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CYCLO[-HIS-HIS-] DERIVED C_2-SYMMETRIC DIKETOPIPERAZINE AS CHIRAL LIGAND FOR ASYMMETRIC DIELS-ALDER REACTIONS

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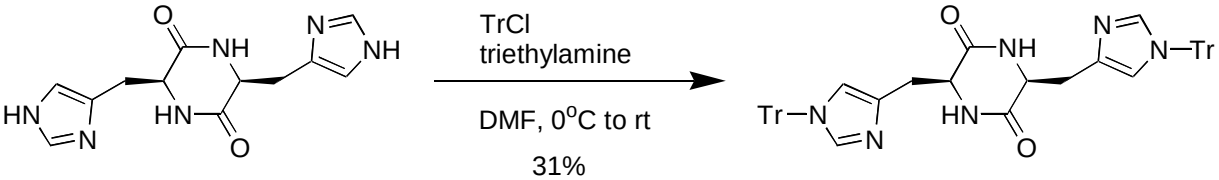
Abstract – A cyclic dipeptide based chiral ligand, cyclo[-His(Tr)-His(Tr)-] (Tr = triphenylmethyl), was designed and prepared through bis-*N*(τ)-tritylation of two imidazole rings of cyclo[-His-His-]. The complex prepared *in situ* by mixing $Cu(OTf)_2$ with equimolar amount of this ligand successfully catalyzed asymmetric Diels-Alder reactions in fair to good yields and moderate selectivities.

Peptide derivatives are potential candidates for chiral ligands in homogeneous asymmetric metal-complex catalysts because they are chiral and can be easily optimized through chemical modification.[1] Dipeptide and tripeptide-derived ligands have been successfully utilized for highly enantioselective metal-complex-catalyzed chemical transformations such as epoxydation,[1] cyanohydrin formation/Strecker reaction,[1-3] conjugate addition,[2,4-6] transfer hydrogenation,[7,8] allylic alkylation,[9] and pinacol coupling.[10] In those examples, the metal coordinating atoms in the ligands is located on the artificial groups introduced at terminus of the peptides, and the peptide skeleton plays a role to make asymmetric microenvironment around the metal center. Gilbertson incorporated a non-natural L-diphenylphosphinoalanine into β-turn peptides, and utilized the peptide side chain as coordinating part of the ligand in chiral Pd catalyst for asymmetric allylic alkylations.[11] Moreover, a side chain of natural amino acid, the sulfide group in methionine, has been also utilized as a coordination site; Christoffers reported L-methionyl-L-methionine ethyl ester (H-Met-Met-OEt) ligand for metal-catalyzed Michael reactions, while it gave enantiomeric excess up to 18% ee.[12] We thought that one of the reasons of the low ee's in their result is due to the highly flexible nature of the peptide ligand, and that those having a rigid skeleton should show better performance. Cyclic dipeptides seem to fulfill this requirement because it contains a rigid diketopiperazine ring and two side chains facing to the same side of the ring.[13] We selected cyclo[-His-His-] **1** having two coordinating imidazole side chains as a candidate for the ligand in

asymmetric metal-complex catalysts because bidentate complex between **1** and Cu(II) ion have been already reported.[14] We designed a ligand **2** (cyclo[-His(Tr)-His(Tr)-], Tr = triphenylmethyl) with expecting the formation of an efficient C_2-symmetric chiral microenvironment around the metal center.



