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Preparation of new bis(oxazoline) ligand bearing non-covalent interaction sites and an application in the highly asymmetric Diels–Alder reaction

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Abstract—New asymmetric bis(oxazoline) (Box) ligand bearing amide group at the oxazoline 4-position, (*S*,*S*)-2,2′-methylenebis-(4-*tert*-butylcarbamoyl-2-oxazoline) (**1S**), was designed and synthesized for selective catalytic reaction. The crystal structure of the ternary copper complex, consisting of **1S** and N-benzoyl-N-phenyl-hydroxylamine, demonstrated interligand interactions, such as hydrogen bonding and CH-π interaction. Catalytic performance of the copper complex with **1S** was investigated for an asymmetric Diels–Alder reaction using benzylidene-2-acetylpyridine and 1,3-cyclohexadiene (CHD). The reaction product was enantio-pure endo-(pyridin-2-yl)(3-phenylbicyclo[2,2,2]oct-5-ene-2-yl)methanone (BPCD), of which crystal structure was analyzed by the X-ray method. No stereo- and enantio-isomer of BPCD was detected by chiral HPLC analysis. Introduction of hydrogen bonding site into **1S** can promote the Diels–Alder reaction even though using poor reactive CHD. Without **1S**, this reaction did not give any product. Addition of 2-propanol to this reaction system inhibited the formation of BPCD, indicating that the designed interligand interaction sites, especially hydrogen bonding, play an important role for catalytic performance.

Interligand interactions around metal center are important for demonstrating selectivity and specificity in catalysis of transition metal complexes. In order to achieve high selectivity and efficiency for asymmetric reactions, ternary complexes consisting of metal–ligand–substrate have been designed.[1] Generally, biologically specific and efficient reactions are demonstrated at or near the active site of enzyme–substrate complex through a combination of some weak non-covalent interactions, such as hydrogen bond, steric repulsion, electrostatic interaction, and hydrophobic one, etc., which are realized upon simple metal complexes.[2] In the viewpoint of the bio-inspired chemistry, introduction of hydrogen bonding site into the ternary complexes provides an approach to high selectivity and efficiency of catalysis.[3] Recently, chiral bis(oxazoline) (Box) compounds, bearing 4-phenyl or 4-*tert*-butyl group at oxazoline ring with C_2-symmetry, have been utilized for various asymmetric reactions.[4,5] The large phenyl or *tert*-butyl group substituted at 4-position of the oxazoline ring is designed to sterically block approach of the substrate to the active center of the catalyst from another side.[6,7] Although there have been many reports on the catalysts containing these chiral Box ligands, few reports have discussed an attractive interligand interaction mediated upon the ternary complexes.[6,8,9] To our knowledge, hydroxymethyl or ester group substituted at the 4-position has been reported as a recognition site for the substrate.[6,8,10] Introduction of amide group at or near the ternary complex might become an efficient way of regulating the geometry of the transition state, because hydrogen bonding interactions between amide groups are known to stabilize the structure of supramolecules.[11] Here, we describe preparation of novel Box derivatives bearing amide group as hydrogen bonding site at the oxazoline 4-position and their catalytic application to asymmetric Diels–Alder reaction (Fig. 1).

The novel Box derivative, (*S*,*S*)-2,2′-methylenebis(4-*tert*-butylcarbamoyl-2-oxazoline) ((*S*,*S*)-^{t}BuboxamH$_2$, **1S**) and its enantio-isomer, (*R*,*R*)-^{t}BuboxamH$_2$, (**1*R***), was synthesized by reaction of the corresponding L- and D-serine amide hydrochlorides (7.5 mmol) and diethyl malonoimidate dihydrochloride (3.0 mmol) in the presence of triethylamine (6.0 mmol) in acetonirile solution (40 mL) at room temperature for three days

