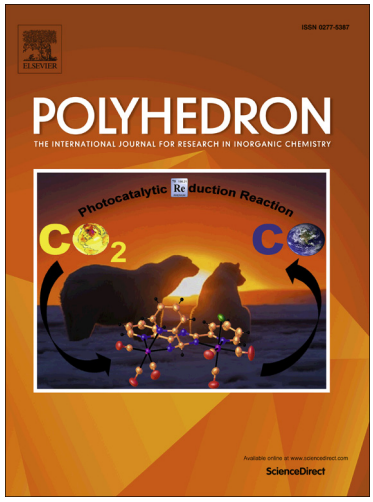

Copper complexes bearing methylthiophenyl and methylfuranyl derivatives of (*R,R*)-1,2-diaminocyclohexane: X-ray structures and catalytic exploitation in Henry reaction

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PII: S0277-5387(15)00378-2
DOI: http://dx.doi.org/10.1016/j.poly.2015.07.023
Reference: POLY 11409

To appear in: *Polyhedron*

Received Date: 4 May 2015
Accepted Date: 8 July 2015

Please cite this article as: J. Cho, G.H. Lee, S. Nayab, J.H. Jeong, Copper complexes bearing methylthiophenyl and methylfuranyl derivatives of (*R,R*)-1,2-diaminocyclohexane: X-ray structures and catalytic exploitation in Henry reaction, *Polyhedron* (2015), doi: http://dx.doi.org/10.1016/j.poly.2015.07.023

- Revised -

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Copper complexes bearing methylthiophenyl and methylfuranyl derivatives of (*R,R*)-1,2-diaminocyclohexane: X-ray structures and catalytic exploitation in Henry reaction

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Abstract

Two novel dichloro Cu(II) complexes of (*R*,*R*)-N^1,N^2-bis((5-methylthiophen-2-yl)methyl)cyclohexane-1,2-diamine (MTCHD) and (*R*,*R*)-N^1,N^2-bis((5-methylfuran-2-yl)methyl)cyclohexane-1,2-diamine (MFCHD) ligands have been synthesised and structurally characterised using X-ray diffraction. The geometry around the Cu(II) centres was distorted square planner. A strong Cu…$O_{furanyl}$ interaction exists in Cu(MFCHD)Cl_2 that leads to the disappearance of original C_2-symmetry of the ligand, resulting in selective *R*,*S*-coordination of N atoms in (1*R*,2*R*)-1,2-diaminocyclohexane. Catalytic activities of dichloro and diacetato Cu(II) complexes with 3 mol% of *i*Pr_2NEt were assessed in asymmetric Henry reactions that resulted in moderate to high yields with an enantiomeric excess up to 92%, without air/moisture exclusion.

Keywords: Enantiopure *N*,*N*-diamines, copper complexes, *R*,*S*-coordination *N*,*N*-diamines,

enantioselective Henry reaction.

Introduction

Chiral secondary *vic*-diamines, specifically those derived from enantiomerically pure (*R*,*R*)-1,2-diaminocyclohexane and its *N*,*N*-disubstituted derivatives, are attractive ligands and organocatalysts in many asymmetric transformations[1] including Michael additions,[2] aza-Henry reactions,[3] enantioselective reductions,[4,5] allylation,[6] and aldehyde crotylation.[7] Despite the increased acidity of the N-H proton,[8] these C_2-type symmetrical ligand precursors form stable metal complexes, creating chiral environments for catalytic reactions. Coordination of the (*R*,*R*)-1,2-diaminocyclohexane ligand to metal prevents N-inversion, and thus resulted in fixing the chirality of N atoms. [9] The resultant configurations of N atoms; i.e. (*R*,*R*), (*S*,*S*), and (*R*,*S*), may be interesting in terms of structure and coordination modes of the metal centre. Similarly, modification of the various groups attached to the (*R*,*R*)-1,2-diaminocyclohexane by different small substituents can effectively tune the electronic and steric properties of the ligands, and thus affect the coordination properties of the resultant complexes.[10] Recently, the use of chiral complexes to control stereochemical outcomes in asymmetric Henry reactions have been described by various groups including Jørgensen,[11] Trost,[12] Yamada,[13] and Palomo[14]. The Bandini and Skarzewski groups independently applied chiral complexes derived from (*R*,*R*)-1,2-diaminocyclohexane as catalysts to asymmetric Henry reactions that resulted in high enantioselectivity.[15,16] Since then, efforts have been devoted to develop novel Cu(II) complexes based on (*R*,*R*)-1,2-diaminocyclohexane with various moieties to yield the corresponding β-nitroalcoholes with high yield and enantioselectivities.[17-20] However, the structural properties and X-ray

diffraction characteristics of these complexes have not been well-studied. The potential merits of (*R*,*R*)-1,2-diaminocyclohexane framework and recent results in asymmetric Henry reaction for Cu(II) complexes supported by such ligands reported by our group encouraged us to evaluate more broadly these C_2-symmetric chiral diamines in asymmetric Henry reaction.[21] To increase our understanding of the effect of ligand architecture (S *vs*. O-heterocycle) on the level of asymmetric induction, we explored structural characteristics of these complexes and the efficiency of novel copper complexes as catalysts with an organic base in asymmetric Henry reactions (Scheme 1).