1 **2**

Scheme 1

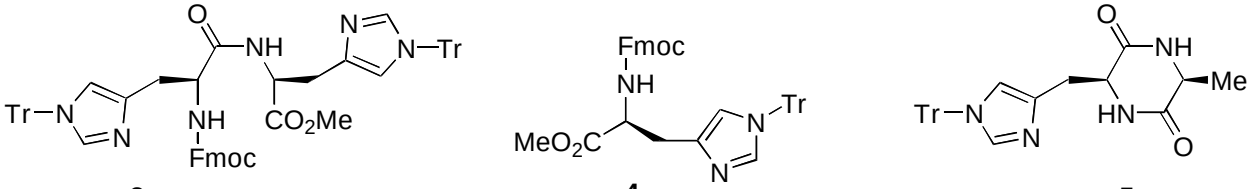
Cyclo[-His-His-] **1** was prepared according to a procedure described in the literature (white solid, 24%, mp >300˚C).[15] Ligand **2** was synthesized through conventional tritylation of **1** (light yellow solid, 31%, mp 118-120˚C, Scheme 1).[16] Theoretically, tritylation can be possible at one of the two nitrogen atoms of His side chain, N(τ) and N(π). In the present case, position of tritylation is considered to be at N(τ) nitrogen according to the previous study on related compounds.[17] Ligand **2** dissolved in relatively less polar solvents such as CH_2Cl_2 or $CHCl_3$, while the parent compound **1** dissolved only in highly polar solvents such as DMSO or DMF. When ligand **2** was added to a dispersion of $Cu(OTf)_2$ in CH_2Cl_2, the mixture became homogeneous, dark green solution in a few minutes. This implies the formation of a soluble complex between Cu(II) ion and ligand **2**.

In the UV-VIS spectrum of the above mixture in DMF,[18] a peak attributable to ligand-to-metal charge transfer between imidazole moiety and Cu(II) ion was observed at 322 nm.[19] In the case of non cyclic dipeptide **3** and Cu salt,[20] only a weak peak was observed at 334 nm. As Cu(II)-cyclo[-His-His-] **1** mixture gave a peak at 320 nm, the absorbance of Cu(II)-ligand **2** mixture seemed to be specific to cyclo[-His-His-] skeleton.

In the CD spectrum of Cu(II)-ligand **2** mixture in DMF,[18] a negative Cotton effect was observed at 332 nm. A similar negative Cotton effect was observed at 317 nm in the case of cyclo[-His-His-] **1**. In contrast, Cu(II)-ligand **3** mixture gave a weak positive Cotton effect at 365 nm.

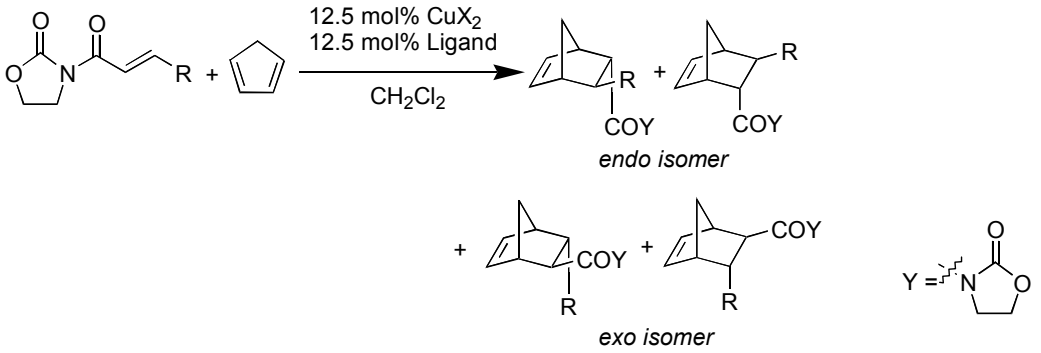
These results imply that chemical structure of ligands strongly influences their microenvironment around Cu(II) ion. Asymmetric microenvironment around Cu(II) center generated by ligand **2** should be similar with that by parent compound **1**, and quite different from those by linear ligand **3**.

FAB-MS measurement of the evaporation residue of the $Cu(OTf)_2$/ligand **2** solution showed a main peak at 821.6, which is corresponding to the sum of one copper atom and one ligand **2** molecule.



3 **4** **5**

Table 1. Asymmetric Diels-Alder reaction of (*E*)-3-(2-alkenoyl)-2-oxazolidinone with cyclopentadiene



Entry	Ligand	X	R	Temperature / ˚C	Time / h	Yield / %	*Endo*/*exo*	% ee (*endo, config.*)
1	**2**	OTf	H	0	2.5	76	12	35 (*R*)
2	**3**	OTf	H	0	2.5	43	12	2 (*S*)
3	**4**	OTf	H	0	2.5	49	14	1 (*R*)
4	**5**	OTf	H	0	2.5	67	10	8 (*R*)
5	**2**	OTf	Me	rt	72	50	6.0	52
6	**2**	ClO_4	Me	rt	72	33	4.7	59

