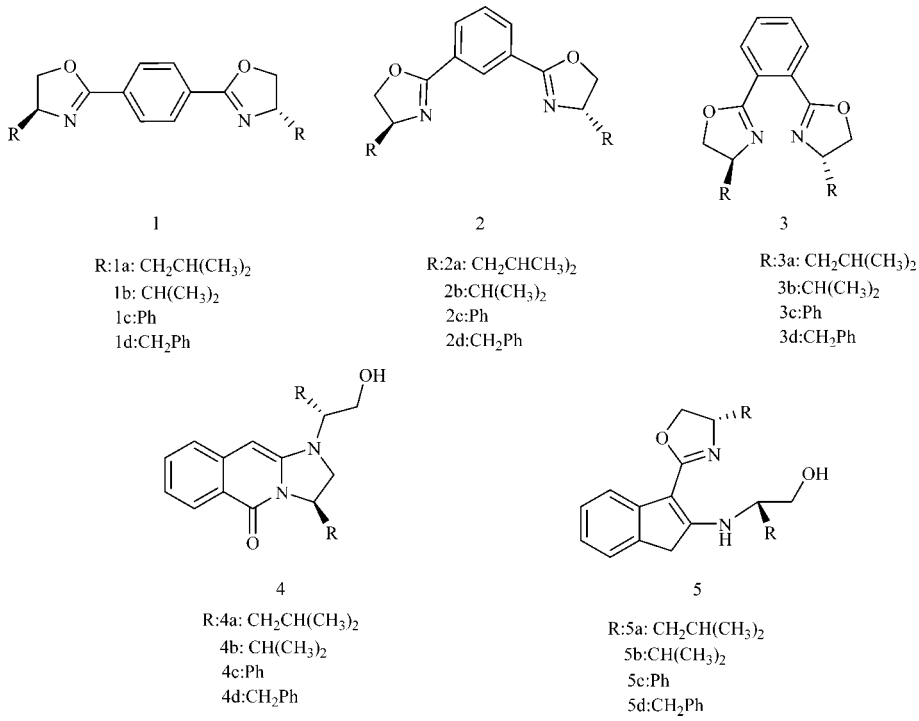


Figure 1. Structures of the oxazolines and their derivatives.

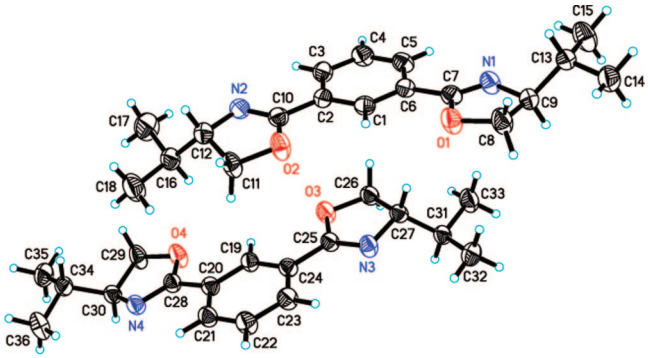


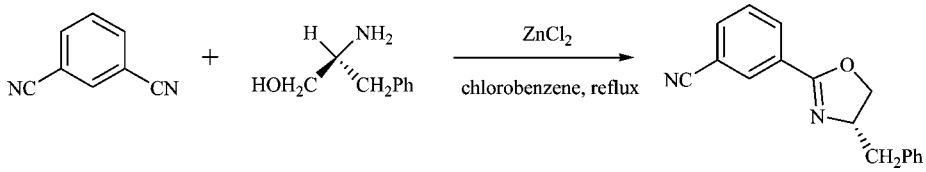
Figure 2. Crystal Structure of **2b**.

Galaxy Series FTIR 3000 spectrometer; peaks are reported in cm^{-1}. High resolution mass spectra (HRMS) were obtained on Micro GCT-MS equipped with an EI ion source. Optical rotations were measured on WZZ-1 automatic polarimeter with a 2 cm cell at the sodium D-line.