Experimental Section

General Consideration

(*R,R*)-1,2-diaminoniumcyclohexane mono-(*L*)-(+)-tartrate salt (1) (99%), 5-methyl-2-furaldehyde, 5-methyl-2-thiophenecarboxaldehyde, and copper(II) chloride dihydrate $CuCl_2 \cdot 2H_2O$ (99%) were obtained from Aldrich chemical company. Silica gel 60 (230–400 mesh) from Merck, ethanol (99.8%) and methanol (99.9%) from Aldrich. The ligand, (*R,R*)-*N,N'*-bis(5-methylthiophen-2-ylmethyl)cyclohexane-1,2-diamine (MTCHD) and (*R,R*)-*N,N'*-bis(5-methylfuran-2-ylmethyl)cyclohexane-1,2-diamine (MFCHD) were obtained using reported method.[22]

NMR spectra were recorded on a Bruker advance digital 400 (400 Hz)-NMR Spectrometer at ambient temperature. FT-IR spectra were measured on Jasco FT/IR-620 spectrophotometer. Band positions in IR spectra were reported as wave number (m) in cm^{-1} and band intensity in semiquantitative terms (w = weak, m = medium, s = strong). Elemental analyses were determined on EA 1108-Elemental Analyzer at the Chemical Analysis

Laboratory of the Center of Scientific Instruments of Kyungpook National University. Enantiomeric excesses (ee) were determined by HPLC with a chiralcel OD-H column and OJ-H column using HPLC grade isopropanol (IPA) and n-hexane (n-hex) as eluting solvents.[21b]

Copper Complexes

*Synthesis of Cu(**MTCHD**)Cl_2*

A solution of MTCHD (1.00 g, 2.99 mmol) in CH_2Cl_2 (10 mL) was added dropwise to suspension of $CuCl_2 \cdot 2H_2O$ (0.51 g, 2.99 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred overnight at ambient temperature. The solvent was removed to get light blue solid as final product (0.89 g, 64%). Calcd. for $C_{18}H_{26}Cl_2CuN_2S_2$: C, 46.10; H, 5.59; N, 5.97. Found: C, 46.13; H, 5.56; N, 5.99. IR (solid neat; cm^{-1}): 3234 (w), 2940 (w), 2858 (w), 1699 (w), 1651 (w), 1541 (w), 1444 (m), 1421 (w), 1228 (w), 1150 (w), 1091 (w), 1041 (w), 977 (w), 955 (w), 920 (m), 817 (s), 801 (s).

*Synthesis of Cu(**MFCHD**)Cl_2*

The analogues method to that of Cu(MTCHD)Cl_2 was applied to Cu(MFCHD)Cl_2 except that (MFCHD) (0.92 g, 3.04 mmol) and $CuCl_2 \cdot 2H_2O$ (0.52 g, 3.04 mmol) were used. Removal of solvent yielded dark green solid as final product (0.91 g, 69%). Calcd. for $C_{18}H_{26}Cl_2CuN_2O_2$ C, 49.49; H, 6.00; N, 6.41. Found C, 49.46; H, 6.03; N, 6.42. IR (solid neat; cm^{-1}): 3149 (w), 2935 (w), 2858 (w), 1559 (m), 1518 (w), 1438 (m), 1217 (m), 1020 (s), 999 (s), 928 (m), 785 (s), 751 (w).

X-ray Crystallography

X-ray quality single crystals of (MFCHDA)$CuCl_2$ and (MTCHDA)$CuCl_2$ were obtained by slow evaporation of 95% MeOH solutions. An X-ray quality single crystals were mounted in a thin-walled glass capillaries on an Enraf-Noius CAD-4 diffractometer with Mo *K*α radiation (λ = 0.71073 Å). Unit cell parameters were determined using least-squares analysis of 25 reflections (10° < θ < 13°). Intensity data were collected in ω/2θ scan mode, and three standard reflections were monitored every hour during data collection. Empirical absorption corrections with *ψ*-scans were performed to the data using the ABSCALC program.[23] The structures were solved using direct methods and refined using the full-matrix least-squares techniques on F^2 using SHELX*L*-97 and SHELX*S*-97 program packages.[24] Absolute structures were confirmed using anomalous dispersion effects with Friedel pairs, which were not merged. All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were positioned geometrically using the riding model with fixed isotropic thermal factors.

