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SYNTHESIS OF NEW CHIRAL BIS-OXAZOLINE LIGAND WITH ZINC TRIFLATE-SELECTIVE CHELATING ABILITY AND ITS APPLICATIONS

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Abstract – New chiral bis-oxazoline ligand (**10**) with a dihydroanthracene skeleton was synthesized and its application to enantioselective Diels-Alder reaction and Henry reaction has revealed extremely zinc triflate-selective chelating ability of **10**.

INTRODUCTION

Enantioselective synthesis using chiral semicorrins as bidentate ligands with nitrogen was first described by Pfaltz and co-workers in 1986.[1] Since then a number of chiral bis-oxazolines equivalent to chiral semicorrins have been developed and become an important family of chiral auxiliaries and their combinations with metal salts have been shown to be especially useful and versatile catalysts for a variety of enantioselective reactions, for example, Diels-Alder cycloaddition, aldol condensation, cyclopropanation, and ene reaction processes.[2] We describe here the synthesis of a new bis-oxazoline ligand with zinc triflate-selective chelating ability and its application to enantioselective Diels-Alder cycloaddition reaction and Henry reaction.

RESULTS AND DISCUSSION

In designing the bis-oxazoline ligand we envisaged that flexibility of the space distance between two oxazolines in the chiral auxiliary might serve to enhance its chelating ability despite various sizes of the metals. Thus, we chose a dihydroanthracene as flexible tether between two oxazolines and designed

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This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

ligand (**1**) with *cis*-two oxazolines at C9 and C10-quaternary carbons serving as a hinge between two aromatic rings as shown in Figure 1.

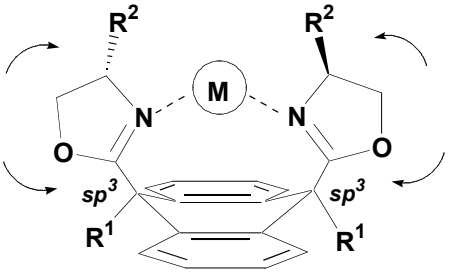

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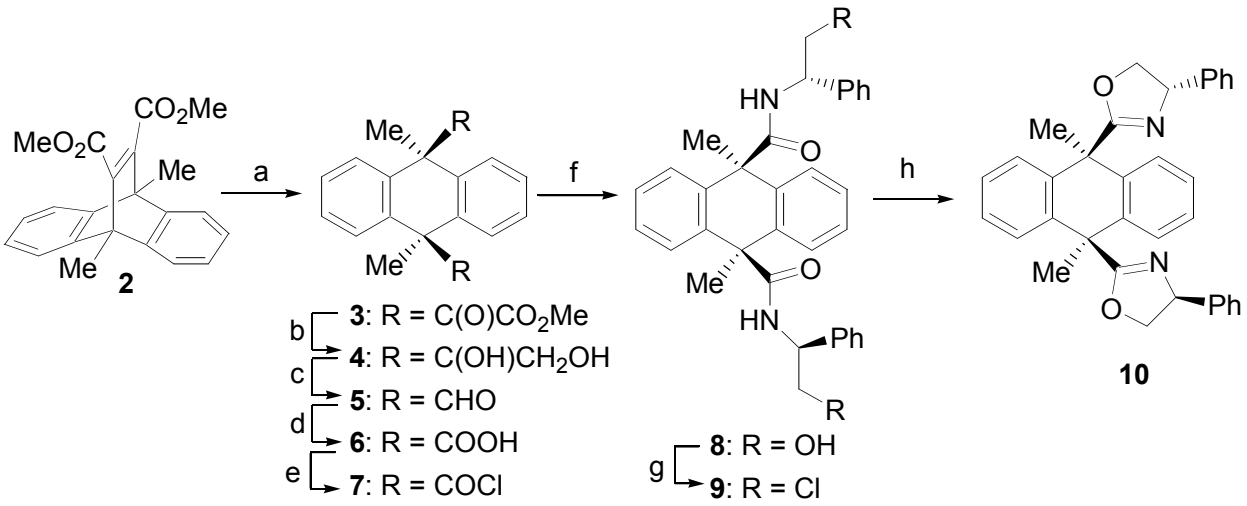
Figure 1

