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Bis(formamidine–urea) Complexes of Ni^{II} and Cu^{II}: Synthesis, Characterization, and Reactivity

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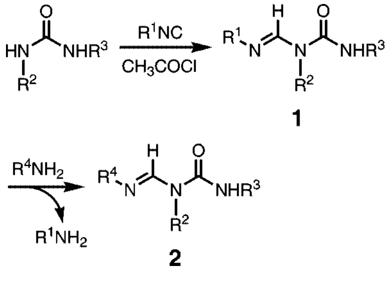
A novel chelating chiral bis(formamidine–urea) ligand was synthesized and used to prepare the corresponding Ni^{II} and Cu^{II} complexes. Spectroscopic and X-ray crystallographic analysis of the former revealed that the urea moiety of the acyclic tetradentate ligand is deprotonated and binds to the square-planar Ni^{2+} ion through amide nitrogen atoms. This complex showed quasi-reversible redox behavior in cyclic voltammetry, with $E_{1/2}$ = 640 mV vs. Cp_2Fe^+/Cp_2Fe corresponding to the Ni^{III}/Ni^{II} couple. The Cu complex was shown by EPR spectroscopy to also adopt a square-planar geometry [$g_{\parallel}$ = 2.25 ($A_{\parallel}$ = 184 G), $g_{\perp}$ = 2.06 at 6 K], and reduction was found to be irreversible, perhaps due to the rigid nature of the tetradentate ligand. The nickel complex was found to be a modestly active catalyst for epoxidation of electron-rich alkenes under Mukaiyama's conditions, likely involving a radical mechanism.

Introduction

The coordination chemistry of urea and substituted ureas with nickel(II) is a topic of significant interest primarily because these compounds serve as structural and functional models of the metalloenzyme urease.[1–4] This enzyme activates the otherwise inert urea molecule toward hydrolysis by coordination of the substrate to one or both Ni^{II} ions located at the active site, ultimatedly affording carbon dioxide and ammonia.[5–7] Considerable research has been dedicated to investigating the interaction of nickel(II) with urea[1–3,8–10] and urea derivatives.[11–13] X-ray crystallographic analysis of these compounds indicates that the geometry around the metal ion is typically octahedral and coordination of urea to Ni^{2+} occurs predominately through the oxygen atom, although cases in which urea nitrogen atoms are involved in binding have been identified.[13,14] It is possible to stabilize higher oxidation states of nickel by coordination of deprotonated amides, as demonstrated by tetra(amido) macrocyclic ligands.[15,16] Because high-valent nickel complexes are believed to be the active catalytic species in epoxidation reactions,[17] complexes in which urea binds nickel(II) through a deprotonated amide nitrogen atom may function as robust oxidation catalyst precursors.

We recently reported a practical synthesis of the formamidine–ureas **1** by condensation of substituted urea derivatives with isocyanides in the presence of acid chloride (Scheme 1).[18] The imine fragment of these compounds undergoes exchange with primary nitrogen nucleophiles to afford the derivatives **2**, at rates determined primarily by the electron-donating ability of the formamidine–urea substituents.[19–21] Using this synthetic methodology, we report the preparation and characterization of the chiral bis(formamidine–urea) ligand **4** and its mononuclear nickel(II) (**5**) and copper(II) (**6**) complexes (Scheme 2). To the best of our knowledge, this is the first example of a chiral multidentate urea-based acyclic ligand that binds metal ions through the *endo* nitrogen of the deprotonated urea in a square-planar



Scheme 1. Synthesis of formamidine–ureas **1** and subsequent imine exchange with primary amines to afford formamidine–urea derivatives **2**.