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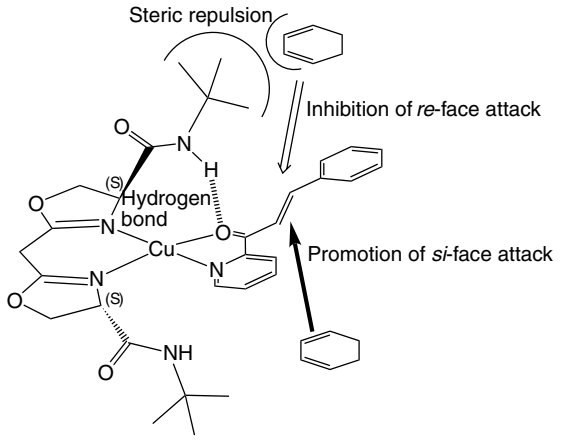
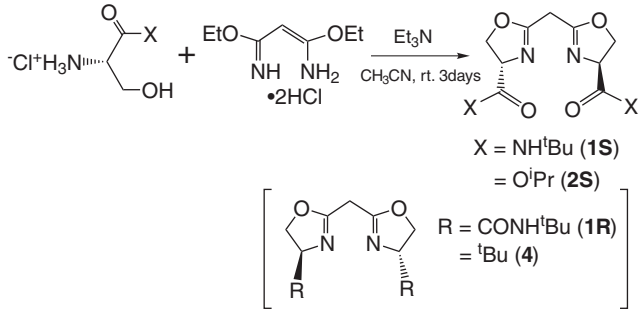


Figure 1. Interligand interactions controlling the selectivity for asymmetric Diels–Alder reaction.



Scheme 1. Synthesis of novel Box ligands.

(Scheme 1). After evaporation of the reaction solution, 30 mL of water was added to the residue. Organic phase was extracted with ethyl acetate twice and washed with brine. Formation of amide compounds, **1*S*** (56% isolated yield) was confirmed on the basis of their ^{1}H NMR and ESI-mass spectra.[12] The ester derivative, (*S*,*S*)-2,2′-methylenebis(4-isopropoxycarbonyl-2-oxazoline) ((*S*,*S*)-^{i}PrboxesH$_2$, **2S**), was synthesized according to the same procedure using L-serine ester hydrochloride (74% isolated yield). The designed interligand interaction was demonstrated on the ternary copper(II) complex consisting of **1S** and *N*-benzoyl-*N*-phenylhydroxylamine (BPHA), which was synthesized as follows: a solution of **1S** (35.8 mg, 0.10 mmol), Cu(OTf)$_2$·6H$_2$O (47.2 mg, 0.10 mmol), and BPHA (21.8 mg, 0.10 mmol) in THF (5 mL) was stirred at room temperature, to which a few drops of triethylamine in mixture of CH_2Cl_2 and diethylether were added. Slow evaporation of the solvent gave an orange platelet of single crystals of [Cu(1S)(bpha)] (**3**) suitable for X-ray diffraction analysis.[13]

In the crystal structure of **3** (Fig. 2), two bidentate ligands, **1S** and BPHA, coordinated to copper(II) ion with square planar geometry, of which torsion angle between N1A–Cu1–N1B and O1L–Cu–O2L plane was 7.5°. The absolute configuration of **3** was determined on the basis of the Flack parameter of X-ray analysis.[14] Notably, the distances between the amide nitrogens of

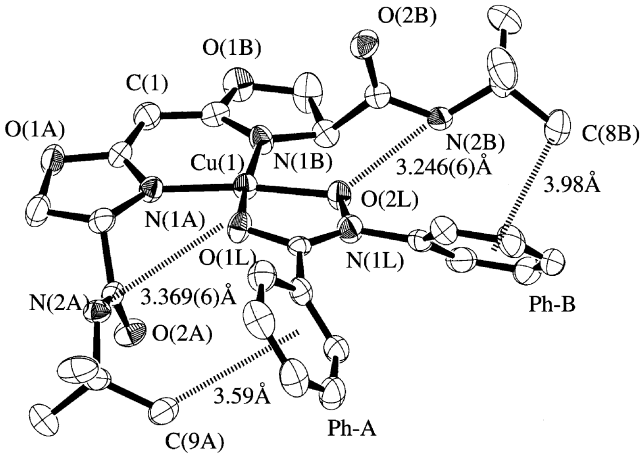
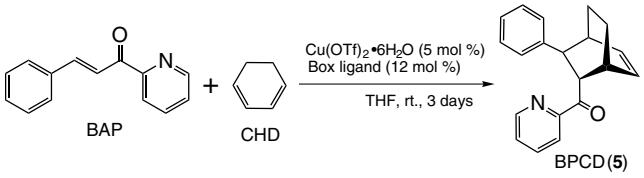