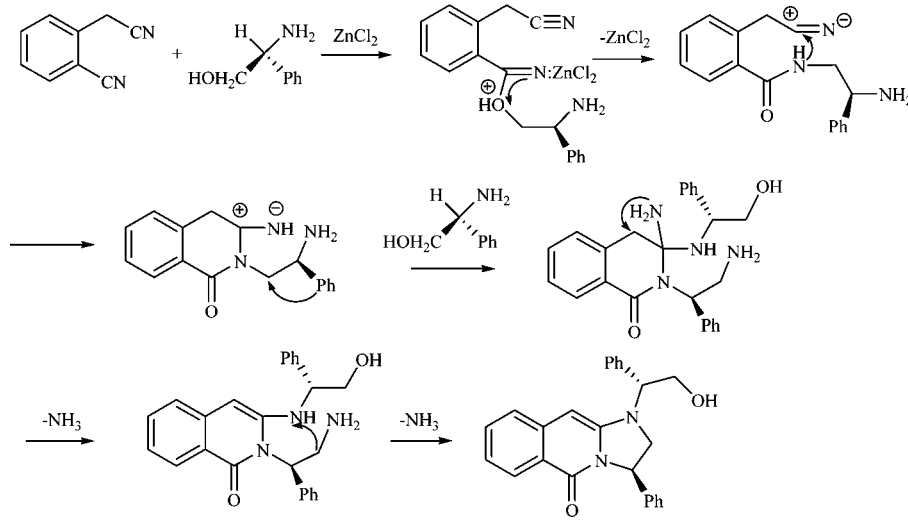
Structure Determination

1. The crystal of the title compound **2b** of approximately 0.475 × 0.411 × 0.100 mm was selected for the data collection on a BRUKER SMART diffractometer with graphite monochromated Mo*K*α radiation ($\lambda = 0.7103$ Å). A total of 5054 reflections were collected in the range of $1.87 < \theta < 27.00°$ by using "phi and omega" scan techniques at 293(2) K, $C_{18}H_{24}N_2O_2$, $M = 300.39$, triclinic, P1, $a = 5.8138(15)$ Å, $\alpha = 84.585(4)°$, $b = 9.773(3)$ Å, $\beta = 88.440(5)°$, $c = 15.314(4)$ Å, $\gamma = 79.196(5)°$, $V = 850.8(4)$ Å^3, $Z = 2$, $D_{calc.} = 1.173$ mg/m^3, the final R factor was $R_1 = 0.0592$, 3620 for reflections with $I_0 > 2\sigma(I_0)$, R_ω=0.1334 for all data, largest peak and hole were 0.212 and −0.201eÅ^{-3}, respectively. The structures were solved by full-matrix least-squares on F^2 using the SHELXTL PROGREM.[28,29]
2. A crystal of the title compound **2d-1** of approximately 0.479 × 0.321 × 0.097 mm was selected for the data collection on a BRUKER SMART diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.7103$ Å). A total of 9915 reflections were collected in the range of $1.87 < \theta < 27.00°$ by using φ and ω scan techniques at 293(2) K, $C_{17}H_{14}N_2O$, $M = 262.30$, orthorhombic, $P2_12_12_1$, $a = 7.8004(7)$ Å, $\alpha = 90°$, $b = 11.6387(11)$ Å, $\beta = 90°$, $C = 30.824(3)$ Å, $\gamma = 90°$, $V = 2798.4(4)3$ Å^3, $Z = 8$, $D_{calcd.} = 1.245$ mg/m^3; the final R factor was $R_1 = 0.0614$, 3472 for reflections with $I_0 > 2\sigma(I_0)$, $R_\omega = 0.1328$ for all data, and largest peak and hole were 0.208 and −0.281 e Å^{-3}, respectively. The structure were solved by full-matrix least-squares on F^2 using the SHELXTL program.[28,29]
3. A crystal of the title compound **4c** of approximately 0.22 × 0.13 × 0.07 mm was selected for the data collection on a Gemini S Ultra diffractometer with mirror monochromated Cu Kα radiation ($\lambda = 0.7103$Å). A total of 56 926 reflections were collected in the range of $2.6359 < \theta < 62.6290°$ by using multiscan techniques at 293(2) K, $C_{25}H_{22}N_2O_2$, $M = 382.45$, orthorhombic, $P2_12_12_1$, $a = 5.341(5)$ Å, $\alpha = 90.000(5)°$, $b = 16.735(5)$ Å, $\beta = 90.000(5)°$, $c = 22.129(5)$ Å, $\gamma = 90.000(5)°$, $V = 1978(2)$ Å^3, $Z = 4$, $D_{calcd} = 1.284$ mg/m^3, The final R factor was $R_1 = 0.0473$, 2269 for reflections with $I_0 > 2\sigma(I_0)$, R_ω=0.0771 for all data. The structures were solved by full-matrix least-squares on F^2 using the SHELXTL program.[28,29]
4. A crystal of the title compound **5a** of approximately 0.38 × 0.12 × 0.10 mm was selected for the data collection on a Gemini S Ultra diffractometer with mirror monochromated Cu Kα radiation ($\lambda = 0.7103$ Å). A total of 24 210 reflections were collected in the range of $1.6784 < \theta < 62.6796°$ by using multiscan

Scheme 2. Synthetic Routes to **2d-1**



Scheme 3. Proposed Mechanism of Formation for **4c**



techniques at 293(2) K, $C_{44}H_{64.67}N_4O_{4.33}$, $M = 719.00$, hexagonal, $P64$, $a = 30.3427(3)$ Å, $\alpha = 90°$, $b = 30.3427(3)$ Å, $\beta = 90°$, $c = 12.0057(10)$ Å, $\gamma = 120°$, $V = 9572.52(16)$ Å^3, $Z=9$, $D_{calcd} = 1.123$ mg/m^3. The final R factor was $R_1 = 0.0385$, 6593 for reflections with $I_0 > 2\sigma(I_0)$, $R_\omega = 0.1107$ for all data. The structures were solved by full-matrix least-squares on F^2 using the SHELXTL program.[28,29]

Preparation of Oxazolines and Their Derivatives 1−5. General Procedure. Sixty milligrams of dry $ZnCl_2$, dicyanobenzene, 2-cyanophenyacetonitrile, or 1,2-bis(cyanomethyl)benzene (7.8 mmol) and L-amino alcohol (22.4 mmol) were added under free-water and free-oxygen condition in a dry 100 mL Schlenk flask. They were dissolved in 30 mL of dry chlorobenzene, and the reaction mixture was refluxed for 72 h. The solvent was removed under reduced pressure, and the residue was dissolved in 15 mL of H_2O and extracted with 10 × 3 mL of dichloromethane; the solvent was removed under vacuum to give the crude red oil. Further purification was performed by silica gel (petroleum ether/dichlormethane 4/1).