Typical catalytic procedure for Henry reaction

All the reactions were carried out at -20 ºC. 10 mol% of the dichloro copper complexes were dissolved in 15 mL IPA. Then nitromethane (0.50 mL, 20 mmol) and benzaldehyde (0.50 mL, 10 mmol) were added followed by addition of 3.0 mol% or 5.0 mol% of *i*Pr_2Net as a cocatalyst owing to its good activity.[25,26] Similarly 10 mol% of the diacetato-copper catalysts were obtained *in situ* by treating dichloro-complexes with Ag(OAc) in IPA and the resultatnt solution was applied to Henry reaction under aforementioned reaction conditions. Reactions were monitored by TLC. After stirring for specified time, reactions were quenched with 1 mL of 1 *M* HCl solution and then evaporated. The products were extracted by CH_2Cl_2 (3 times x 20 mL) and dried over anhydrous $MgSO_4$, then filtered and the

solvents were removed under reduced pressure. The crude products were purified by column chromatography (10% EtOAc/hexane) to give a yellowish oil of 1-phenyl-2-nitroethanol. ^{1}H-NMR (400 Hz, $CDCl_3$): δ 7.30 (5H, m, Ar-*H*), 5.38 (1H, dd, -C*H*), 4.51(1H, dd, CH_2), 4.41 (1H, dd, -CH_2), 2.89 (1H, br,s, -O*H*). Enantiomeric excess (ee) was determined using HPLC on Chiracel OD-H column (n-Hex: isopropanol = 95:5; flow rate = 1.5 mL/min; k = 215 nm); (*R*) enantiomer tr = 15.63 min, (*S*) enantiomer tr = 19.52 min (Table 3).[21b]

Results and Discussion

Synthesis of Cu(MTCHD)Cl_2 and Cu(MFCHD)Cl_2

Complexes Cu(MTCHD)Cl_2 and Cu(MFCHD)Cl_2 were obtained in good yields (up to 89%) by treating MTCHD and MFCHD[22] ligands at a 1:1 ratio with $CuCl_2.2H_2O$ in CH_2Cl_2 at ambient temperatures (Scheme 2). These complexes were structurally characterised using IR, elemental analysis, and X-ray diffraction studies. A comparison of the IR spectra of ligands with that of the complexes was performed, specifically in the N-H region. The characteristic broad N-H peaks for MTCHD and MFCHD ligands in the IR spectra were observed at 3300 and 3302 cm^{-1}, while in Cu(II) complexes the N-H absorption band appeared at 3234 and 3149 cm^{-1} for Cu(MTCHD)Cl_2 and Cu(MFCHD)Cl_2, respectively. Blue crystals of complexes suitable for single-crystal X-ray crystallography were obtained by slow evaporation of concentrated MeOH solution.

Description of X-ray crystal structures of Cu(MTCD)Cl_2 and Cu(MFCD)Cl_2

The molecular structures of the synthesised complexes, Cu(MTCHD)Cl_2 and Cu(MFCD)$CuCl_2$, have been determined based on X-ray diffraction studies. The

crystallographic data and refinements are summarised in Table 1. The crystal systems were trigonal with space group $P3_1$ for Cu(MTCHD)Cl_2•H_2O and orthorhombic with space group $P2_12_12_1$ for (MFCHD)$CuCl_2$. The expected distorted square planner geometry of Cu(II) was observed in both complexes (Fig. 1 and Fig. 2). Selected bond lengths and angles are presented in Table 2 for both complexes. However, a strong Cu…$O_{furanyl}$ interaction with a distance of 2.704(2) Å was observed in Cu(MFCHD)Cl_2 (Fig. 2), which is longer compared to similar reported complexes[21b] where exocyclic oxygen strongly interacts with the Cu(II) centre, having an average distance of 2.45(3) Å. The Cu-N and Cu-Cl bond lengths in both complexes do not vary from similar reported complexes.[21a,15a] However, the Cl1–Cu–Cl2 angle of 103.10(4)° was larger in Cu(MTCHD)Cl_2 compared to 96.20(2)° in Cu(MFCHD)Cl_2, which may be due to the Cu…$O_{furanyl}$ interaction in the latter case. Similarly, N1–Cu–N2 angles in Cu(MTCHD)Cl_2 and Cu(MFCHD)Cl_2 are 85.1° and 83.71°, respectively and illustrative of the distortion from ideal geometry.

Complexation of the metal to ligand framework with stereogenic centres R_C, R_C in the carbon skeleton derived from (*R*,*R*)-1,2-cyclohexadiamine fragment leads to a 5-membered metalla-heterocyclic ring that blocks the nitrogen (increases the N-inversion barrier), and thus induces chirality provided there is nonequivalence of the nitrogen substituents. It is clear from crystal structures that both nitrogens are in the R_N configuration in Cu(MTCHD)Cl_2[21b,27], while R_N and S_N configurations exist in Cu(MFCHD)Cl_2, which is consistent with the reported Pd complex.[28] In addition, upon coordination to the Cu(II) centre, the original C_2-symmetry of MFCHD ligand is lost, which may be due to one of the furanyl moieties that shows hindered free rotation due to the Cu...$O_{furanyl}$ interaction. It has been shown in Fig. 2 that both furanyl moieties are on the same side of the cyclohexadiamine plane and opposite to the metal; i.e. the furanyl moiety at the nitrogen is