Figure 2. Crystal structure of [Cu(**1S**)(bpha)] complex (**3**). Typical bond lengths (Å) and angles (deg) are as follows: Cu(1)–O(1L) 1.936(3), Cu(1)–O(2L) 1.933(3), Cu(1)–N(1A) 1.927(4), Cu(1)–N(1B) 1.917(4). O(1L)–Cu(1)–O(2L) 83.0(1), O(1L)–Cu(1)–N(1A) 93.4(2), O(1L)–Cu(1)–N(1B) 170.0(2), O(2L)–Cu(1)–N(1A) 173.1(2).

1S and the hydroxamate oxygens of BPHA in **3** were 3.369(6) Å for N2A–O1L and 3.246(6) Å for N2B-O2L, respectively, which were within hydrogen bonding distances. This finding indicates that the amide moiety introduced into the Box derivative acts as the hydrogen bonding site. In comparison with the generally used Box ligand, (*S*,*S*)-2,2′-methylenebis(4-*tert*-butyl-2-oxazoline) ((*S*,*S*)-^{t}BuboxH$_2$, **4**), the stereochemistry around the oxazoline 4-position of **1S** was reverse. In addition, two *tert*-butyl groups attached to the amide moiety of **1S** were very close to the phenyl substituents of BPHA. The mean distance of C9A···PhA was 3.59 Å and that of C8B···PhB was 3.98 Å, respectively. Such an attractive approach of methyl group to aromatic ring is interpreted by the CH-π interaction, although the ^{1}H NMR spectroscopic investigation is not carried out because of the paramagnetic character of copper(II) species.[15] In complex **3**, the bond lengths and angles between copper ion and the nitrogen atoms (Cu1–N1A = 1.927(4), Cu1–N1B = 1.917(4) Å and N1A–Cu1–N1B = 93.3(2)°) were similar to those of the other Cu(II)–box complexes previously reported.[4,16,17] The coordination mode of hydroxamic acid moiety of BPHA to copper(II) was also similar to that of Cu(aminophenylhydroxamic acidato)$_2$ complex.[18]

Since chiral bis(oxazoline) copper(II) complexes are known to be versatile catalysts for asymmetric Diels–Alder reactions,[4,16] the catalytic performance of the transition metal complex consisting of **1S** was investigated as illustrated in Scheme 2. Asymmetric Diels–Alder



Scheme 2. Asymmetric Diels–Alder reaction catalyzed by copper-Box complex.

reaction was carried out using benzylidene-2-acetylpyridine (BAP) as a dienophile and 1,3-cyclohexadiene (CHD) as a diene.[19] Generally, CHD is known to be a less reactive diene in comparison with cyclopentadiene,[20] but in this system catalyzed by copper(II) complex with **1S**, the Diels–Alder reaction product was obtained.

To a reaction mixture of Box ligand (**1S**, 0.12 mmol) and $Cu(OTf)_2{\cdot}6H_2O$ (0.05 mmol) in THF (4 mL) was added benzylidene-2-acetylpyridine (BAP, 1.0 mmol) and then stirred for 20 min at room temperature. After complexation of the ternary copper(II) complex, 1,3-cyclohexadiene (CHD, 5 mmol) in THF (1 mL) was added. The reaction solution was stirred for three days at 20 °C and monitored at appropriate time by HPLC analysis. Evaporation of THF in vacuo gave a crude residue, which was purified through silica gel column eluted with a mixture of hexane/ethyl acetate (10:1). Recrystallization of the obtained residue from column separation in acetone/ethanol solution gave single crystals of the reaction product, endo-(pyridin-2-yl)(3-phenylbicyclo[2,2,2]oct-5-ene-2-yl)methanone (BPCD **5**, isolated yield 51% based on BAP used).[21] The crystal structure of **5** is shown in Figure 3.[22] To our knowledge, **5** is the first Diels–Alder reaction product. Introduction of hydrogen bonding site into the Box ligand can promote the Diels–Alder reaction even though using CHD as a poor reactive diene.