Diels-Alder reactions of 3-(2-alkenoyl)-2-oxazolidinones with cyclopentadiene catalyzed by Cu(II) complex were performed.[21,22] The complex was prepared *in situ* by mixing $Cu(OTf)_2$ with equimolar amount of each ligand in CH_2Cl_2. When the ligand **2** was employed as a ligand, cycloadduct of acrylamide derivative was obtained in 76% yield and 35% ee (Table 1, entry 1). Lowering the temperature of this reaction to -40˚C did not improve the result (41% yield, 23% ee). In the case of ligands **3** and **4**,[20,23] the enantiomeric excesses were low (Entries 2 and 3). Although the ligand **3** is an open chain analogue of **2**, behavior of these two ligands in the catalytic process was quite different to each other. This fact coincides with the above mentioned spectroscopic observation and supports our initial hypothesis that the rigid ligand should bring about better stereoselectivities. Removal of one of the two tritylated imidazole moieties in **2** resulted in the lowering of enantiomeric excess (Entry 4).[24] This implies that both of the two imidazole side chains cooperatively contributed to the formation of asymmetric microenvironment for the reaction.

Use of a crotonamide as a dienophile improved the enantiomeric excess at the expense of chemical yields probably due to the poor reactivity of the dienophile (Entries 5 and 6). Parent compound **1** was also examined as a chiral ligand, however catalytic performance was quite low (26% yield, 2% ee). This result demonstrates the importance of the sterically demanding trityl groups in ligand **2**.

Concerning the mechanism for stereoselectivity, we performed semiempirical molecular orbital calculation using MOPAC software with PM6 parameter set.[25] As shown in Figure 1, *Re*-face of the dienophile is likely to be shielded to give predominantly the (*R*)-product.

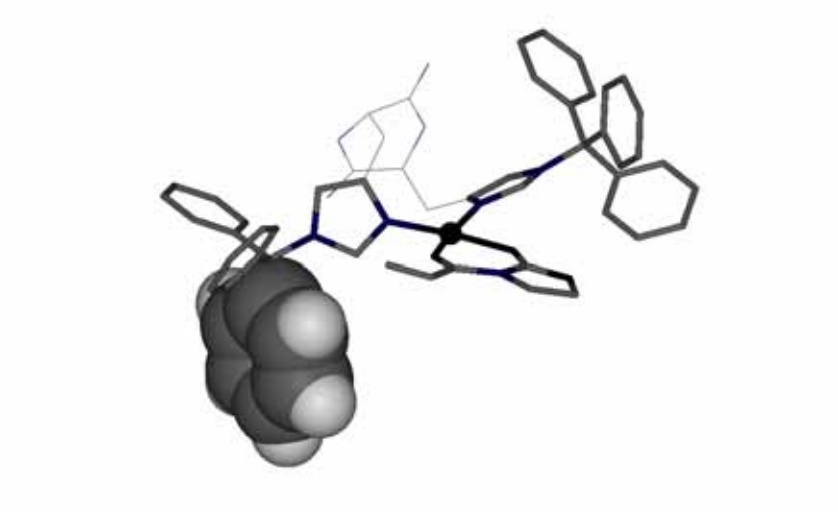
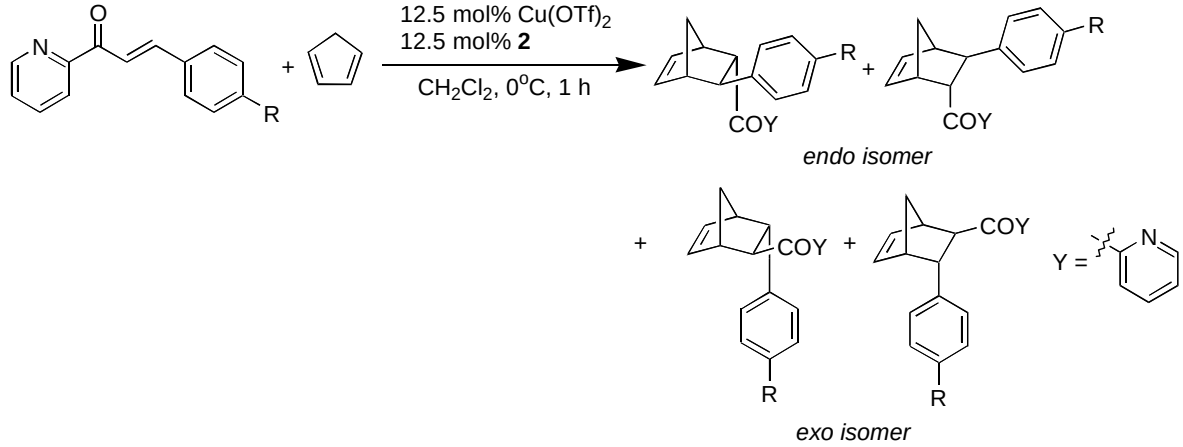