pseudo-axial at one and pseudo equatorial at the other nitrogen. One of the factors for this selective *R*,*S*-coordination of N atoms of (*R*,*R*)-1,2-diaminocyclohexane to the Cu(II) centre in Cu(MFCHD)Cl_2 may be the Cu…$O_{furanyl}$ interaction (Fig. 3). Hydrogen atoms of the chiral carbons and nitrogens are found to be in head-to-tail conformation in Cu(MTCHD)Cl_2 and in head-to-head conformation in Cu(MFCHD)Cl_2 (Fig. 3). Furthermore, the resultant five membered chelate rings Cu-N-C-C-N in both complexes were solely in λ conformations.

Catalytic activities of Cu(II) complexes in Henry reactions

As a part of our ongoing investigations towards the application of versatile enantiopure copper initiators in asymmetric Henry reactions, the association of benzaldehyde and nitromethane was examined using synthesised complexes as catalysts with varying amounts of *i*Pr_2NEt. The results are summarised in Table 3. The diacetato derivatives generated *in situ* by treating dichloro Cu(II) complexes with Ag(OAc) were also subjected to asymmetric Henry reactions. No product formation was observed in the absence of *i*Pr_2NEt for dichloro and diacetato derivatives of both catalytic systems (Table 3, entries 1,4,7,10). The recent concept of double catalytic activation i.e. transition metal complexes as a Lewis acid are not powerful enough to form bonds through single activation of nucleophiles; thus, deprotonation of a nucleophile precursor with an amine base is required to activate the reaction.[29] Therefore, in the presence of 3 mol % *i*Pr_2NEt as a promoter, the best results in terms of yield (70%), and enantioselectivity (92%) of corresponding *β*-nitroalcohol was achieved with (MTCHD)Cu$(OAc)_2$. With increasing amounts of *i*Pr_2NEt to 5 mol %, the product yield was increased with loss of ee, which may be due to the interaction of achiral amine with Cu(II) complexes. Chloro derivatives were less active (required longer reaction

times with lower conversion yields) than their diacetato counterparts under the same experimental conditions for both catalytic systems (Table 3).[21a,30] With dichloro catalytic species using 3 mol% *i*Pr_2NEt, reactions took longer and the corresponding product was obtained at a lower yield, although the ee was quite high (91%) (Table 3, entries 2 and 8). Thus, enantiopure Lewis acid complex/amine promoter ratio strongly influences the reaction outcomes. Blank reactions without the use of chiral complex resulted in higher conversion but low selectivity. The catalytic reaction with Cu(II) complexes containing MTCHD resulted in higher yields compared to MFCHD containing complexes, and this decrease in yield may be due to the Cu…$O_{furanyl}$ interaction that hinders substrate approach (Table 3, entries 5 and 11). However, the enantiomeric excess was comparable for Cu(II) complexes of both ligands under the same experimental conditions. A plausible mechanism can be represented by a transition state model shown in Fig. 4. We assume that the favorable positioning of the reactants taking into account the steric and electronic considerations is where the carbonyl oxygen atom is coordinated at one of the equatorial positions, and the oxygen atom of nitromethane approaches the metal center from the axial side. Thus, after deprotonation by the external base, the resulting nitronate ion approaches the aldehydes from the *Re* face to give corresponding *β*-nitroalcohols with an (*S*)-conformation. Other possibilities seem to be restricted by the unfavorable steric interactions of the phenyl group of benzaldehyde and aromatic moieties of the ligand framework.[31,32] Hence, this study provides a combination of complementary synthetic, structural, and catalytic studies, and increases our understanding on the chemistry of Cu(II) complexes and their application in the Henry reactions.

Conclusion

In conclusion, Cu(II) complexes bearing methylthiophenyl and methylfuranyl derivatives of (*R*,*R*)-1,2-diaminocyclohexane have been synthesised and characterised. The C_2-symmetry of the MFCHD ligand was lost upon coordination to the metal centre and resulted solely in *R*,*S*-configurations at nitrogen atoms. The dichloro and diacetato complexes bearing the MTCHD ligand function as efficient catalyst precursors for the asymmetric nitroaldol reaction of benzaldehydes and nitromethane to yield corresponding β-nitroalcohols (up to 92% ee) with 3 mol% iPr$_2$NEt, whereas MFCHD ligand-containing complexes show a modest catalytic activity with comparable ee (90%). In general, the dichloro derivatives were less active than their diacetato counterparts under the same experimental conditions for both catalytic systems.

Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (NRF-2011-0023197).