In HPLC analysis with chiral column,[23] two product peaks were observed; one was enantio-pure BPCD (**5**, 78% yield, >99% ee) and another was an unidentified compound. Regrettably, the unidentified compound was unable to be characterized, because it was easily decomposed to BAP after isolation. Any other peak estimated to be exo-isomer was not detected. The enantio-isomer of **5**, which was formed from the reaction catalyzed by the copper complex consisting of **1R**, was not detected. Obviously, no stereo- and enantio-isomer of

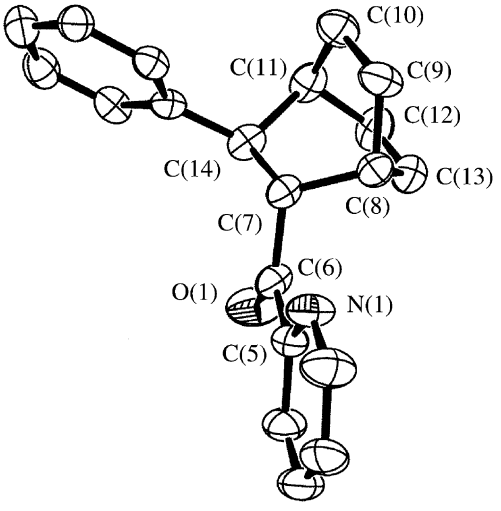


Figure 3. Crystal structure of BPCD (**5**). Typical bond lengths (Å) and angles (deg) are as follows: O(1)–C(6) 1.214(5), C(7)–C(14) 1.535(5), C(9)–C(10) 1.537(6), C(12)–C(13) 1.330(6). O(1)–C(6)–C(5) 118.1(4), O(1)–C(6)–C(7) 123.0(4), C(7)–C(8)–C(9) 106.7(3), C(11)–C(12)–C(13) 113.0(4), C(8)–C(13)–C(12) 114.9(4).

Table 1. Asymmetric Diels–Alder reaction with BAP and CHD[a]

Box ligand	Yield (%)[b] of **5**	ee (%)[c]
1S	78	>99
	51[d]	>99
	0[e]	—
2S	4	>99
4	4	>99
None[f]	0	—

[a] Reaction condition: Box ligand (0.12 mmol), $Cu(OTf)_2{\cdot}6H_2O$ (0.05 mmol), BAP (1.0 mmol), and CHD (5.0 mmol) in THF (5 mL), 20 °C, 3 days.
[b] Yield was based on the starting BAP and analyzed by HPLC.
[c] Determined by chiral HPLC.
[d] Isolated yield.
[e] Addition of 2-propanol (0.5 mL).
[f] Only copper salt without Box ligand.

5 was formed in this reaction system. In the cases without copper(II) ion or the Box ligand, this reaction did not give any reaction product at 25 °C. Using **1R** instead of an antipodal form of **1S**, the enantio-isomer of BPCD was obtained selectively. In the case of ester ligand, (*S*,*S*)-^{i}PrboxesH$_2$ (**2S**), the yield of **5** was very low (4% yield in HPLC analysis, after 3 days). The copper(II) complex having chiral ligand **4** also showed poor catalytic activity for Diels-Alder reaction (4% yield of **5** in HPLC analysis, after 3 days). These results summarized in Table 1 indicate that the copper complexes with **2S** and **4** show less reactivity than those with **1S** and **1R**. Neither electron-withdrawing ester group such as **2S** nor electron-donating *tert*-butyl one such as **4** attached to oxazoline ring affects the reactivity. In order to clarify the effect of amide group, 2-propanol was added to the above reaction system consisting of **1S**. With co-existence of 2-propanol, as known to inhibit formation of hydrogen bonding interaction, Diels–Alder reaction product **5** was not obtained. Accordingly, the interligand hydrogen bonding interaction as designed plays an important role for the catalytic activity.