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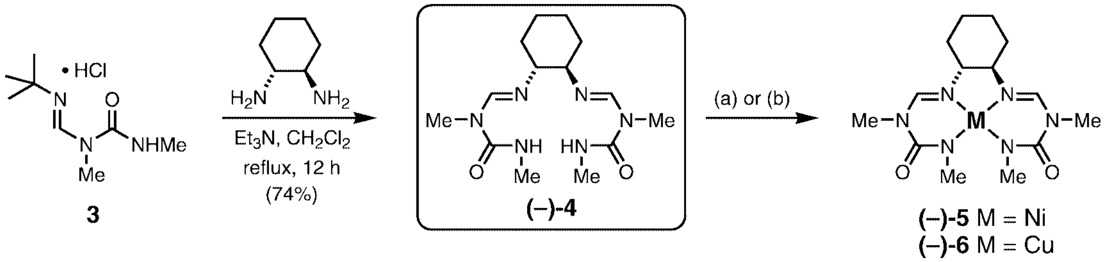


Scheme 2. Synthesis of compounds [Ni(N_4L)] (**5**) and [Cu(N_4L)] (**6**). (a) 3 equiv. $Ni(OAc)_2·4H_2O$, CH_3CN, 45 °C, 91%. (b) 1 equiv. $Cu(OAc)_2·H_2O$, CH_3OH, 50 °C, 76%.

geometry. The ability of **5** to catalyze olefin epoxidation is also described.

Results and Discussion

Synthesis of Ligand H_2N_4L (4) and Coordination Compounds [Ni(N_4L)] (5) and [Cu(N_4L)] (6)

The displacement of *tert*-butylamine from 2 equiv. of 1-(*tert*-butyliminomethyl)-1,3-dimethylurea hydrochloride (**3**) and (1*R*,2*R*)-(–)-1,2-diaminocyclohexane afforded the bis(formamidine–urea) ligand **4** in 74% yield (Scheme 2). Although ligand **4** was very easily made, the practical synthesis of bis(formamidine–ureas) cannot yet be said to be modular, because changes in the components gave widely different yields and sometimes severe difficulties in purification (data not shown). Addition of excess nickel(II) acetate to a gently heated solution of **4** in MeCN gave the red-brown complex **5**. Deprotonation of both amide nitrogen atoms of **4** (substantiated by electrospray ionization mass spectrometry with good agreement of the isotopically resolved mass peaks with the theoretical distribution, elemental analysis, and single-crystal X-ray crystallography) was achieved without addition of external base. The analogous reaction of **4** and copper(II) acetate afforded the purple complex **6**, in which ligand **4** was again found to be in its doubly-deprotonated form. Attempts to obtain pure complexes of other transition metals were not successful.

Structural Characterization of [Ni(N_4L)] (5)

Single X-ray quality crystals of compound **5** were obtained by slow vapor diffusion of Et_2O into a saturated solution of **5** in CH_3CN. X-ray structure analysis revealed the geometry of the metal center to be approximately square planar, as shown in Figure 1. Ligation of the nickel ion by tetradentate **4** is accomplished by the two imine and two deprotonated urea nitrogen atoms. Due to the greater basicity of the oxygen lone pair, it is typical for the urea oxygen atom rather than the nitrogen atom to bind transition metals. Both coordination modes should be accessible with ligand **4**, and we suggest that binding through the nitrogen atom is not geometrically enforced. The preference for N-donor coordination may be linked to the low spin nature of Ni^{II} in **5**. The average $Ni–N_{urea}$ bond length is approximately 1.89 Å, which compares favorably with Ni–N bond lengths in complexes bearing anionic N-based ligands.[8,14,22,23] Deprotonation of the nitrogen atom results in delocalization through the urea moiety as evidenced by the short N(1)–C(1) and N(6)–C(6) distances of ca. 1.34 Å. These bond lengths are in good agreement with those of a related nickel(II) complex bearing both deprotonated NH (N–C ca. 1.31 Å) and neutral NH_2 urea groups (N–C ca. 1.43 Å).[8] The geometry at the deprotonated urea nitrogen atom is approximately trigonal planar with bond angles ranging from 111–121°. The Ni atom rests centrally in the binding pocket (the $N_{urea}–Ni–N_{imine}$ bond angles are both approximately 89.5°) and the ligand is twisted to relieve potential steric interactions between the two terminal urea *N*-methyl groups, presumably in a manner dictated by the chiral 1,2-diaminocyclohexane backbone.