Synthesis of the chiral bis-oxazoline ligand commenced with preparation of *cis*-dicarboxylic acid (**6**) as shown in Scheme 1. Adduct (**2**) derived from known Diels-Alder reaction of readily available 9,10-dimethylanthracene[3] was ozonized at –65 to –55 °C for 8 h and quenched with triphenylphosphine at –55 to 5 °C for 13 h to give bis-α-keto ester (**3**). Reduction of **3** with lithium aluminum hydride and glycol cleavage of the obtained diol (**4**) with sodium periodate produced aldehyde (**5**), which was oxidized with sodium chlorite to afford the *cis*-dicarboxylic acid (**6**) in 31% yield (four steps). Conversion of **6** to acid chloride (**7**) and subsequent condensation with (*S*)-phenylglycinol in the presence of triethylamine afforded amide (**8**) in 75% yield (two steps). Oxazoline-formation from **8** in one step was unexpectedly difficult. Therefore, after conversion of **8** to chloride (**9**) the oxazoline ring was formed by treatment of **9** with potassium hexamethyldisilazide in tetrahydrofuran to furnish bis(oxazolinyl)dihydroanthracene (**10**) in 88% yield.



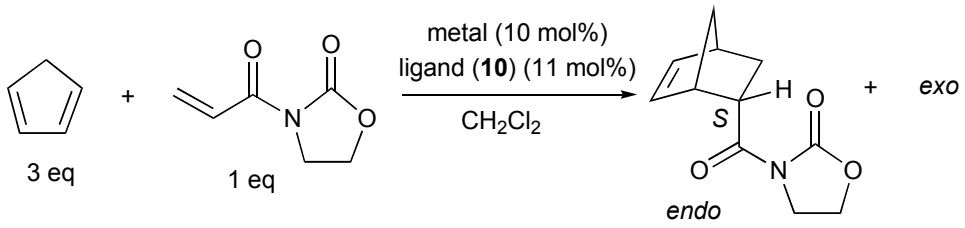
Reagents amd conditions: (a) O_3, CH_2Cl_2, -65 to - 55 °C, 8 h, then Ph_3P, -55 to 5 °C, 13 h (b) $LiAlH_4$, THF, 0 to 23 °C, 15 h (c) $NaIO_4$, MeOH, H_2O, 23 °C, 30 h (d) $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, *t*-BuOH, H_2O, 0 to 23 °C , 27 h, 31%(4 steps) (e) $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 to 23 °C, 22.5 h (f) (*S*)-phenylglycinol, Et_3N, CH_2Cl_2, 0 to 23 °C, 20 h, 75% (2 steps) (g) $SOCl_2$, THF, 23 °C to reflux, 16 h, 49% (h) KHMDS, THF, 0 to 23 °C, 16 h, 88%

Scheme 1

We chose Diels-Alder cycloaddition reaction[4] of cyclopentadiene with *N*-acryroyloxazolidinone as a bench-mark reaction for bis-oxazoline ligand (**10**) and extensively surveyed metal salts for combination with **10**. The results are summarized in Table 1. The chiral catalyst was prepared prior to the reaction by complexation of metal salts (10 mol%) with **10** (11 mol%) in methylene chloride at 23 °C for 8.5 h. After

the catalyst solution was cooled to –78 °C, the Diels-Alder reaction was carried out by adding cyclopentadiene and *N*-acryroyloxazolidinone. Ferric chloride, nickel chloride, silver triflate, scandium triflate, and ytterbium triflate catalyzed the reaction with excellent *endo*-selectivity but gave no enantioselectivity. These results suggest that the reaction might proceed in incomplete or no complexation of the metal salts with **10**. Enantioselectivity of stannic triflate and cupric triflate was low (entries 1 and 3). Zinc triflate afforded the products with moderate *endo*/*exo* (75:25) selectivity. However, we were pleased to find that the analysis of the products showed surprisingly high enantiomeric excesses of both *endo*- and *exo*-products (entry 4). The enantiomeric excesses and absolute configurations of the products were determined by HPLC analysis and comparison with the literature value.[5] From the result of zinc triflate we carefully examined several zinc salts, zinc chloride, zinc iodide, zinc cyanide, and zinc acetate, which were found to be fruitless in the Diels-Alder reaction (entries 5-8). The above results reveal that **10** has extremely selective chelating ability to zinc triflate and completely forms the chiral catalyst for the Diels-Alder reaction.