Appendix A. Supplementary data

CCDC 1049315 **&** 1049316 contain the supplementary crystallographic data for (MTCD)$CuCl_2$ and (MFCD)$CuCl_2$. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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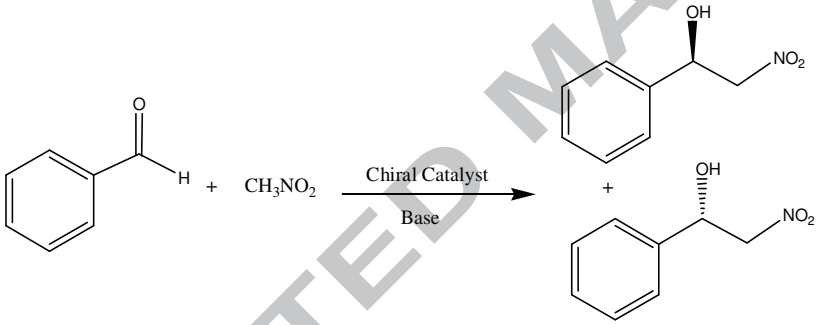
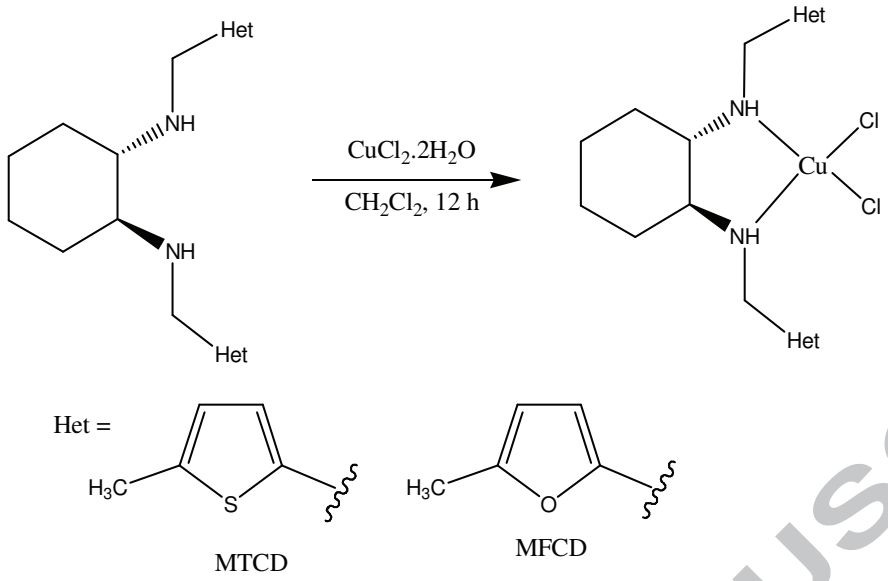


Scheme 1. Formation of β-nitroalcohols by Henry reaction



Scheme 2. Synthesis of Cu(MTCHD)Cl_2 and Cu(MFCHD)Cl_2.

Table 1 Crystallographic data and structure refinements for $Cu(MTCHD)Cl_2 \cdot H_2O$ and $Cu(MFCHD)Cl_2$

	$Cu(MTCHD)Cl_2 \cdot H_2O$	$Cu(MFCHD)Cl_2$
Empirical formula	$C_{18}H_{26}Cl_2CuN_2S_2 \cdot H_2O$	$C_{18}H_{26}Cl_2CuN_2O_2$
Formula weight	486.98	436.85
Crystal system	Trigonal	Orthorhombic
Space group	$P3_1$	$P2_12_12_1$
Unit cell dimensions		
a (Å)	10.0522(6)	9.4594(7)
b (Å)	10.0522(5)	14.3118(9)
c (Å)	18.5907(16)	15.1239(8)
γ(°)	120	
Volume (Å^3), *Z*	1626.85(19), 3	2047.5(2), 4
Density (calcd.) (Mg/m^3)	1.491	1.417
Absorption coefficient (mm^{-1})	1.456	1.341
Reflections collected	6832	4517
Independent reflections	4034 [R(int) = 0.0374]	3808 [R(int) = 0.0138]
Reflections observed (>2σ)	3598	3307
Data/ restraints/ parameters	4034 / 1 / 237	3808 / 0 / 228
Final R indices [I>2σ(I)]	$R_1 = 0.0342$ $wR_2 = 0.0848$	$R_1 = 0.0232$ $wR_2 = 0.0594$
R indices (all data)	$R_1 = 0.0410$ $wR_2 = 0.0866$	$R_1 = 0.0338$ $wR_2 = 0.0614$
Absolute structure parameter	0.002(12)	0.001(10)
Largest diff. peak and hole (e/ Å^3)	0.477 and -0.404	0.169 and -0.163

Table 2 Selected bond lengths (Å) and bond angles (°) of $Cu(MTCHD)Cl_2 \cdot H_2O$ and $Cu(MFCHD)Cl_2$.