1a: Preparation of (*S*,*S*)-1,4-Bis(4-butyl-oxazolin-2-yl)benzene. This product was prepared according to the general procedure. The title compound was obtained as a white solid 1.19 g (65%): mp = 36−38 °C, $[\alpha]^5_D = -107.14°$ ($c = 0.112$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) δ (ppm) 7.96 (s, 4H), 4.48−4.54 (m, 2H), 4.32−4.36 (m, 2H), 3.99 (t, $J = 0.25$ Hz, 2H), 1.68−1.88 (m, 4H), 1.34−1.44 (m, 2H), 0.96−1.00 (m, 12H);^{13}C NMR 22.89 (×2), 23.08 (×2), 25.69 (×2), 45.73 (×2), 65.48 (×2), 73.44 (×2), 128.32 (×4), 130.55 (×2), 162.92 (×2); IR 3431, 2955, 2926, 2905, 2870, 1641, 1514, 1470, 1449, 1409, 1372, 1360, 1324, 1273, 1245, 1131, 1085, 1073, 1034, 1020, 971, 861, 691; HRMS (EI) *m*/*z* (%) calcd for $C_{20}H_{28}N_2O_2$ 328.2148; found 328.2151.

1b: Preparation of (*S*,*S*)-1,4-Bis-(4-isopropyl-2-oxazolin-2-yl)benzene. This product was prepared according to the general procedure: yield 68%; white crystal; mp = 48−50 °C, $[\alpha]^5_D = -113.7°$ ($c = 0.469$, $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$, 27 °C) δ (ppm) = 7.97 (s, 4H), 4.41 (t, $J =$ 0.155 Hz, 2H), 4.09−4.15 (m, 4H), 1.85−1.86 (m, 2H), 1.02 (d, $J = 6.23$ Hz, 6H), 0.91 (d, $J = 6.24$ Hz, 6H); ^{13}C NMR 18.13 (×2), 19.02 (×2), 32.85 (×2), 70.26 (×2), 72.76 (×2), 128.10 (×2), 128.16 (×2), 130.32 (×2), 162.82 (×2); IR 3273, 2976, 2960, 2932, 2889, 2869, 1643, 1512, 1469, 1408, 1382, 1366, 1350, 1320, 1296, 1276, 1214,1180, 1108, 1077, 1047,1014, 971, 955, 900, 891, 838, 726, 698, 675, 659, 540; HRMS (EI) *m*/*z* (%) calcd for $C_{18}H_{24}N_2O_2$ 300.1838; found 300.1835.

1c: Preparation of (*S*,*S*)-1,4-Bis(4-phenyl-2-oxazolin-2-yl) enzene. This product was prepared according to the general procedure: yield 57%; white solid; mp = 42−44 °C; $[\alpha]^5_D = -61.3°$ ($c = 0.04$, $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$, 27 °C) δ (ppm) = 8.12 (t, $J = 7.56$ Hz, 4H), 7.74 (t, $J = 4.45$ Hz, 4H), 7.23−7.40 (m, 6H), 5.40−5.46 (m, 2H), 4.82−4.87 (m, 2H), 4.30−4.35 (m, 2H);^{13}C NMR 70.36 (×2), 75.28 (×2), 132.24 (×2), 129.06 (×2), 128.94 (×2), 127.94 (×2), 128.94 (×2), 132.24 (×2), 141.68 (×2), 163.17 (×2); IR 3420, 3081, 3054, 3031, 2988, 2956, 2893, 2231, 1647, 1608, 1497, 1454, 1406, 1359, 1343, 1317, 1293, 1276, 1262, 1201, 1174,1073, 1046, 1017, 967, 953, 860, 840, 755, 697, 669, 548, 527; HRMS (EI) *m*/*z* (%) calcd for $C_{24}H_{20}N_2O_2$ 368.1525; found 368.1518.

1d: Preparation of (*S*,*S*)-1,4-Bis(4-benzyl-2-oxazolin-2-yl)benzene. This product was prepared according to the general procedure: yield 60%; pale yellow solid; mp 40−42

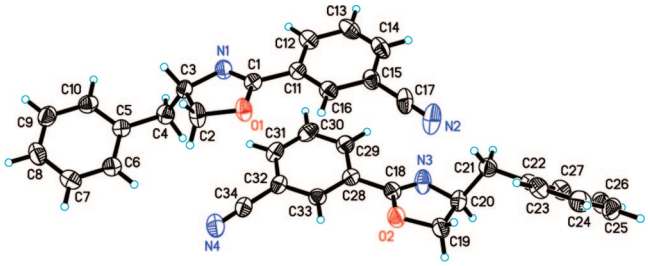


Figure 3. Crystal structure of **2d-1**.