Table 1 Catalytic Asymmetric Diels-Alder Reaction[a]



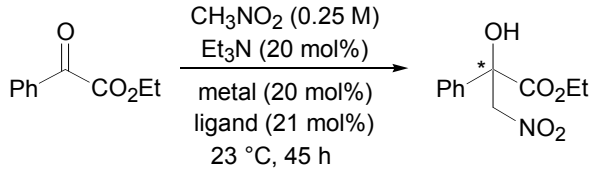
entry	metal salt	conditions	*endo* : *exo*[b]	*endo* ee (%)	*exo* ee (%)
1	$Sn(OTf)_2$	-78 to 23 °C, 36 h	93 : 7	20	22
2	$Yb(OTf)_3$	-78 to -10 °C, 14 h	85 : 15	3	N.D.
3	$Cu(OTf)_2$	-78 to 23 °C, 14 h	36 : 64	35	0
4	$Zn(OTf)_2$	-78 to 5 °C, 12 h	75 : 25	>99	>99
5	$ZnCl_2$	-78 to 10 °C, 18 h	95 : 5	16	0
6	ZnI_2	-78 to 10 °C, 18 h	94 : 6	12	17
7	$Zn(CN)_2$	-78 to 10 °C, 18 h	94 : 6	15	14
8	$Zn(OAc)_2$	-78 to 10 °C, 18 h	93 : 7	13	19

a) The yield was quantitative. *b*) The *endo*/*exo* ratio was determined by ^{1}H-NMR spectral analysis.

To explore the potential of the bis-oxazoline (**10**), we next investigated catalytic asymmetric Henry reaction.[6] We chose ethyl benzoylformate as the substrate and surveyed metal salts for the bis-oxazoline ligand (**10**) as shown in Table 2.[7] The chiral catalyst was prepared by mixing metal salts (20 mol%) and **10** (21 mol%) in nitromethane at 23 °C for 1 h. The Henry reaction was performed by adding ethyl benzoylformate and triethylamine (20 mol%) to the chiral catalyst solution and stirring at 23 °C for 45 h

under argon atmosphere. Again, zinc triflate in combination with **10** was indicated to be the most effective chiral catalyst for the Henry reaction. In addition, cupric triflate was found to catalyze enantioselectively the reaction in 85%ee but the yield was moderate with recovery of the starting material. Other zinc salts were again ineffective.

Table 2 Catalytic Asymmetric Henry Reaction



entry	metal salt	yield (%)[a]	ee (%)
1	$Cu(OTf)_2$	52 (quant)	85 (-)
2	$Zn(OTf)_2$	92 (quant)	71 (+)
3	$ZnCl_2$	51(79)	11 (+)
4	ZnI_2	76 (87)	4 (+)
5	$Zn(CN)_2$	89 (quant)	11 (+)

a) The value in the parenthesis shows the conversion yield.

In conclusion, we have demonstrated the synthesis of new chiral bis-oxazoline ligand (**10**) with a dihydroanthracene tether and its application to the enantioselective Diels-Alder cycloaddition and Henry reaction. The new bis-oxazoline ligand (**10**) was found to bear extremely selective chelating ability to zinc triflate. Further applications of the bis-oxazoline ligand (**10**) are underway in this laboratory.

EXPERIMENTAL

Melting points were measured with a SIBATA NEL-270 melting point apparatus. Infrared spectra were recorded on a JASCO FT/IR-230 Fourier Transform infrared spectrophotometer. Optical rotations were measured on a JASCO DIP-14 polarimeter and a JASCO P-1020 polarimeter with a sodium lamp and were recorded as follows: $[\alpha]_D^T$ (*c* g/100 mL, solvent). ^{1}H NMR spectra were recorded on a JEOL JNM-GSX 400A spectrometer (400 MHz) and a JNM ECP400 spectrometers (400MHz). Chemical shifts were recorded in ppm from tetramethylsilane or chloroform as the internal standard. FAB mass spectra were obtained with a JEOL JMS-HX110A spectrometer. HPLC was carried out with JASCO UV-970 (detector) and PU-980 (pump) high pressure liquid chromatography.

9,10-Dimethyl-9,10-dihydroanthracene-9,10-dicarboxylic acid (6)

To methylene chloride (CH_2Cl_2, 200 mL) saturated with O_3 at –65 ºC was added dropwise a solution of **2** (12.0 g, 34.4 mmol) in CH_2Cl_2 (125 mL) over 5 h. After the mixture was additionally stirred at –55 ºC for 3 h, argon gas was bubbled into the mixture for 30 min. Triphenylphosphine (36.1 g, 138 mmol) was

added to the stirred solution at –55 ºC and the resulting mixture was allowed to gradually warm to 5 ºC over 13 h. After the mixture was concentrated *in vacuo*, the residue was washed with ethyl acetate-hexane to afford **3** (5.80 g) as brown solids, which were used for the next step without further purification.

