A SYNTHESIS OF 2,6-BIS(4*R*-HYDROXYMETHYLOXAZOLYL)PYRIDINE AS A WATER SOLUBLE LIGAND

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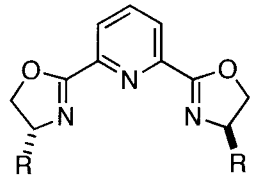
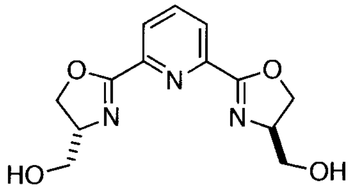
Abstract– C_2 Symmetric 2,6-bis(oxazolyl)pyridine bearing hydroxymethyl group on the oxazoline rings was synthesized from L-serine methyl ester hydrochloride and pyridine-2,6-dicarboxylic acid in four steps (54 % overall yield).

Although many excellent homogeneous catalytic systems in asymmetric synthesis have been reported,[1] they often suffered from one general problem in industrial applications and also on laboratory scales, separation of the products from the expensive catalysts. There are several methods to consider the problem as mentioned above which are mainly to use the molecular catalyst supported on polymers or to use water-soluble catalysts containing hydrophilic ligands to increase the solubility in water.[2] Especially, use of water as a reaction medium is quite attractive because of not only the unique physical and chemical properties but also application of an environmentally friendly material and low cost.[3] Many other advantages have been reported in the literature.[4] To use this promising reaction medium, we have started to prepare a new water-soluble ligand for catalytic asymmetric synthesis in water phase or biphasic media.[5] Here we report the synthesis of a new water soluble ligand, 2,6-bis(4*R*-hydroxymethyloxazolyl)pyridine (**2**).



1a; R=iPr
1b; R=tBu
1c; R=C_6H_5



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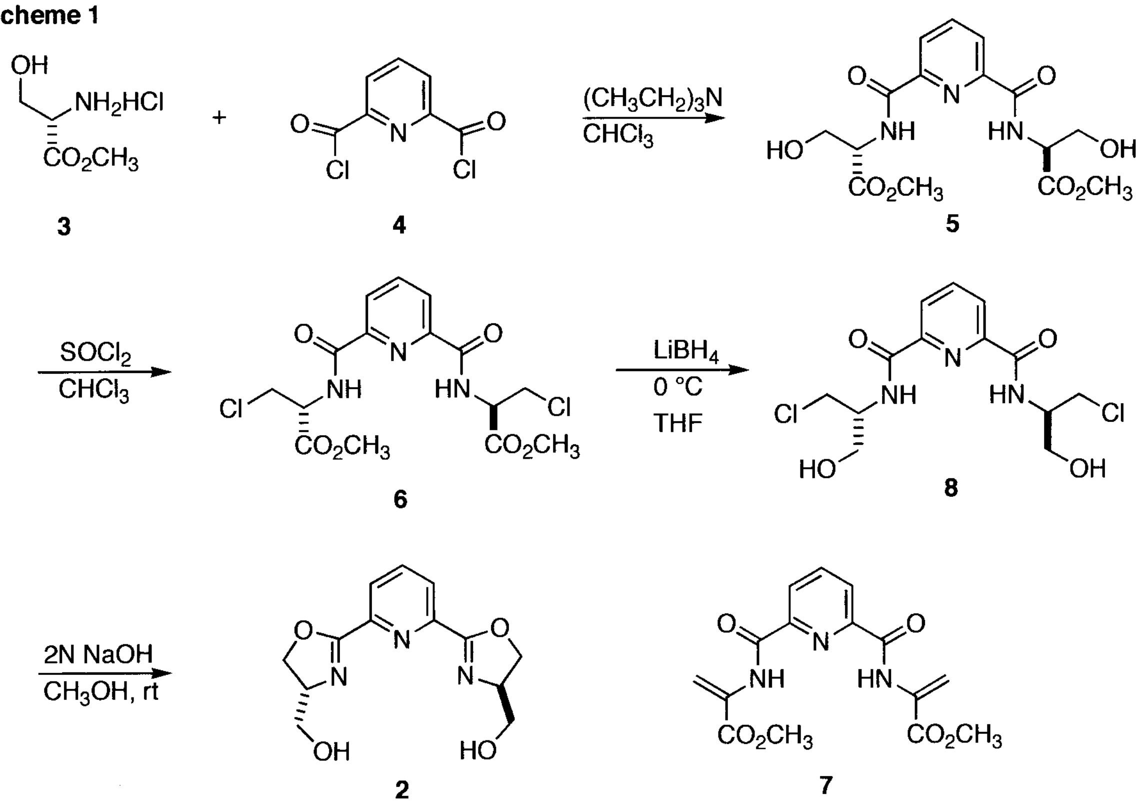
Since the general utility of C_2-symmetric bis(oxazolyl)pyridine (Pybox)(**1**) system as a tridentate ligand has been demonstrated in many asymmetric catalytic processes,[6] these catalytic reactions, however, have been carried out in standard organic solvents such as CH_2Cl_2, toluene, DMF, THF, etc., we designed and synthesized a water soluble bisoxazoline-pyridine system. Most of the water-soluble catalysts involve sulfonated ligands.[7] However, sulfonylation of pyridine ring requires more harsh reaction condition that can destroy the oxazoline rings next to pyridine ring. First of all, therefore, we tried to introduce hydrophilic functional groups such as poly-ether and hydroxyl groups onto pyridine ring of pybox system. All of the attempts, using well-known ortho-lithiation procedures for this objective were, however, failed because of the poor solubility of bis(oxazolyl)pyridine at low temperature.[8]