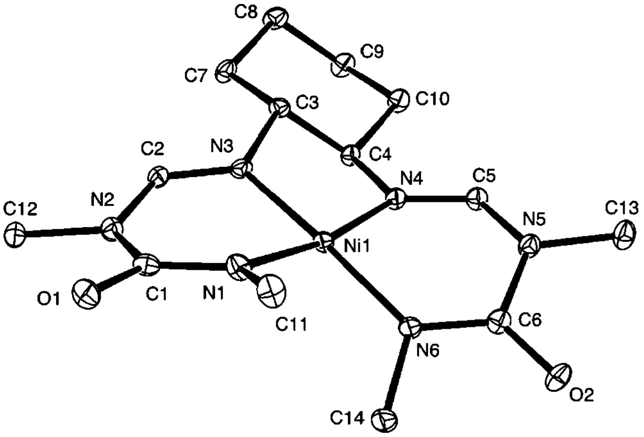


Figure 1. ORTEP diagram of [Ni(N_4L)] (**5**) showing 50% probability ellipsoids for all non-hydrogen atoms.

EPR Spectroscopy of [Cu(N_4L)] (6)

Compound **6** was obtained as a crystalline solid from MeOH/Et_2O. The crystals suffered from the same crystallographic difficulties as **5** (pseudomerohedral twinning) and satisfactory refinement of the molecule was not possible. Examination of **6** by EPR spectroscopy, however, provided insight into the metal ion coordination geometry. A frozen glass of **6** (2:1 EtOH/MeOH) gave a four-line EPR spectrum at 6 K typical of square-planar copper(II) compounds, as shown in Figure 2.[24] ESI-MS and elemental analysis of **6** indicate loss of two protons from the ligand, and we speculate that the detailed structure of this compound is very similar to its nickel(II) analogue **5**.

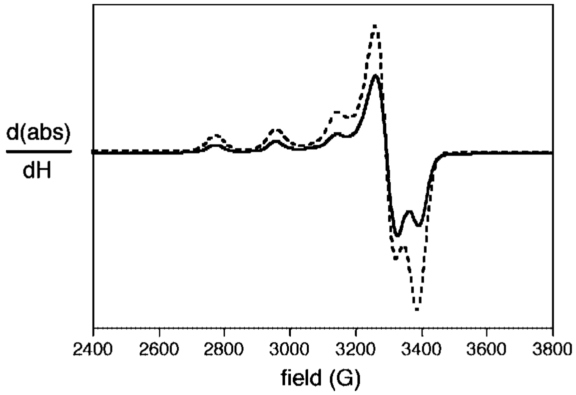


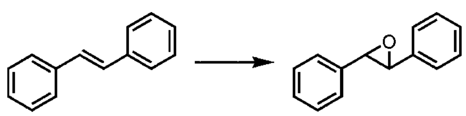
Figure 2. Solid line: X-band EPR spectrum of [Cu(N_4L)] (**6**) as a frozen solution (5 mM in 2:1 EtOH/MeOH) at 6 K. Dotted line: simulated spectrum giving the values $g_{\parallel} = 2.248$ ($A_{\parallel} = 185$ G), $g_{\perp} = 2.08$, linewidth parameter = 55 G.

Electrochemical Studies

Cyclic voltammograms (CVs) of **5** in CH_2Cl_2 were recorded to investigate the ease of oxidation of the Ni^{II} center. The CV of compound **5** reveals a quasi-reversible one-electron redox wave with an $E_{1/2}$ value of 650 mV (ΔE_p = 80 mV) vs. Cp_2Fe^+/Cp_2Fe, corresponding to the Ni^{III}/Ni^{II} couple (see Supporting Information). The $E_{1/2}$ value of **5** is 1.2 V more positive than that of a related square-planar nickel(II) tetra(amide) macrocycle,[15] but comparable to square-planar $[Ni(cyclam)]^{2+}$ ($E_{1/2}$ = 560 mV vs. Cp_2Fe^+/Cp_2Fe) and its derivatives.[16,25,26] The deprotonated urea ligand of **5**, therefore, does not favor the formation of a high valent Ni^{III} species. The CV of complex **6** shows an irreversible reduction wave (data not shown). The enforced square-planar geometry of the bis(formamidine–urea) ligand does not permit the corresponding copper(I) species to form. This finding is not surprising, given the preference of Cu^I for nonplanar coordination geometries.