$Cu(MTCHD)Cl_2 \cdot H_2O$		$Cu(MFCHD)Cl_2$	
Cu1- N2	2.014(3)	Cu1- N1	2.019(2)
Cu1- N1	2.015(3)	Cu1- N2	2.056(2)
Cu1- Cl1	2.232(1)	Cu1- Cl1	2.225(6)
Cu1- Cl2	2.234(1)	Cu1- Cl2	2.278(7)
		Cu1···· O2	2.704(2)
N1- Cu1- N2	85.10(1)	N1- Cu1- N2	83.71(7)
N1- Cu1- Cl1	149.12(9)	N1- Cu1- Cl1	169.05(5)
N2- Cu1- Cl2	149.15(9)	N2- Cu1- Cl2	148.34(6)
Cl1- Cu1- Cl2	103.10(4)	Cl1- Cu1- Cl2	96.20(2)
C11- S1- C8	93.20(2)	N1- Cu1··· O2	74.89(6)
C14- S2- C17	93.20(2)	N2- Cu1··· O2	122.24(7)

Table 3 Enantioselective Henry reaction of Ph-CHO and $MeNO_2$ promoted by enantiopure Cu(II) catalysts [a]

Entry	Catalyst	Time (days)	*i*Pr_2NEt (mol %)	Conv. (%)[b]	ee(%)[c]
1	(MTCD)$CuCl_2$	14	0	0	0
2	(MTCD)$CuCl_2$	14	3	6	91(*S*)
3	(MTCD)$CuCl_2$	14	5	28	86(*S*)
4	(MTCD)Cu$(OAc)_2$	3	0	19	84(*S*)
5	(MTCD)Cu$(OAc)_2$	3	3	70	92(*S*)
6	(MTCD)Cu$(OAc)_2$	3	5	81	89(*S*)
7	(MFCD)$CuCl_2$	14	0	0	0
8	(MFCD)$CuCl_2$	14	3	6	88(*S*)
9	(MFCD)$CuCl_2$	14	5	47	87(*S*)
10	(MFCD)Cu$(OAc)_2$	3	0	7	90(*S*)
11	(MFCD)Cu$(OAc)_2$	3	3	43	85(*S*)
12	(MFCD)Cu$(OAc)_2$	3	5	57	84(*S*)

[a] Reaction condition: Molar ratio employed were 0.1: 1: 2 of Catalyst: Benzaldehyde: Nitromethane, Solvent (IPA), Temp (-20 ºC). [b] Conversion determined by ^{1}H-NMR spectroscopic analysis. [c] The enantiomeric excess (ee) was determined by HPLC analysis using OD-H column (Hexane: IPA = 95:05; flow rate = 1.5 mL/min; λ = 215 nm, *R* enantiomer t_r = 18.4 min, *S* enantiomer t_r = 22.3 min) as reported in our earlier work. [21b]

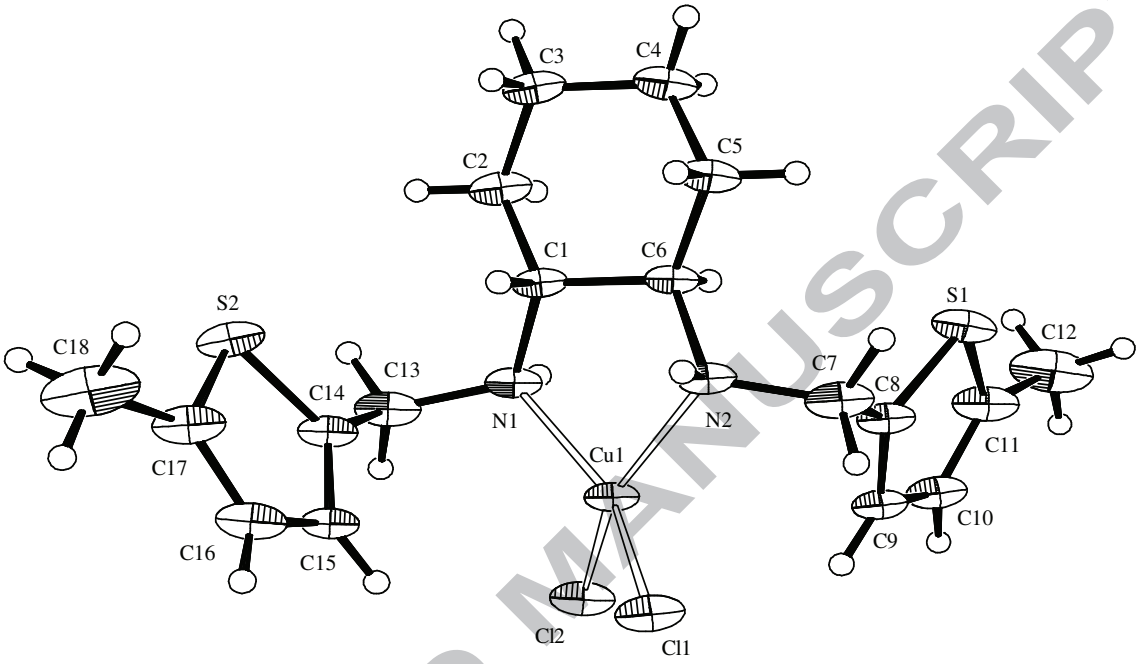


Fig. 1. An ORTEP drawing of $Cu(MTCHD)Cl_2.H_2O$ with the numbering scheme at 30% probability level.