In conclusion, novel chiral bis(oxazoline) ligand bearing amide group attached to oxazoline 4-position were synthesized from chiral amino acid derivatives. The copper complex with this ligand showed the catalytic performance of the asymmetric Diels–Alder reaction with high enantio- (>99%) and stereo-selectivities (endo-form only). Such higher selectivity of the copper complex with newly prepared ligand compared with the previous Box one is interpreted by the introduction of the non-covalent interaction sites.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.06.108.

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12. Spectral data for **1S**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 18H), 3.42 (br s, 2H), 4.45–4.55 (m, 4H), 4.59–4.62 (m, 2H), 6.41 (br s, 2H). ESI-mass $m/z = 353$ $[C_{17}H_{28}N_4O_4+H]^+$. For **2S**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25–1.30 (dd, 12H), 3.47 (br s, 2H), 4.42–4.53 (m, 4H), 4.69–4.76 (m, 2H), 5.07 (br s, 2H). ESI-mass $m/z = 327$ $[C_{15}H_{22}N_2O_6+H]^+$.
13. Crystal data for **3**: Formula weight = 627.20 ($C_{30}H_{37}CuN_5O_6$), orthorhombic, space group $P2_12_12_1$ (No. 19), $Z = 4$, $a = 9.818(2)$, $b = 13.469(2)$ $c = 23.000(4)$ Å, $V = 3041.3(8)$ Å^3, μ(MoKα) = 7.68 cm^{-1}, $F(000) = 1316.00$, $D_{calcd.} = 1.370$ g cm^{-3}. All measurements were made on a Rigaku/MSC Mercury CCD diffractometer with graphite monochromated MoKα radiation ($\lambda = 0.71070$ Å). The final cycle of full-matrix least-squares refinement was based on 2632 observed reflections ($I > 2.00\sigma(I)$) and 386 variable parameters, $R = 0.057$, $R_w = 0.083$.
14. Flack parameter x is defined as follows: $|F|^2 = (1-x)|F(+)|^2 + x|F(-)|^2$. In the analysis of **3**, the value of x is 0.018808, which is very close to 0 and far from 1, indicating that the analyzed structure of **3** is established.
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21. Spectral data for **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (m, 1H), 1.43 (m, 1H), 1.80 (m, 1H), 2.02 (m, 1H), 2.68 (m, 1H), 3.04 (m, 1H), 3.55 (d, 1H), 4.57 (d, 1H), 6.04 (t, 1H), 6.60 (t, 1H), 7.18 (m, 1H), 7.30 (m, 2H), 7.36 (m, 2H), 7.42 (m, 1H), 7.78 (m, 1H), 7.99 (m, 1H), 8,88 (m, 1H). ESI-mass $m/z = 290.1$ $[C_{20}H_{19}NO+H]^+$. Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.90; H, 6.63; N, 4.82.
22. Crystal data for **5**: Formula weight = 289.38 ($C_{20}H_{19}NO$), orthorhombic, space group $P222_1$ (No. 20), $Z = 8$, $a = 11.886(1)$, $b = 14.941(2)$, $c = 17.519(2)$ Å, $V = 3112.2(6)$ Å^3, μ(MoKα) = 0.75 cm^{-1}, $F(000) = 1232.00$, $D_{calcd.} = 1.235$ g cm^{-3}. The final cycle of full-matrix least-squares refinement was based on 2637 observed reflections ($I > 2.00\sigma(I)$) and 240 variable parameters, $R = 0.087$, $R_w = 0.169$.
23. HPLC condition for analysis of the asymmetric Diels–Alder reaction: Chiral column, Chiralcel OD-H 25 cm × 4.6 mmϕ. Eluent: hexane/2-propanol = 97:3; $\lambda = 254$ nm.