A solution of **3** (5.80 g) in THF (75 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (2.31 g, 60.8 mmol) in THF (35 mL) at 0 ºC under argon atmosphere and the mixture was gradually warmed to 23 ºC over 15 h. After the reaction was quenched with 6M hydrochloric acid, the mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford **4** (6.16 g), which was used for the next step without purification.

Sodium periodate (12.7 g, 59.3 mmol) was added to a solution of **4** (6.16 g) in MeOH (240 mL) and H_2O (60 mL) at 23 ºC and the mixture was stirred for 30 h. After filtration, saturated aqueous $NaHCO_3$ was added to the filtrate. The resulting mixture was concentrated *in vacuo* and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford **5** (4.0 g), which was used for the next step without further purification.

A solution of $NaClO_2$ (80%, 10.1 g, 89 mmol) in H_2O (17 mL) was added dropwise to a stirred solution of **5** (4.0 g), 2-methyl-2-butene (15.7 mL, 148 mmol), and KH_2PO_4 (4.03 g, 29.7 mmol) in *t*-BuOH (60 mL) at 0 ºC. After stirring the mixture for 27 h at 23 ºC, aqueous NaOH (1M in H_2O) was added and the resulting mixture was washed with CH_2Cl_2. The aqueous layer was acidified with concd HCl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford **6** (3.14 g, 31% in 4 steps) as yellow solids: mp 292-294 ºC; IR (KBr): 2975, 1710, 1490, 1447, 1405, 1376, 1283, 1109, 1038, 928, 758, 721, 676 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO): δ 1.60 (s, 6H), 7.22-7.25 (m, 4H), 7.29-7.32 (m, 4H), 12.6 (s, 2H); ^{13}C-NMR (100 MHz, DMSO): δ 31.7, 49.0, 125.5, 126.2, 135.8, 17.2. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.76; H, 5.40.

9,10-Dimethyl-9,10-dihydroanthracene-9,10-dicarboxylic acid bis[(1*S*)-2-hydroxy-1-phenylethyl]-amide (8)

To a solution of the carboxylic acid (**6**) (4.03 g, 13.6 mmol) in CH_2Cl_2 (68 mL) at 0 °C was added dropwise oxalyl chloride (3.5 mL, 40.3 mmol) and DMF (1 drop) and the solution was stirred at 23 °C for 22.5 h. The mixture was concentrated *in vacuo* to afford **7** (3.91 g) as white solids, which were used for the next step without further purification.

Triethylamine (17 mL, 123 mmol) and a solution of **7** (3.91 g,) in CH_2Cl_2 (190 mL) were added dropwise to a stirred solution of (*S*)-phenylglycinol (3.92 g, 28.5 mmol) in CH_2Cl_2 (68 mL) at 0 °C. After stirring the mixture at 23 °C for 20 h, the reaction mixture was washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column

chromatography ($CHCl_3$/MeOH = 20:1) to afford **8** (5.46 g, 75% in 2 steps) as white amorphous solids: $[\alpha]_D^{25}$ +7.9° (*c* 1.05, $CHCl_3$); IR (KBr): 3384, 3060, 1648, 1523, 1277, 1036 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 6H), 3.57 (dd, *J* = 11.5, 5.6 Hz, 2H), 3.61 (dd, *J* = 11.7, 4.1 Hz, 2H), 4.85-4.89 (m, 2H), 6.95 (d, *J* = 7.6 Hz, 2H), 6.97-7.00 (m, 4H), 7.20-7.36 (m, 12H), 7.47-7.50 (m, 2H); ^{13}C-NMR(100 MHz, $CDCl_3$): δ 29.4, 50.1, 55.7, 65.6, 126.4, 127.2, 127.5, 127.6, 127.9, 128.1, 128.5, 136.7, 137.2, 139.1, 175.9; HRMS(FAB): Calcd for $C_{34}H_{35}N_2O_4$: 535.2597 $(M+H)^+$; Observed: 535.2562.