Epoxidation Studies

Nickel(II) complexes of macrocyclic tetraamines such as cyclam,[17] salen-type ligands,[27] and *N*,*N'*-disubstituted oxamides[28] are catalysts for epoxidation reactions using iodosylbenzene or dioxygen (in presence of aldehydes) as oxidants. The similarity in $E_{1/2}$ values between **5** and $[Ni(cyclam)]^{2+}$ complexes prompted us to explore the catalytic activity of **5**, and *trans*-stilbene was chosen as the model substrate for a variety of oxidation conditions. The results of our initial experiments are outlined in Scheme 3. In the presence of 2-methylpropanal, dioxygen and **5** at 50 °C (Mukaiyama's conditions[29]), *trans*-stilbene oxide was produced in 73% yield. The use of aqueous sodium hypochloride with 4-Å molecular sieves afforded the epoxide in 66% yield, but twice as much catalyst was needed, presumably due to partial hydrolysis of **5** in the presence of water (see below). No epoxidation was observed when PhIO was used as terminal oxidant in CH_2Cl_2 in the presence of 10 mol-% of **5**, and low yields of epoxide were obtained with *t*BuOOH (10 mol-% **5**, 3 equiv. *t*BuOOH in isooctane, 2 equiv. pyridine, CH_2Cl_2). Activated alkenes such as *trans*-anethole were unreactive under Mukaiyama conditions (Table 1), and $Ni(OAc)_2{\cdot}5H_2O$ as catalyst did not promote the epoxidation of substrates for which **5** was effective, demonstrating that complexation of Ni^{II} to **4** is necessary for catalysis.



- **5** (10 mol-%), O_2 (1 atm), 2 Me_2CHCHO, 50 °C, 1,2-dichloroethane, 15 h, 73%
- **5** (20 mol-%), 4 NaOCl (aq.), 4-Å mol. sieves, r.t., CH_3CN, 15 h, 66%
- **5** (10 mol-%), 1 PhIO, r.t., CH_2Cl_2, 15 h, no reaction

Scheme 3. Epoxidation of *trans*-stilbene using [Ni(N_4L)] (**5**) as catalyst under different conditions.

Table 1. Epoxidation of olefins using [Ni(N_4L)] (**5**) as catalyst under Mukaiyama's conditions (1 equiv. alkene, 0.1 equiv. **5**, 1 atm O_2, 2 equiv. isobutyraldehyde, CH_2Cl_2, 50 °C, 12–20 h). Yields are of products purified by column chromatography on alumina and giving satisfactory spectroscopic characterization. Isomer ratios were determined by ^1H NMR spectroscopy.

Entry	Olefin	Product	Yield [%]
1	*trans*-stilbene	*trans*-epoxide	73
2	*cis*-stilbene	*cis*- + *trans*-epoxides	4, 61
3	styrene	epoxide	58
4	α-Me-styrene	epoxide	51
5	*trans*-β-Me-styrene	*trans*-epoxide + benzaldehyde	62, 4
6	*p*-OMe-*trans*-β-Me-styrene	*trans*-epoxide + aldehyde	65, 5
7	1,2-dihydronaphthalene	epoxide	26
8	cyclohexene	epoxide	53
9	1-Me-cyclohexene	epoxide	47
10	cyclooctene	epoxide	51
11	1-octene	epoxide	49
12	2-hexen-1-ol	epoxide	31
13	1-bromo-4-pentene	epoxide	44
14	geranyl benzoate	6,7-epoxide + diepoxide	41, 29