°C, $[\alpha]^5_D = 38.2°$ ($c = 0.098$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) δ (ppm) = 7.98 (s, 4H), 7.20−7.34 (m, 10H), 4.57−4.63 (m, 2H), 4.37 (t, J = 1.1 Hz, 2H), 4.16 (t, J = 1.75 Hz, 2H), 3.22−3.28 (dd, J = 8.45, 8.5 Hz, 2H), 2.71−2.78 (dd, J = 14.55, 14.6 Hz, 2H); ^{13}C NMR 41.95 (×2), 68.19 (×2), 72.21 (×2), 126.78 (×2), 128.43 (×4), 128.79 (×4), 129.00 (×4), 130.49 (×2), 138.01 (×2), 163.62 (×2); IR 3420, 3081, 3054, 3031, 2988, 2956, 2893, 2231, 1647, 1608, 1497, 1454, 1406, 1359, 1343, 1317, 1293, 1276, 1262, 1201, 1174,1073, 1046, 1017, 967, 953, 860, 840, 755, 697, 669, 548, 527; HRMS (EI) *m/z* (%) calcd for $C_{26}H_{24}N_2O_2$ 396.1838; found 396.1833.

2a: Preparation of (*S*,*S*)-1,3-Bis(4-butyl-oxazolin-2-yl)benzene. This product was prepared according to the general procedure. The title compound was obtained as a white solid in a 1.16 g (63%) yield: mp = 20−22 °C; $[\alpha]^5_D = -129.9°$ ($c = 0.404$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) δ (ppm) = 8.48 (s, 1H), 8.03−8.06 (dd, J = 2.56, 2.556 Hz, 2H), 7.44 (t, J = 0.035, 1H) 4.48−4.54 (m, 2H), 4.31−4.39 (m, 2H), 3.99 (t, J = 0.29 Hz, 2H), 1.75−1.88 (m, 2H), 1.66−1.73 (m, 2H), 1.33−1.42 (m, 2H), 0.96−0.99 (m, 12H);^{13}C NMR 22.72 (×4), 25.40 (×2), 45.55 (×2), 65.19 (×2), 73.13 (×2), 127.95 (×2), 128.21 (×2), 130.68 (×2), 162.48 (×2); IR 2956, 2927, 2899, 2870, 1652, 1600, 1581, 1468, 1438, 1367, 1306, 1284, 1243, 1168, 1081,1061, 1034, 979, 950, 924, 812, 702; HRMS (EI) *m/z* (%) calcd for $C_{20}H_{28}N_2O_2$ 328.2151; found 328.2160.

2b: Preparation of (*S*,*S*)-1,3-Bis(4-isopropyl-oxazolin-2-yl)benzene: yield 62%; white solid; mp = 18−20 °C, $[\alpha]^5_D = -136.6°$ ($c = 0.26$, $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$, 27 °C) δ (ppm) = 8.49 (s, 1H), 8.03−8.07 (dd, J = 2.5, 3 Hz, 2H), 7.40−7.46 (m,1H), 4.38−4.45 (m,2H) 4.06−4.16 (m, 4H),1.79−1.90 (m, 2H), 1.01(d, J = 11.5 Hz, 6H), 0.90(d, J = 6.9 Hz, 6H);^{13}C NMR 18.14 (×2), 18.92 (×2),

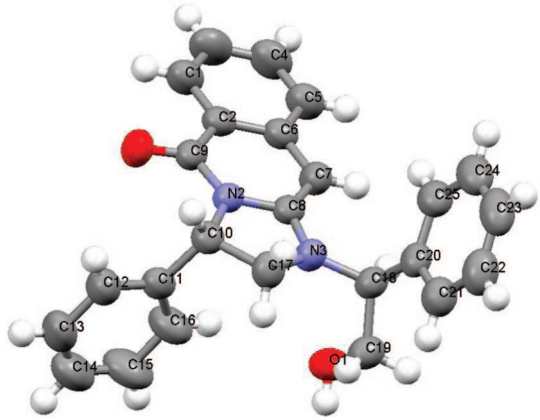


Figure 4. Crystal structure of **4c**.

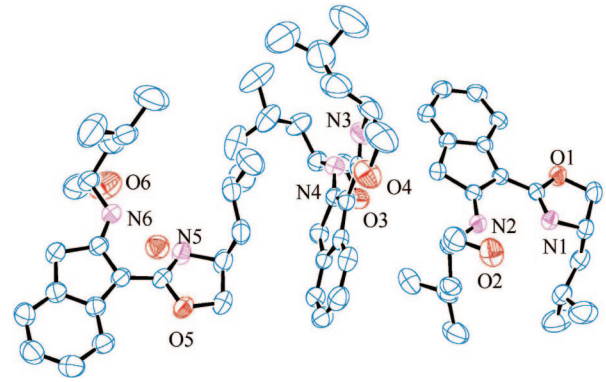


Figure 5. Crystal structure of **5a**.