9,10-Dimethyl-9,10-dihydroanthracene-9,10-dicarboxylic acid bis[(1*S*)-2-chloro-1-phenylethyl]-amide (9)

To a stirred solution of **8** (5.20 g, 9.73 mmol) in THF (92 mL) at 23 °C was added dropwise $SOCl_2$ (3.5 mL, 47.9 mmol) and the mixture was refluxed for 16 h. The resulting mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1) to afford **9** (2.71 g, 49%) as white amorphous solids: $[\alpha]_D^{13}$ -8.9° (*c* 1.08, $CHCl_3$); IR (KBr): 3341, 3259, 3061, 1651, 1265, 1032 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 6H), 3.54 (dd, *J* = 11.5, 7.1 Hz, 2H), 3.65 (dd, *J* = 11.5, 4.6 Hz, 2H), 5.19 (dt, *J* = 7.1, 4.9 Hz, 2H), 6.56 (d, *J* = 7.6 Hz, 2H), 6.96-7.00 (m, 4H), 7.17-7.36 (m, 12H), 7.47-7.49 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 30.0, 47.2, 50.3, 54.3, 60.4, 126.4, 127.5, 127.8, 127.9, 128.0, 128.5, 136.6, 136.8, 138.4, 175.3; HRMS(FAB): Calcd for $C_{34}H_{33}N_2O_2Cl_2$: 571.1919 $(M+H)^+$; Observed: 571.1886.

9,10-Bis[(4'*S*)-4'-phenyl-2'-oxazolinyl]-9,10-dimethyl-9,10-dihydroanthracene (10)

To a solution of dichloride (**9**) (905.8 mg, 1.58 mmol) in THF (16 mL) at –20 °C was added dropwise KHMDS (0.5 M in toluene, 6.4 mL, 3.20 mmol) under argon atmosphere and the resulting mixture was gradually warmed to 23 °C. After stirring for 16 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3:1) to afford **10** (695.9 mg, 88%) as white amorphous solids: $[\alpha]_D^{13}$ -254.4° (*c* 1.14, $CHCl_3$); IR (KBr): 2979, 1649, 1491, 1446, 1228, 1096, 963 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.91 (s, 6H), 4.07 (t, *J* = 8.8 Hz, 2H), 4.56 (dd, *J* = 10.0, 8.8 Hz, 2H), 5.34 (dd, *J* = 10.0, 8.8 Hz, 2H), 7.32–7.45 (m, 14H), 7.48–7.54 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 34.2, 44.7, 69.7, 75.4, 127.0, 128.8, 136.7, 142.2, 172.3; HRMS (FAB): Calcd for $C_{34}H_{31}N_2O_2$: 499.2386 $(M+H)^+$; Observed: 499.2373.

Diels-Alder Cycloaddition Reaction

A mixture of metal salt (10 mol%) and ligand (**10**) (11 mol%) in CH_2Cl_2 (1 mL) at 23 °C was stirred for 8.5 h under argon atmosphere. After the mixture was cooled to –78 °C, a solution of the *N*-acryroyloxazolidinone (71.4 mg, 0.506 mmol) in CH_2Cl_2 (1 mL) followed by cyclopentadiene (125 μL, 1.52 mmol) were added dropwise. The resulting solution was gradually warmed to 5 °C over 12 h. The reaction mixture was then diluted with ethyl acetate (1 mL) and hexane (1.5 mL) at 5 °C and applied directly to silica gel column chromatography with ethyl acetate/hexane (1:1). After concentration of the collected fractions, the Diels-Alder adduct was obtained quantitatively. Enantiomeric excess was determined by HPLC analysis with Daicel Chiralcel OD-H column (hexane/isopropanol/ethyl acetate = 95:2:3, flow rate: 0.9 mL/min, *exo*: t_{minor} = 30.7 min, t_{major} = 31.9 min; *endo*: t_{major} = 35.1 min, t_{minor} = 42.1 min).

Henry Reaction

The mixture of metal salts (20 mol%) and ligand (21 mol%) was dried in vacuo for 2 h. Then, $MeNO_2$ (960 μL, 0.25 M) was added and the solution was stirred for 1 h. Ethyl benzoylformate (95%, 40 μL, 0.239 mmol) and Et_3N (20 mol%) were added dropwise to the mixture. After stirring the mixture at 23 °C for 45 h under argon atmosphere, the reaction mixture was applied directly to a short column of silica gel and then eluted with hexane/ethyl acetate (6:1) to remove the metal salts. After concentration of the fractions, the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 8:1) to afford β-nitro-α-hydroxy ester. Enantiomeric excess was determined by HPLC analysis with Daicel Chiralcel OJ column (hexane/isopropanol = 9:1, flow rate: 1.0 mL/min, t_{minor} = 25.1, t_{major} = 30.8 min).

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