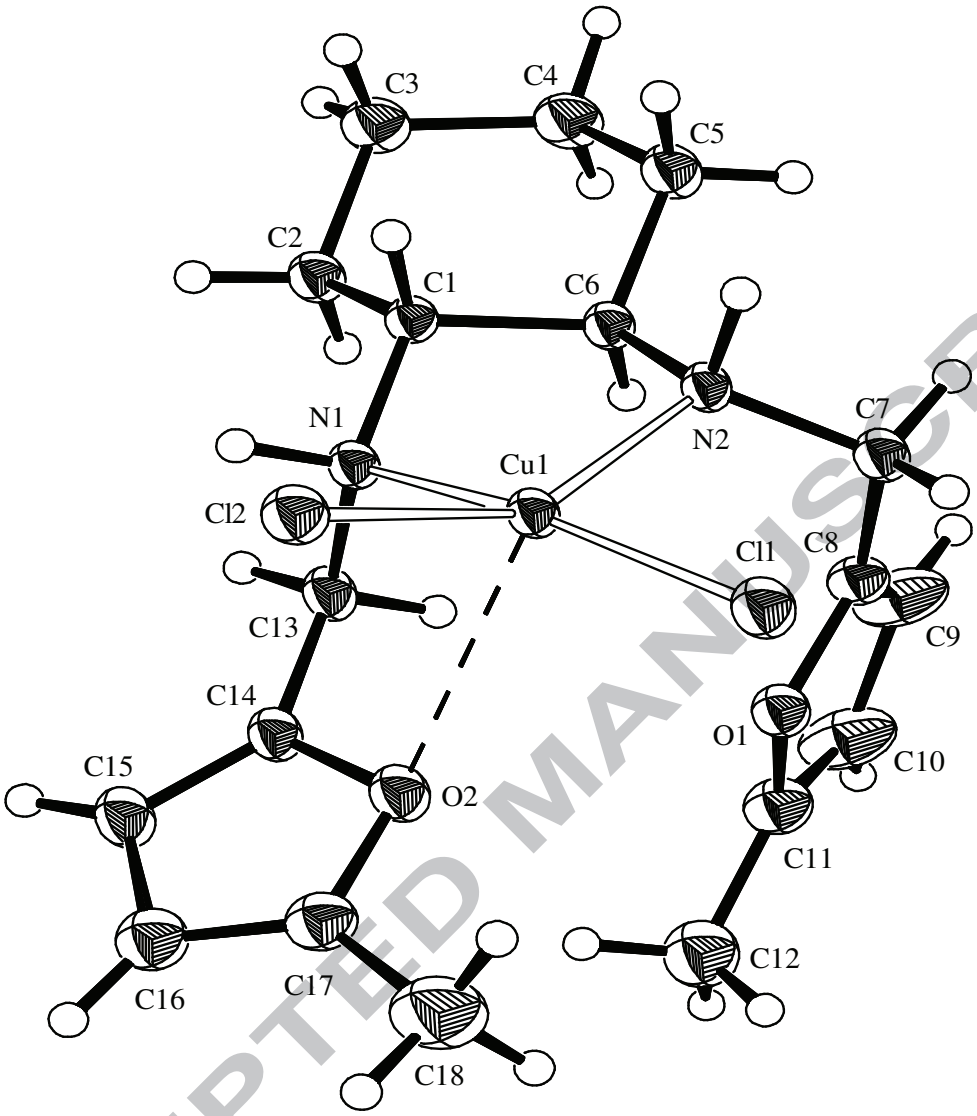


Fig. 2. An ORTEP drawing of Cu(MFCHD)Cl_2 with the numbering scheme at 30% probability level.