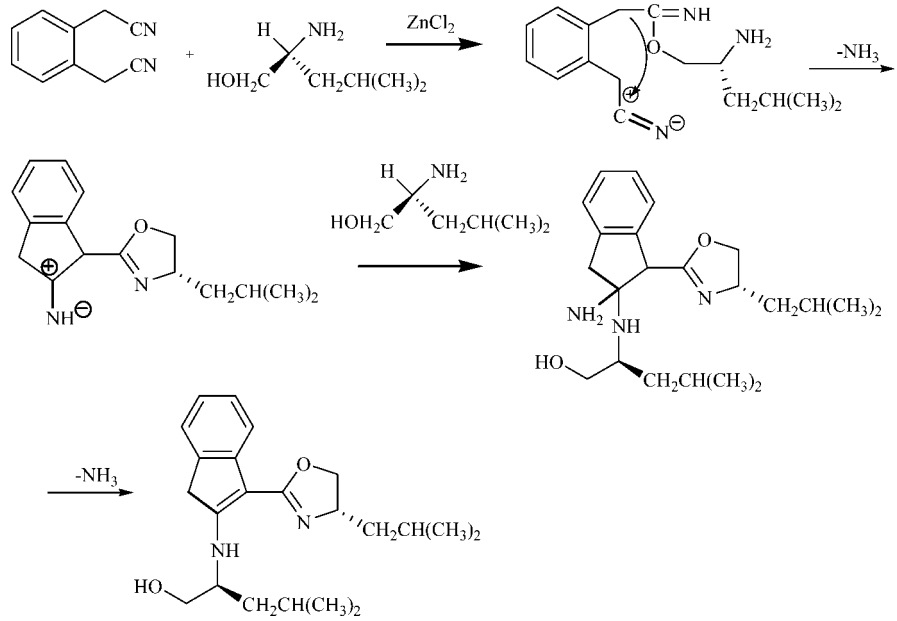
32.85 (×2), 70.22 (×2), 72.70 (×2), 128.07, 128.21, 128.34 (×2), 130.85, 130.92, 162.72 (×2); IR 2961, 2897, 2869, 1650, 1597, 1475, 1464, 1362, 1327, 1314, 1269, 1103, 1066, 1040, 1020, 975, 955, 935, 925, 900, 818, 701; HRMS (EI) *m/z* (%) calcd for $C_{18}H_{24}N_2O_2$ 300.1838; found 300.1835.

2c: Preparation of (*S*,*S*)-1,3-Bis(4-phenyl-oxazolin-2-yl)benzene. This product was prepared according to the general procedure: yield 66%; yellow solid; mp = 34−36 °C; $[\alpha]^5_D = -59.7°$ ($c = 0.148$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) δ (ppm) = 8.69 (s, 1H), 8.19−8.21 (dd, J = 1.2, 1.25 Hz, 1H), 7.50 (t, J = 0.05, 2H), 7.23−7.40 (m, 2H), 7.29−7.38 (m, 8H), 5.40 (t, J = 1.1 Hz, 2H), 4.79−4.82 (m, 2H), 4.30 (t, 2H); ^{13}C NMR 70.39 (×2), 75.18 (×2), 126.88 (×2), 126.94 (×2), 127.88 (×2), 128.14, 128.71, 128.79 (×2), 128.98 (×2), 129.04, 129.08, 131.58 (×2), 142.36 (×2), 164.26 (×2); IR 3280, 3082, 3062, 3028, 2978, 2900, 2231, 1651, 1601, 1581, 1494, 1454, 1298, 1267, 1237, 1206, 1166, 1080, 1067, 1030, 980, 960, 914, 890, 807, 761, 734, 699, 671, 612, 542; HRMS (EI) *m/z* (%) calcd for $C_{24}H_{20}N_2O_2$ 368.1525; found 368.1520.

2d: Preparation of (*S*,*S*)-1,3-Bis(4-benzyl-oxazolin-2-yl)benzene. This product was prepared according to the general procedure: yield 67%; yellow liqud; $[\alpha]^5_D = 5.73°$ ($c = 0.174$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 27 °C) δ (ppm) = 8.12−8.19 (m, 3H), 7.87(t, J = 2.4 Hz, 2H), 7.70(t, J = 2H), 7.49(t, J = 9 Hz, 2H), 7.20−7.30 (m, 5H), 4.56−4.61 (m, 2H), 4.36(t, J = 0.6 Hz, 2H), 4.14 (t, J = 0.9 Hz, 2H), 3.13−3.19 (dd, J = 5.4 Hz, 5.4 Hz, 2H), 2.69−2.76 (dd, J = 8.4 Hz, 8.1 Hz, 2H); ^{13}C NMR: 41.48, 41.61, 67.81(×2), 72.14 (×2), 112.56, 117.96, 126.40, 126.51, 128.32 (×2), 128.46 (×2), 128.96 (×2), 129.12 (×2), 131.71 (×2), 132.16 (×2), 134.29 (×2), 137.42 (×2), 161.83 (×2); IR 3083, 3064, 3028, 2923, 2901, 2232, 1702, 1652, 1603, 1578, 1496, 1475, 1454, 1439, 1312,1291, 1179, 1088, 1059, 1030, 924, 808, 754, 706, 681, 574; HRMS (EI) *m/z* (%) calcd for $C_{26}H_{26}N_2O_2$ 368.1525; found 368.1518.

3a: Preparation of (*S*,*S*)-1,2-Bis-(4-butyl-oxazolin-2-yl)benzene. This product was prepared according to the general procedure. The title compound was obtained as a white solid in a 1.02 g (56%) yield: $[\alpha]^5_D = -81.6°$ (c = 0.177, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) δ (ppm) = 7.70−7.72 (dd, J = 3.5, 3.5 Hz, 2H), 7.44−7.45 (dd, J = 3, 3 Hz, 2H), 4.46 (t, J = 1 Hz, 2H), 4.32−4.37 (m, 2H), 3.91 (t, 2H), 1.82−1.85 (m, 2H), 1.69−1.73 (m, 2H), 1.36−1.40 (m, 2H), 0.94−0.98 (m, 12H); ^{13}C NMR 22.66

Scheme 4. Proposed Mechanism of Formation for **5a**



(×2), 22.88 (×2), 25.38 (×2), 45.27 (×2), 65.40 (×2), 73.49 (×2), 128.53 (×2), 129.74 (×2), 130.22 (×2), 163.46 (×2); IR 3426, 2925, 2870, 1467, 1449, 1356, 1310, 1089, 1049, 1032, 971, 946, 909, 775, 708; HRMS (EI) *m/z* (%) calcd for $C_{20}H_{28}N_2O_2$ 328.2148; found 328.2151.