On the other hand, the idea to introduce a hydroxymethyl group as a hydrophilic functional group on oxazoline rings of pybox system was succeeded by using L-serine derivative as a starting material. (**Scheme 1**) The reaction of pyridine-2,6-dicarboxylic acid chloride with L-serine methyl ester hydrochloride under basic condition afforded the corresponding bis-hydroxyamide (**5**) in quantitative yield.[9]

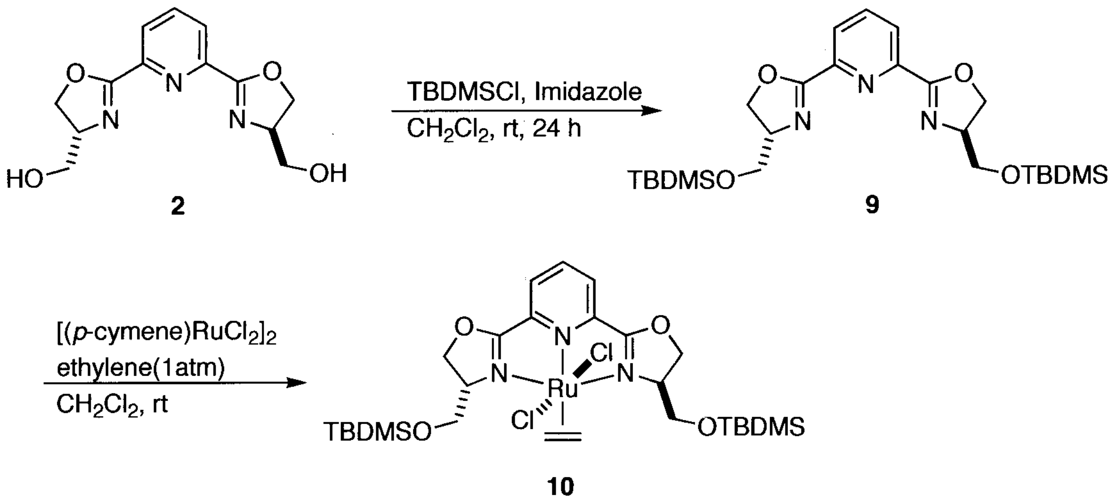
Scheme 1



The bis-hydroxyamide (**5**) was slightly unstable during flash column chromatography on silica gel. The decomposed product was the dehydrated compound (**7**).[10] To avoid this difficulty, the crude reaction product (**5**) can be used for the next step without any purification. The bis-hydroxyamide (**5**) was easily transferred to the bis-chloroamide (**6**) in quantitative yield. **6** was also not so stable under both acidic and basic conditions. At this stage, there are two ways for oxazoline ring formation reaction. One is the direct oxazoline ring formation of the chloroamide followed by reduction of the ester group. The other one is, at first, to convert the ester group to the hydroxyl group by a suitable reducing reagent. The former route was not successful because the bis-chloroamide (**6**) was extremely unstable under various reaction conditions affording the olefin (**7**) in a high yield. Most of the reaction conditions for oxazoline formation could not give the desired product. The elimination reaction of hydrochloride was extremely fast at even low temperature. Therefore, we chose the later method followed by reduction with $LiBH_4$ in THF. The final step was carried out in CH_3OH with 2N NaOH solution to give a white solid which was bis-2,6-bis(4*R*-hydroxymethyloxazolyl)pyridine (**2**).

Since the final desired product is water-soluble itself, the purification of **2** was not easy. In order to confirm the structure, **2** was treated with TBDMSCl and imidazole in CH_2Cl_2 under standard condition to give TBDMS ether (**9**) in 96 % yield[11] and 54 % total yield from L-serine derivatives. (**Scheme 2**) The silyl compound (**9**) was easily purified by simple flash column chromatography and soluble in standard organic solvent even in hexane. The complexation of the silyl compound with ruthenium (II) using [(*p*-cymene)$RuCl_2]_2$[12] in CH_2Cl_2 under ethylene atmosphere provided the ethylene complex.