Table 1 summarizes the ability of **5** to epoxidize a variety of unfunctionalized alkenes under Mukaiyama's conditions using 10 mol-% catalyst (the use of less catalyst gives very poor yields of oxidized products after 24 h). Epoxides were obtained in moderate yields from *trans* di- and tri-substituted alkenes (Entries 1, 5, 6, 12, 14). Geranyl benzoate, bearing electronically dissimilar double bonds, afforded a mixture of regioisomers (Entry 14). Both *cis* and *trans* epoxides (1:15, Entry 2) were isolated from *cis*-stilbene, whereas *trans*-stilbene gave the *trans*-epoxide exclusively (Entry 1). In two cases, approximately 5% of benzaldehyde was also formed (Entries 5, 6). Di- and tri-substituted cyclic olefins were found to be modestly reactive (Entries 7, 8, 9, 10). Acid-sensitive epoxides could be isolated in moderate yields (Entries 3, 4, 5, 8), and a variety of functional groups were tolerated (Entries 6, 12, 13, 14). However, electron-deficient olefins such as 2-cyclohexen-1-one or methyl methacrylate were unreactive to **5**. No enantiomeric excess was detected in products isolated from reactions catalyzed by enantiopure **5**.

The above observations are all consistent with the dominance of a radical oxidation mechanism. Furthermore, epoxidation does not occur in the presence of the one-electron acceptor 2,6-di-*tert*-butyl-4-methylphenol. Aside from requiring somewhat higher concentrations, the catalytic properties of **5** are similar to those of nickel(II) compounds supported by tetradentate sulfonamide,[26] and di-*N*,*N'*-substituted oxamide ligands,[27] and differ from the cyclam- and salen-based systems, which are not catalytically active under Mukaiyama's conditions. Compound **5**, in the presence of aldehyde and dioxygen, probably generates an acylperoxy radical, as proposed by Valentine and co-workers,[30] which has been shown to be a competent oxidant for olefin epoxidation. Although the $E_{1/2}$ values of **5** and $[Ni(cyclam)]^{2+}$ complexes are comparable, epoxidation of alkenes by **5** and PhIO was not observed. This is probably due to the inability of **5** to generate the kind of high-valent oxo–nickel species that is the active oxidant in such processes.[17]

Conclusions

Complexes of a bis(formamidine–urea) ligand have been made here for the first time in the form of the mononuclear species $[Ni(N_4L)]$ (**5**) and $[Cu(N_4L)]$ (**6**). X-ray crystallography and EPR studies indicate that these coordination compounds adopt a square-planar geometry. In contrast to most nickel(II) urea complexes, the urea component of this multidentate urea-based acyclic ligand binds the metal center through a deprotonated amide nitrogen bond. Examination of **5** by CV indicates that access to the +3 oxidation state is possible, as indicated by quasi-reversible redox waves, although the redox potentials are more comparable to nickel complexes of tetra(amine) ligands than tetra(amido) derivatives. Compound **5** was found to be a moderately active epoxidation catalyst for electron-rich olefins operating by a radical mechanism, as evidenced by product distributions and the quenching of the process upon addition of a radical scavenger. We are currently preparing variations in the general structure, with the goal, among others, of producing a more active and enantioselective Ni^{II} catalyst.

Experimental Section

General Remarks: All solvents and reagents were ACS reagent grade or better and were used as received or purified in an appropriate manner. Compound **3** was synthesized according to the published procedure.[18]

A) Physical Measurements: Optical spectra were collected with a Hewlett–Packard 8453 diode-array spectrophotometer. NMR spectra were obtained with a 200 MHz Varian Mercury instrument. Elemental analyses were performed by Microanalytical Labs (Indianapolis, IN), and high-resolution MS by the mass spectrometry facility at The Scripps Research Institute. ESI-MS were recorded with an Agilent 1100 LC/MS spectrometer eluting with CH_3OH/H_2O (90:10). IR spectra were obtained with a MIDAC FTIR instrument using samples dispersed on a horizontal attenuated total reflectance (HATR) accessory (Pike Instruments). Melting points were measured in a Thomas Hoover capillary melting point apparatus and are uncorrected. TLC analysis was facilitated by the use of phosphomolybdic acid or anisaldehyde/EtOH stains, in addition to UV light with fluorescent-indicating plates (silica gel on aluminum, Sigma). Analytical HPLC was performed with Hewlett–Packard series 1100 instrument, using a commercial chiral column (Chiralcel OD; *i*PrOH/hexane, 0.5 $mL\,min^{-1}$).