3b: Preparation of (*S*,*S*)-1,2-Bis(4-isopropyl-oxazolin-2-yl)benzene. This product was prepared according to the general procedure: yield 58%; pale yellow liquid; $[\alpha]^5_D = -14.4°$ ($c = 0.139$, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) δ (ppm) = 7.73−7.76 (dd, $J = 5.57$, 5.71 Hz, 2H), 7.44−7.47 (m, 2H), 4.38 (t, $J = 17.26$ Hz, 2H), 4.04−4.12 (m, 4H), 1.84−1.91 (m, 1H), 1.03 (d, $J = 11.20$ Hz, 6H), 0.90 (d, $J = 3.88$ Hz, 6H); ^{13}C NMR 18.39 (×2), 19.22 (×2), 32.81 (×2), 70.73 (×2), 73.16 (×2), 128.71 (×2), 130.03 (×2), 130.39 (×2), 163.89 (×2); IR 3305, 3273, 3067, 2959, 2930, 2898, 1726, 1713, 1655, 1576, 1492, 1468, 1354, 1309, 1293, 1288, 1248, 1178,1089, 1053, 1033, 966, 908, 773, 706; HRMS (EI) *m/z* (%) calcd for $C_{18}H_{24}N_2O_2$ 300.1838; found 300.1833.

3c: Preparation of (*S*,*S*)-1, 2-Bis(4-phenyl-oxazolin-2-yl)benzene. This product was prepared according to the general procedure: yield 60%; pale yellow liquid; $[\alpha]^5_D = -61.8°$ ($c = 0.42$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) δ (ppm) = 7.86−7.89 (m, 2H), 7.52−7.55 (m, 2H), 7.23−7.36 (m, 10H), 5.34 (t, $J = 1$ Hz, 2H), 4.68−4.72 (m, 2H), 4.18 (t, $J = 0.115$ Hz, 2H); ^{13}C NMR 29.78 (×2), 70.68 (×2), 75.38 (×2), 127.06 (×4), 127.64 (×2), 128.48 (×2), 128.74 (×4), 130.20, 130.76, 142.39 (×2), 165.06 (×2); IR 3061, 3029, 2956, 2924, 2897, 2854, 1651, 1601, 1494, 1470, 1454, 1356, 1313, 1303, 1236, 1090, 1054, 1032, 971, 950, 901, 893, 758, 700; HRMS (EI) *m/z* (%) calcd for $C_{24}H_{20}N_2O_2$ 368.1525; found 368.1475.

3d: Preparation of (*S*,*S*)-1,2-Bis(4-benzyl-oxazolin-2-yl)benzene. This product was prepared according to the general procedure: yield 68%; yellow liquid; $[\alpha]^5_D = -27.2°$ ($c = 0.349$, CH_2Cl_2); ^{1}H NMR (500 MHz,$CDCl_3$, 27 °C) δ (ppm) = 7.71−7.74 (m, 2H), 7.41−7.44 (m, 2H), 7.16−7.30 (m, 10H), 4.49−4.59 (m, 2H), 4.24 (t, $J = 1.01$ Hz, 2H), 4.02 (t, $J = 0.135$ Hz, 2H), 3.14−3.20 (dd, $J = 9.18$ Hz, 9.14 Hz, 2H), 2.72−2.78 (dd, $J = 7.06$ Hz, 8.78 Hz, 2H); ^{13}C NMR 41.24 (×2), 67.89 (×2), 72.03 (×2), 126.27 (×2), 128.24 (×2), 128.32 (×4), 129.06 (×4), 129.20, 129.60, 130.18 (×2) 137.82 (×2), 163.92 (×2); IR 3061, 3027, 2924, 2895, 1710, 1650, 1602, 1494, 1471, 1452, 1356, 1354, 1312, 1288, 1288, 1252, 1091, 1053, 1053, 1031, 965, 918, 752, 702; HRMS (EI) *m/z* (%) calcd for $C_{26}H_{24}N_2O_2$ 396.1838; found 396.1833.

4a: Preparation of 5*H*-Imidazol[2,3-*b*]isoquinoline-1-ethanol-5-one,1,2,3,10*b*-tetrahydro, *β*(S)-butyl, 3(S)-butyl. This product was prepared according to the general procedure. The title compound was obtained as a yellow liquid in a 1.38 g (72%) yield: $[\alpha]^5_D = -90.9$ ($c = 0.35$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) δ (ppm) = 8.08−8.09(d, $J = 8$ Hz, 1H), 7.34 (t, 1H), 7.13 (d, $J = 8$ Hz, 1H), 6.99 (t, 1H), 4.66 (t, $J = 0.5$ Hz, 1H), 3.70−3.71 (m, 4H), 3.56 (t, 1H), 3.32−3.34 (d, $J = 8.5$ Hz, 2H), 1.92−1.96 (d, $J = 0.5$ Hz, 1H), 1.36−1.48 (m, 5H), 0.85−0.98 (m, 12H);^{13}C NMR 21.48, 22.51, 22.83, 23.52, 24.83, 25.23, 36.54, 40.52, 47.84, 53.83, 54.37, 62.63, 77.73, 119.97, 121.40, 123.90, 126.96, 132.07, 140.65, 147.02, 160.91; IR 3404, 3068, 2962, 2929, 2874, 1653, 1603, 1530, 1466, 1370, 1232, 1159, 1074, 756; HRMS (EI) *m/z* (%) calcd for $C_{21}H_{30}N_2O_2$ 342.2307; found 342.2302.