[13] After flash column chromatography on silica gel, the corresponding ethylene complex (**10**) of ruthenium (II), which was also soluble in hexane, was obtained in 88 % yield as a purple solid. The reaction between **2** and [(*p*-cymene)$RuCl_2]_2$ in water was examined under the same reaction condition to give the dark reddish solution, which was probably containing the corresponding ethylene complex. However the complex could not isolated. The dark reddish water phase was not extracted with common organic solvents such as CH_2Cl_2 or EtOAc and toluene.

Scheme 2



In conclusion, we have synthesized a new optically active water-soluble chiral ligand, bis(4*R*-hydroxymethyloxazolyl)pyridine (**2**) starting from L-serine methyl ester hydrochloride in four steps. The use of the new ligand and complexes with ruthenium (II) for asymmetric catalysis either under organic or aqueous conditions is now under investigation.

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EXPERIMENTAL

General Methods: Common solvents were purified before use. THF (anhydrous), Et_2O (anhydrous) and CH_2Cl_2 (anhydrous) commercially available from Kanto Chemical Co. Ltd., were used without further purification. All reagents were reagent grade and purified when necessary. Reactions were monitored by TLC using 250 μm Merck (Art. 5715) precoated silica gel. Flash column chromatography was performed over Merck (Art. 7734) silica gel. Melting points were measured on a Thomas Hoover melting point apparatus and are uncorrected. ^1H- and ^{13}C-NMR spectra were recorded on JEOL JNM-GX270 spectrometer. ^1H NMR chemical shifts are reported as δ values(ppm) relative to internal tetramethylsilane and splitting patterns are designated as: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad. Coupling constants are given in Hz. IR spectra were recorded with JASCO FT/IR-

230 spectrophotometer and are reported in reciprocal centimeter (cm^{-1}). Elemental analyses were performed with Yanagimoto MT-3 CHN corder. Optical rotations were measured on JASCO DIP-140 polarimeter at the sodium D line (1 mL sample cell).