Figure 1 Optimized structure of the substrate-catalyst complex. The phenyl group relevant to the enantiotopic face differentiation is shown with CPK model. All other hydrogens are omitted for clarity.

Diels-Alder reaction using another type of dienophile, (*E*)-2-(3-phenylpropenoyl)pyridines were also examined with Cu^{2+} and ligand **2** complex (Table 2).[21,26] Good yields and modest enantioselectivities were observed. In some cases, lowering of the reaction temperature improved enantioselectivity.

Table 2. Asymmetric Diels-Alder reaction of (*E*)-2-(3-phenylpropenoyl)pyridine with cyclopentadiene



Entry	R	Yield / %[a]	*Endo*/*exo*[a]	% ee[a,b]
1	NO_2	89 (70)	6.3 (9.0)	40 (60)
2	H	89 (79)	10 (18)	39 (45)
3	OMe	82 (19)	14 (56)	29 (26)

[a]Values in parentheses were results at -40 °C. Reaction time was 5 to 9 h.
[b]For *endo* isomers.

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16. For ligand **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 2H), 7.38 (s, 2H), 7.32 (m, 18H), 7.10 (m, 12H), 6.67 (s, 2H), 4.21 (dd, 2H), 3.32 (dd, 2H), 2.76 (dd, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.3, 142.1, 138.7, 136.9, 129.6, 128.0, 119.2, 75.3, 55.0, 30.7; FT-IR (KBr) 3427, 3266, 3060, 1684, 1489, 1443, 1317, 755, 698 cm^{-1}; FAB-MS: *m/z* 759.7 MH^+; $[\alpha]_D^{28}$ -60.7 deg (*c* 0.3, $CHCl_3$).

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21. General procedure of asymmetric Diels-Alder reaction: To a solution of Cu source (0.01 mmol) and ligand (0.01 mmol) in CH_2Cl_2 was added dienophile (0.08 mmol) at rt under argon atmosphere. After the mixture was stirred for 30 min, it was cooled to the predetermined temperature. Cyclopentadiene (0.8 mmol) was added, and the mixture was stirred until the reaction was quenched by adding water and EtOAc. The organic layer was washed with brine, evaporated, and then purified by preparative thin layer chromatography (hexane : EtOAc = 2 : 1). The ratio of *endo* isomer and enantiomeric excess were determined by chiral HPLC.
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23. Two equivalent of ligand **4** was used toward Cu(II) ion.
24. Ligand **5** was prepared through liquid phase peptide synthesis (white solid, mp 247-249˚C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.37 (s, 1H), 7.34 (m, 9H), 7.12 (m, 6H), 6.67 (s, 1H), 6.26 (s, 1H), 4.26 (dd, 1H), 4.08 (q, 1H), 3.32 (dd, 1H), 2.80 (dd, 1H), 1.47 (d, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 168.2, 168.1, 142.1, 138.8, 136.6, 129.6, 128.1, 128.0, 119.2, 75.4, 55.1, 50.6, 30.6, 19.3; FT-IR (KBr) 3443, 3276, 3171, 1679, 1650, 1491, 1453, 1316, 766, 749, 707 cm^{-1}; FAB-MS: *m/z* 451.3 MH^+; $[\alpha]_D^{23}$ -78.7 (*c* 0.3, $CHCl_3$).
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