4b: Preparation of 5*H*-Imidazol[2,3-*b*]isoquinoline-1-ethanol-5-one,1,2,3,10*b*-tetrahydro, *β*(S)-isopropyl-3(S)-isopropyl. This product was prepared according to the general procedure: pale yellow liquid; yield 76%; $[\alpha]^5_D = -114.59°$ ($c = 0.0676$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) δ (ppm) = 7.81−7.82 (d, $J = 7.5$ Hz, 1H), 7.26 (m, 3H), 4.34 (d, $J = 6.5$ Hz, 1H), 4. 07−4.22 (m, 6H), 3.86−3.92 (m, 3H), 1.72−1.82 (m, 2H), 0.84−1.04 (m, 12H);^{13}C NMR 18.37, 18.80, 19.06, 19.45, 29.01, 32.90, 41.99, 58.09, 64.47, 69.86, 73.17, 127.62, 129.99, 131.38, 131.48, 132.94, 136.57, 164.14, 172.87; IR 3412, 3269, 3060, 2926, 2873, 2853, 1710, 1549, 1359, 1248, 1162, 1061, 965,

773, 723; HRMS (EI) *m/z* (%) calcd for $C_{19}H_{28}N_2O_2$ 316.2151; found 316.2152.

4c: Preparation of 5*H*-Imidazol[2,3-*b*]isoquinoline-1-ethanol-5-one, 1,2,3,10*b*-tetrahydro-, *β*(S)-phenyl-3(S)-phenyl. This product was prepared according to the general procedure: yellow solid; yield 74%; mp = 87−90 °C; $[\alpha]^5_D$ = 217.39° (*c* = 0.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) *δ* (ppm) = 8.08 (d, *J* = 13.5 Hz, 1H), 7.25−7.45 (m, 12H), 7.11 (t, *J* = 0.5 Hz, 1H), 5.65−5.68 (dd, *J* = 4 Hz, 3.5 Hz, 2H), 5.04 (t, *J* = 9.9 Hz, 1H), 4.08−4.11 (m, 3H), 3.88 (t, *J* = 1 Hz, 1H). 3.63 (t, *J* = 3 Hz, 1H);^{13}C NMR 52.49, 57.86, 60.08 (×2), 62.13 (×2), 120.95, 122.41, 124.42, 125.92 (×2), 127.68, 127.73, 128.27 (×2), 128.63 (×2), 129.10, 129.17, 132.57 (×2), 135.50, 140.09, 160.69 (×2); IR 3290, 3031, 2894, 1650, 1616, 1593, 1551, 1486, 1455, 1432, 1269, 1258, 1151, 1051, 1026, 770, 753, 699, 691; HRMS (EI) *m/z* (%) calcd for $C_{25}H_{22}N_2O_2$ 382.1681; found 382.1676.

4d: Preparation of 5*H*-Imidazol[2,3-*b*]isoquinoline-1-ethanol-5-one, 1,2,3,10*b*-tetrahydro, *β*(S)-benzyl-3(S)-benzyl. This product was prepared according to the general procedure: yellow liquid; yield 78%; $[\alpha]^5_D$ = 29.7° (*c* = 0.34, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) *δ* (ppm) = 8.36(d, *J* = 13.5 Hz, 1H), 7.21−7.58(m, 13H), 5.50(s, 1H), 5.08(t, *J* = 0.5 Hz, 1H), 3.83−3.85 (m, 1H), 3.53−3.68 (m, 4H), 3.23−3.28 (m, 2H), 2.83−2.96 (m, 3H); ^{13}C NMR 33.58, 36.76, 46.67, 55.48, 58.22, 61.68, 78.28, 122.05 (×2), 124.30 (×2), 126.87, 127.04, 127.37 (×2), 128.71, 128.87, 129.72 (×2), 132.47 (×2), 136.62, 137.52,140.68, 147.03, 161.08 (×2); IR 3380, 3062, 3027, 2927, 2874, 2245, 1652, 1617, 1596, 1552, 1486, 1455, 1430, 1361, 1271, 1151, 1173, 1150, 1026, 910, 771, 733, 701, 531; HRMS (EI) *m/z* (%) calcd for $C_{27}H_{26}N_2O_2$ 410.1994; found 410.1991.

5a: Preparation of Indene-2-amino-ethanol-3-[4(*S*)-(1,1-dimethylethyl)-4,5-dihydro]-oxazolyl-*β*(*S*)-isobutyl. This product was prepared according to the general procedure. The title compound was obtained as a yellow liquid in a 1.69 g (85%) yield: $[\alpha]^5_D$ = −54.94° (*c* = 0.11, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) *δ* (ppm) = 7.51 (d, *J* = 7.5 Hz, 1H), 7.18−7.19 (m, 2H), 6.89 (t, *J* = 5.5 Hz, 1H), 4.38 (t, *J* = 0.5 Hz, 1H), 4.20 (t, *J* = 1 Hz, 1H), 3.88 (t, 1H), 3.66−3.67 (m, 3H), 3.49−3.53 (m, 4H), 1.71−1.81 (m, 2H), 1.36−1.41 (m, 4H), 0.89−0.96 (m, 12H); ^{13}C NMR 22.89, 23.08, 25.69, 45.73, 65.48, 73.44, 128.33, 130.55, 162.92; IR 3062, 3030, 2956, 2921, 2850, 2870, 1720, 1659, 1617, 1604, 1492, 1463, 1378, 1290, 1205, 1073, 1027, 909, 759, 700, 505; HRMS (EI) *m/z* (%) calcd for $C_{22}H_{32}N_2O_2$ 356.2464; found 356.2460.