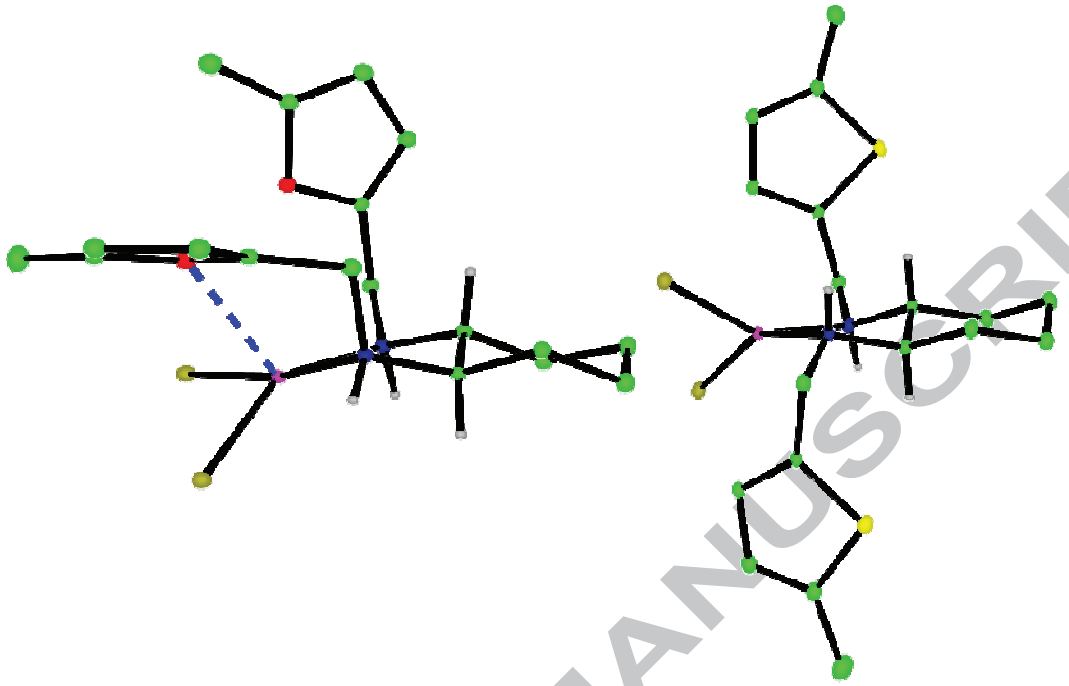


Fig. 3 Comparative view of X-ray structures of $Cu(MFCHD)Cl_2$ and $Cu(MTCHD)Cl_2$ demonstrating the configurations for N atoms of enantiopure ligands. All hydrogen atoms were omitted except those at the chiral atoms for clarity.

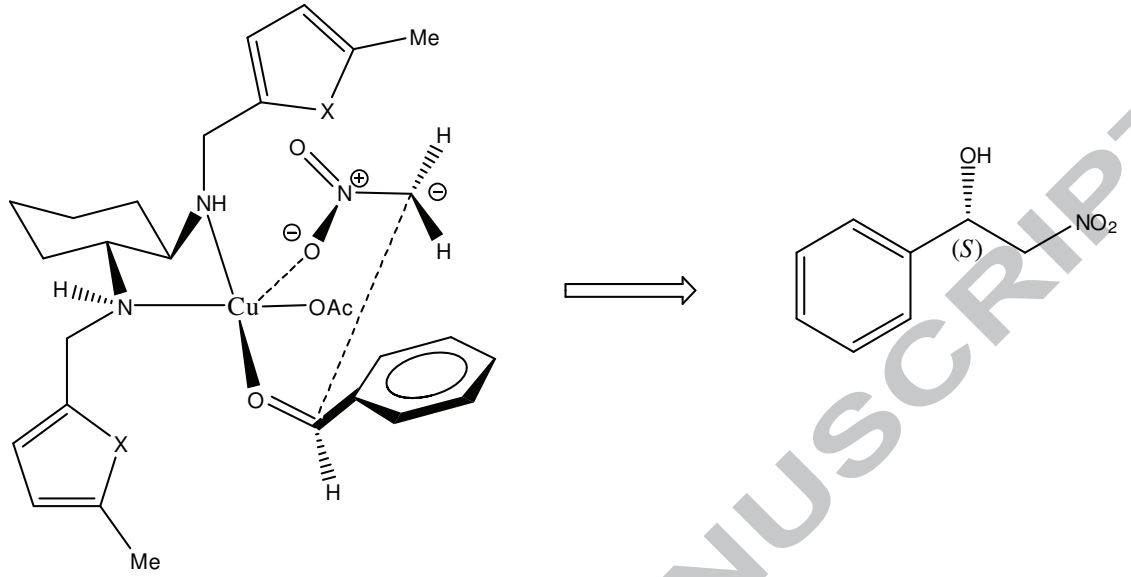


Fig. 4. Transition state model explaining the observed stereochemical outcomes.

Copper complexes bearing methylthiophenyl and methylfuranyl derivatives of (*R,R*)-1,2-diaminocyclohexane: X-ray structures and catalytic exploitation in Henry reaction

Jaewon Cho[a], Gang Ho Lee[a], Saira Nayab[b], and Jong Hwa Jeong*[a]

Novel Cu complexes ligated to methylthiophenyl and methylfuranyl derivatives of (*R,R*)-1,2-diaminocyclohexane were synthesized and characterized by X-ray diffraction. The original C_2-symmetry was lost upon complexation to Cu(II) centre and resulted in selective *R*,*S*-coordination of *N* atoms in case of furanyl containing ligand. The dichloro and diacetato derivatives proved to be active catalysts in asymmetric Henry reaction with moderate yields and enantioselectivities up to 92 %.

Copper complexes bearing methylthiophenyl and methylfuranyl derivatives of (*R,R*)-1,2-diaminocyclohexane: X-ray structures and catalytic exploitation in Henry reaction

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