Bis-hydroxyamide (**5**) A mixture of 2,6-dicarboxylic acid (5.00 g, 29.9 mmol) and $SOCl_2$ (25.0 mL, 353 mmol) was heated to reflux for 8.5 h. under argon atmosphere. After cooling the reaction mixture, the excess $SOCl_2$ was removed under reduced pressure to give 2,6-dicarboxylic acid chloride (**4**) in quantitative yield as a white solid. The product was used for next step without any further purification. To a solution of L-serine methyl ester hydrochloride (10.24 g, 65.8 mmol) in $CHCl_3$ (100 mL) was added Et_3N (20.1 mL, 1469.6 mmol) at rt. To this was added a solution of the crude acid chloride (**4**) (6.10 g, 29.9 mmol) in $CHCl_3$ (20 mL) which was prepared as mentioned above. The resulting mixture was stirred for 24 h at rt. The white solid was filtered off under reduced pressure and the filtrate was condensed, purified by flash column chromatography on silica gel (EtOAc/MeOH=15/1-5/1) to give the amide alcohol (**5**) (10.43 g) in 94.4% from 2,6-dicarboxylic acid. **5**; mp 165.0-167.0 °C (recrystallized from EtOAc/MeOH=15/1); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.83 (6 H, s), 3.72-3.99 (2 H, br s), 4.09 (2 H, dd, J= 11.2, 2.9 Hz), 4.20 (2 H, dd, J= 11.7, 4.4 Hz), 4.86-4.91 (2 H, m), 7.88 (1 H, t, J= 7.8 Hz), 8.19 (2 H, d, J = 7.8 Hz), 8.92 (2 H, d, J = 7.8 Hz); ^{13}C NMR (CD_3OD, 67.5 M Hz) δ 53.0, 56.6, 62.7, 126.4, 140.6, 150.0, 165.8, 172.1; IR (KBr) 3323, 2949, 1740, 1663, 1538, 1441, 1228, 1173, 1083, 1038 cm^{-1}; $[\alpha]^{24}_{D}$ = +46.21 ° (c=0.85, CH_3OH); Anal. Calcd for $C_{15}H_{19}N_3O_8$: C, 48.78; H, 5.19; N, 11.38. Found: C, 48.74; H, 5.20; N, 11.18.

Bis-chloroamide (**8**) To a solution of **5** (2.66 g, 7.20 mmol) in $CHCl_3$ (35 mL) was slowly added dropwise $SOCl_2$ (1.12 mL, 62.13 mmol) at 0 °C. The resulting mixture was then refluxed for 1.5 h. After cooling the reaction mixture, the solvent and excess $SOCl_2$ were removed in vacuo to give the crude bis-chloroamide (**6**). This compound was used for next step without purification because **6** was unstable under both acidic and basic conditions to yield dehydrated product (**7**). **7**; mp 146 °C (recrystallized from EtOAc/hexane=1/5); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.97 (6 H, s), 6.12 (2 H, s), 6.87 (2 H, s), 8.12 (1 H, t, J = 7.3 Hz), 8.45 (2 H, d, J = 7.3 Hz), 10.10 (2 H, s); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 53.0, 110.0, 125.6, 131.0, 139.4, 148.6, 161.7, 164.1; IR (NaCl) 3397, 3362, 3088, 2956, 1726, 1687, 1631, 1513, 1441, 1340, 1284, 1202, 1156, 1079, 996, 969, 844, 734 cm^{-1}. To a suspension of $LiBH_4$ (0.354 g, 16.2 mmol) in THF (90 mL) was slowly added a solution of bis-chloroamide (**6**) (3.00 g, 7.39 mmol) in THF (10 mL) at 0 °C and the stirring was continued for 2 h at rt. To this was added carefully water (8 mL) and the organic phase was separated, and dried (Na_2SO_4). The product was purified by flash column chromatography on silica gel (hexane/EtOAc/MeOH =5/5/1) to give pure the desired product (**8**) (2.58 g) in 95.3% yield from **5**. **8**; mp 143.0-146.0 °C (recrystallized from hexane/EtOAc/MeOH=5/5/1); ^{1}H NMR (CD_3OD, 270 MHz) δ 3.76-3.92 (8 H, m), 4.39 (2 H, quin, J= 5.6 Hz), 8.17 (1 H, t, J= 7.8 Hz); ^{13}C NMR (CD_3OD, 67.5 M Hz) δ 44.3, 54.6, 62.0, 126.3, 140.5, 150.2, 165.9; IR (KBr) 3310, 2929, 2473, 1687, 1648, 1590, 1525, 1458, 1412, 1266, 1044, 970, 838, 747 cm^{-1}; $[\alpha]^{24}_{D}$ = -30.90 ° (c=0.85, MeOH); Anal. Calcd for $C_{13}H_{17}N_3O_4Cl_2(H_2O)$: C, 42.40; H, 5.20; N, 11.41. Found: C, 42.64; H, 4.93; N, 11.14.