B) Electrochemistry: Cyclic voltammograms were recorded with a Bioanalytical Systems Epsilon potentiostat. The cell contained a glassy carbon working electrode, a Pt wire pseudoreference electrode, and a platinum wire auxiliary electrode, with 0.5 M $Bu_4N(PF_6)$ in CH_2Cl_2 as the supporting electrolyte. All measurements were externally referenced to ferrocene.

C) EPR Study: Frozen solution EPR spectra of **6** were recorded at 6 K with a Bruker Model E500 of the ELEXSYS series spectrometer operating at 9.47 GHz (University of California, San Diego). The spectrum was simulated using the Bruker SimFonia program as a powder spectrum for $S = 1/2$, $I = 3/2$ (assuming 100% natural abundance $^{63}Cu^{2+}$), with the resulting parameters listed in the caption to Figure 2. The simulated spectrum closely matches the observed one with the use of only an axial g tensor, with no need to include a rhombic distortion.

D) X-ray Crystallographic Study: X-ray quality crystals were obtained by slow vapor diffusion of Et_2O into a saturated of **5** in CH_3CN. Data collection was carried out at 103 K with a Rigaku R-AXIS RAPID single-crystal diffractometer equipped with the R-AXIS3S area detector.[31] Intensities were corrected for absorption with the transmission factors ranging 0.854–0.900. Successful structure solution by direct methods and full-matrix refinement[32] were accomplished in the monoclinic space group $P2_1$ with two independent molecules of the complex in the unit cell. The final R and R_w values were 0.035 and 0.084, respectively, for 10404 reflections with $I > 2\sigma(I)$. All H atoms were found in difference Fourier maps and refined with isotropic thermal displacement parameters. The final difference Fourier map was essentially featureless with the highest peak of 0.45 e/Å^3.

CCDC-615365 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

E) Typical Procedure for Epoxidation Studies: 2-Methylpropanal (21 µL, 0.22 mmol) and **5** (10 µL of 1.0 M CH_2Cl_2, 0.01 mmol) were added to a solution of *trans*-stilbene (20 mg, 0.11 mmol) in 1,2-dichloroethane (1.1 mL) at room temperature. The reaction mixture was warmed to 50 °C and vigorously stirred for 15 h under O_2 (1 atm). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (SiO_2, 2% EtOAc/*n*-hexane) to give *trans*-stilbene oxide as a white solid (15.7 mg, 73%).

Characterization Data

***N*,*N'*-Dimethyl-*N*-[(*E*)-({1*R*,2*R*)-2-[((*E*)-{methyl[(methylamino)carbonyl]amino}methylidene)amino]cyclohexyl}imino)methyl]urea (H_2N_4L, 4):** Et_3N (0.75 mL, 5.31 mmol) was added to a solution of 1-(*tert*-butyliminomethyl)-1,3-dimethylurea hydrochloride (**3**) (1.0 g, 4.8 mmol) in dry CH_2Cl_2 (20 mL) and the resulting solution was stirred for 5 min at room temperature under nitrogen. A solution of (1*R*,2*R*)-(–)-1,2-diaminocyclohexane (188 mg, 1.61 mmol) in dry CH_2Cl_2 (5 mL) was added and the mixture was refluxed for 12 h. The solvent was then removed by rotary evaporation and the residue was triturated with THF. The precipitate was separated by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$, 9:1; $R_f = 0.5$) to afford **4** as a hygroscopic white solid (370 mg, 74%). ^1H NMR ($CDCl_3$): $\delta = 1.23–1.39$ (m, 6 H), 1.80 (m, 4 H), 2.78 (s, 6 H), 3.12 (s, 6 H), 7.65 (s, 2 H), 9.2 (br. s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 24.9$, 26.9, 34.1, 34.3, 70.2, 152.0, 157.0 ppm. IR (thin film): $\tilde{\nu} = 3347$, 3055, 2937, 2857, 1659, 1545, 1307, 1079 cm^{-1}. ESI-MS: $+m/z$ (rel. int.) = 333 $[M + Na]^+$ (45), 312 (20), 311 $[M + 1H]^+$ (100). HRMS ($+m/z$): calcd for $C_{14}H_{27}N_6O_2$, 311.219; found 311.2190. M.p. 136 °C.