5b: Preparation of Indene-2-amino-ethanol-3-[4(*S*)-1,1-methylethyl)-4,5-dihydro]oxazolyl-*β*(*S*)-isopropyl. This product was prepared according to the general procedure: blue liquid; yield 86%; $[\alpha]^5_D$ = −114.59° (*c* = 0.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) *δ* (ppm) = 7.52 (d, *J* = 8 Hz, 1H), 7.18 (t, *J* = 0.5 Hz, 2H), 6.90 (t, *J* = 4.32 Hz, 1H), 4.30 (t, *J* = 0 Hz, 1H), 3.95−4.04 (m, 3H), 3.33−3.74 (m, 5H), 3.31 (d, *J* = 3.5 Hz, 1H), 1.89−1.90 (m, 1H), 1.69−1.71 (m, 1H). 0.89−0.97 (m, 12H); ^{13}C NMR 17.86, 18.61, 18.73, 19.92, 30.32, 33.55, 36.77(×2), 63.25, 64.34, 69.25, 70.89, 118.23, 120.77, 122.99, 127.07, 133.66, 144.01, 164.44 (×2); IR 3062, 2956, 2921, 2870, 2850, 2249, 1720, 1659, 1655, 1617, 1604, 1492, 1463, 1378, 1290, 1205, 1073, 1027, 909, 759, 735, 700, 648; HRMS (EI) *m/z* (%) calcd for $C_{20}H_{28}N_2O_2$ 328.2151; found 328.2149.

5c: Preparation of Indene-2-amino-ethanol-3-[(4(*S*)-phenyl-4,5-dihydro)]-oxazolyl-*β*(*S*)-phenyl. This product was prepared according to the general procedure: blue liquid; yield 88%; $[\alpha]^5_D$ = −62.27° (*c* = 0.55, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) *δ* (ppm) = 7.67 (d, *J* = 7.5 MHz, 1H), 7.18−7.39 (m, 12H), 6.91 (t, 1H), 5.32−5.35 (m, 1H), 4.62−4.72 (m, 3H), 4.17−4.20 (m, 1H), 3.82−3.85 (m, 3H), 3.57 (d, *J* = 22.0 Hz, 1H), 3.27(d, *J* = 21.5 Hz, 1H); ^{13}C NMR 36.52, 61.54, 66.61, 68.09, 73.48, 96.14, 118.65 (×2), 121.06 (×2), 122.97 (×2), 126.36, 126.41, 126.90, 127.22, 127.59 (×2), 128.50, 128.64, 133.96, 139.41, 143.41, 143.72, 163.91, 165.25; IR 3411, 3004, 2957, 2925, 2855, 2252, 1713, 1605, 1492, 1463, 1362, 1221, 1092, 1073, 1027, 939, 912, 760, 734, 701, 648, 531; HRMS (EI) *m/z* (%) calcd for $C_{26}H_{24}N_2O_2$ 396.1838; found 396.1847.

5d: Preparation of Indene-2-amino-ethanol-3-[4(*S*)-benzyl-4,5-dihydro]-oxazolyl]-*β*(*S*)-benzyl. This product was prepared according to the general procedure: blue liquid; yield 90%; $[\alpha]^5_D$ = −115.13° (*c* = 0.091, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 27 °C) *δ* (ppm) = 7.59 (d, *J* = 13 Hz, 1H), 7.27−7.32 (m, 12H), 6.95−6.99 (t, 1H), 4.41−4.46(m, 1H), 4.32 (t, *J* = 0.5 Hz, 1H), 4.09 (t, *J* = 1 Hz, 1H), 3.47−3.67 (m, 5H), 3.13−3.20 (d, *J* = 35.5 Hz, 1H), 2.81−3.00 (m, 5H); ^{13}C NMR 36.35, 38.92, 42.78, 59.29, 64.62, 66.17, 70.68, 95.10, 118.19, 120.83, 122.91, 126.28, 126.64, 126.99, 128,.39, 128.55, 129.21, 133.62, 137.74, 138.86, 143.63, 163.65, 164.52; IR 3373, 3061, 3026, 2924, 1717, 1575, 1494, 1454, 1463, 1362, 1308,9,1205, 1095, 1074, 1029, 1006, 952, 760, 701, 509; HRMS (EI) m − 1/*z* (%) calcd for $C_{28}H_{27}N_2O_2$ 423.2073; found 423.2079.

Acknowledgment. The authors acknowledge University of Science and Technology of China for providing the spectral measurements conditions.

Note Added after ASAP Publication. There were changes made to the experimental data in the version of this paper published ASAP January 12, 2009; the corrected version published ASAP January 16, 2009.

Supporting Information Available. The spectroscopic data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC8001537