Synthesis of bis(hydroxymethyl)pyridine (2) and the TBDMS ether (9)

To a solution of **8** (1,00 g, 2.85 mmol) in CH_3OH (4.5 mL) was added 1N NaOH (14.3 mL) at rt. The resulting mixture was stirred for 24 h. The white solid was formed in the reaction mixture and the solid was filtered to give **2** (0.514 g) as a white solid in 65% yield. **2**; IR (NaCl) 3432, 3202, 2907, 1634, 1571, 1447, 1392, 1283, 1130, 1102, 1029, 993, 842 cm^{-1}. mp 244-246 °C(decomp). To a suspension of **2** in CH_2Cl_2 (0.072 g 0.26 mmol) was added a solid of imidazole (0.13 g, 1.91 mmol) at rt followed by addition of TBDMSCl (0.117 g, 0.78 mmol) in one portion. The resulting mixture was stirred for 15 h at rt. The white suspension was directly purified by flash column chromatography on silica gel (EtOAc/hexane=1/1-4/1) to give desire silylated product (**9**) (0.121 g) in 92 % yield. **9**; mp 93.5-94.0 °C (recrystallized from EtOAc/hexane=1/1); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.04 (6 H, s), 0.07 (6 H, s), 0.86 (18 H, s), 3.65 (2 H, dd, J = 10.3, 6.4 Hz), 3.93 (2 H, dd, J = 9.5, 3.2 Hz), 4.46-4.56 (6 H, m), 7.86 (1 H, t, J = 7.8 Hz), 8.17 (2 H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 270 MHz) δ -5.4, 18.2, 25.8, 65.0, 68.4, 71.2, 125.7, 137.1, 146.8, 163.5; IR (KBr) 3432, 3202, 2907, 2865, 1634, 1571, 1447, 1392, 1130, 1102, 1074, 1029, 993, 842, 677, 589 cm^{-1}; $[\alpha]^{18.5}_D = +105.9°$ (c=1, CH_2Cl_2) Anal. Calcd for $C_{25}H_{43}N_3O_4Si_2$: C, 59.37; H, 8.57; N, 8.31. Found: C, 58.85; H, 8.60; N, 8.35.

Ethylene complex (10). A mixture of (**9**) (0.23 g, 0.455 mmol) and [(*p*-cymene)$RuCl_2$]$_2$ (0.139 g, 0.277 mmol) in CH_2Cl_2 (5.0 mL) was stirred under ethylene atmosphere(balloon) at rt. The reaction was monitored by TLC. After 1 h, the reaction was completed and the solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel(EtOAc/hexane=2/1) to give the ethylene complex (**10**) (0.283 g) in 88.0 % yield. **10**; mp 175.0 °C(decomp) (recrystallized from hexane); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.06 (6 H, s), 0.11 (6 H, s), 0.88 (18 H, s), 3.56 (2 H, dd, J = 9.8, 9.8 Hz), 4.07 (2 H, dd, J = 10.8, 3.9 Hz), 4.51 (2 H, m), 4.88-5.00 (4 H, m), 5.08-5.15 (4 H, m), 7.90 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ -5.5, 17.8, 25.5, 63.0, 66.8, 71.2, 74.8, 123.2, 133.3, 145.8, 164.9; IR (NaCl) 2953, 2856, 1592, 1493, 1468, 1401, 1253, 1127, 1098, 1020, 960, 839, 779 cm^{-1}; Anal. Calcd for $C_{27}H_{47}N_3O_4Cl_2RuSi_2(H_2O)$: C, 44.80; H, 6.82; N, 5.81. Found: C, 44.94; H, 6.55; N, 5.79.

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