[Ni(N_4L)] (5): Solid $Ni(OAc)_2·4H_2O$ (119 mg, 0.48 mmol) was added to a stirred solution of **4** (50 mg, 0.16 mmol) in CH_3CN (2 mL). The resulting red mixture was heated to 45 °C for 1 min, after which time TLC analysis showed complete consumption of **4**. Excess $Ni(OAc)_2·4H_2O$ was removed by filtration and the solvent was evaporated under reduced pressure to afford **5** as a red oil (53 mg, 91%). For epoxidation studies, **5** was recrystallized from CH_3CN/Et_2O to afford a red-brown crystalline solid. ^1H NMR (200 MHz, CD_3OD): $\delta = 1.17–1.23$ (m, 4 H), 1.74–1.75 (m, 2 H), 1.94 (s, 2 H), 2.09–2.11 (s, 2 H), 2.41 (s, 6 H), 3.11 (s, 6 H), 7.30 (s, 2 H) ppm. ^{13}C NMR (50 MHz, CD_3OD): $\delta = 25.5$, 29.3, 36.7, 38.1, 68.4, 153.5, 158.2 ppm. IR (thin film): $\tilde{\nu} = 3297$, 2886, 1687, 1590, 1470, 1289, 983, 858, 757 cm^{-1}. ESI-MS: $+m/z$ (rel. int.) = 366 (100) $[M]^+$, 367 (19) $[M + 1H]^+$, 368 (39) $[M + 2H]^+$, 369 (9), 370 (5), 372 (1). For recrystallized material: $C_{14}H_{24}N_6NiO_2$: calcd. C 45.81, H 6.59, N 22.89; found C 45.86, H 6.64, N 22.91. UV/Vis (MeCN): λ_{max} (ε, $M^{-1}cm^{-1}$) = 439 nm (23.3).

[Cu(N_4L)] (6): Solid $Cu(OAc)_2·H_2O$ (31.9 mg, 0.16 mmol) was added to a solution of **4** (50 mg, 0.16 mmol) in MeOH (5 mL) in a single portion. The purple mixture was heated to 50 °C for 5 min, after which time TLC analysis showed complete reaction of **4**. Evaporation of the solvent under reduced pressure afforded a residue that was successively washed with cold CH_3CN (2 × 1 mL) and Et_2O (2 × 1 mL). The resulting solid was dried under high vacuum for 48 h to afford **6** as hygroscopic blue-purple solid (45 mg, 76% yield). Single crystals were grown by slow vapor diffusion of Et_2O into a saturated solution of **6** in MeOH. IR (thin film): $\tilde{\nu} = 3238$, 2860, 1661, 1598, 1481, 1293, 906, 862, 767 cm^{-1}. ESI-MS: $+m/z$ (rel. int.) = 371 (100) $[M]^+$, 372 (18) $[M + 1H]^+$, 373 (47) $[M + 2H]^+$, 374 (7). $C_{14}H_{24}CuN_6O_2$: calcd. C 45.21, H 6.50, N 22.60; found C 45.22, H 6.49, N 22.62. UV/Vis (MeCN): λ_{max} (ε, $M^{-1}cm^{-1}$) = 573 nm (119).

Supporting Information (see also the footnote on the first page of this article): Two pages with hydrolysis kinetics and cyclic voltammetry data.

Acknowledgments

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