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Synthesis and Metalation of a Chiral, Pyridine-Strapped, Cyclic Bis(benzimidazole) Ligand[†]

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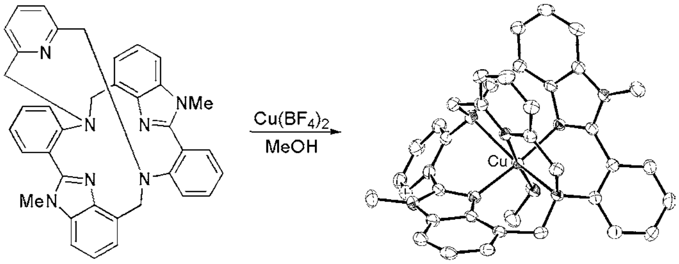
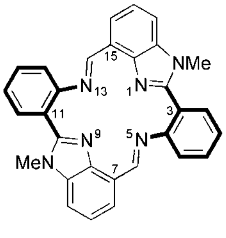
ABSTRACT



Synthesis of a chiral, strapped, cyclic bis(benzimidazole) ligand is reported. This compound forms a stable, Jahn–Teller-distorted, octahedral Cu(II) complex in which the elongated axis is positioned within the main macrocycle. The C_2-symmetric bis(benzimidazole) core adopts a highly ruffled conformation with the ortho-substituted benzene rings located anti relative to the pyridine-bearing strap.

Cyclic, highly ruffled[1] bis(benzimidazole)s (e.g., **1** and **2**, Figure 1) represent a new family of chiral C_2-symmetric ligands capable of creating a well-defined asymmetric environment around a central metal atom.[2] Although we have previously communicated principles for the design of ligands capable of enantiofacial discrimination of (*E*)-alkenes and similarly shaped substrates, the main obstacle in the use of the unmodified ligands **1** and **2** in transition-metal-mediated enantioselective catalysis stems from their rapid racemization via a relatively fast macrocyclic inversion. In previous studies, we found that introduction of bulky substituents ortho to the amide NH groups of **2** significantly increases the barrier to racemization.[3] We also demonstrated that spanning the two external benzimidazole nitrogen atoms with relatively short straps renders these compounds configurationally stable.



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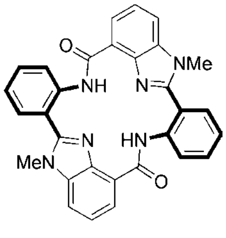

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Figure 1. Ruffled, cyclic, bis(benzimidazole) ligands.

Pursuant to our continued efforts in this arena, we envisaged that an analogous strapping between the two nonbenzimidazole nitrogen atoms (N_5 and N_{13}, Figure 1) in macrocyclic compounds based around **1** and **2** could also potentially lead to extremely ruffled, configurationally stable

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[†] Dedicated to Prof. Sunney I. Chan for his constant support and guidance, on the occasion of his retirement.

(1) For classification of various deformation modes in polyazamacrocyclic ligands, see: Scheidt, W. R.; Lee, Y.-J. *Struct. Bonding (Berlin)* **1987**, *64*, 1−70.

(2) (a) Payra, P.; Hung, S.-C.; Kwok, W.-H.; Johnston, D.; Gallucci, J.; Chan, M. K. *Inorg. Chem.* **2001**, *40*, 4036−4039. (b) Kwok, W.-H.; Zhang, H.; Payra, P.; Duan, M.; Hung, S.-C.; Johnston, D. H.; Gallucci, J.; Skrzypczak-Jankun, E.; Chan, M. K. *Inorg. Chem*. **2000**, *39*, 2367−2376. (c) Payra, P.; Zhang, H.; Kwok, W.-H.; Duan, M.; Gallucci, J.; Chan, M. K. *Inorg. Chem*. **2000**, *39*, 1076−1080.

(3) Fekner, T.; Gallucci, J.; Chan, M. K. *J. Am. Chem. Soc.* **2004**, *126*, 223−236.

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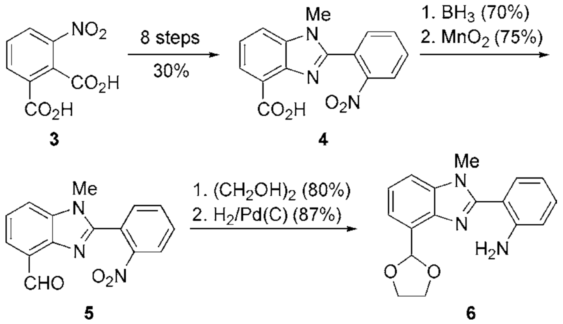
ligands. Herein, we wish to disclose the results of our preliminary synthetic studies of this hypothesis.

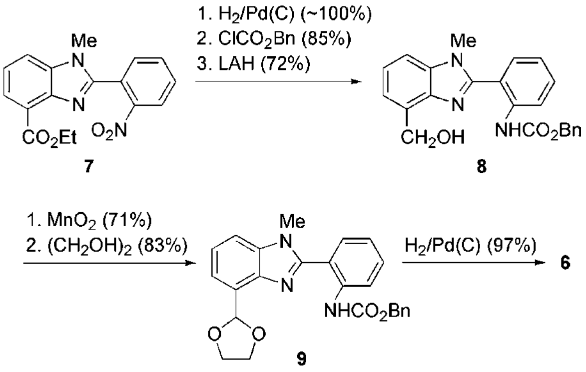
As the previously reported preparation of ligand **1** was tedious and inefficient,[2a] we initially sought to develop an improved procedure that would be amenable to multigram preparations. Our first synthesis (Scheme 1) commenced with conversion of the known acid **4**,[3] obtained in eight steps and 30% overall yield from the commercially available diacid **3**, to aldehyde **5** via BH_3-mediated chemoselective reduction, followed by oxidation with active MnO_2. Protection of aldehyde **5** as its ethylene glycol acetal and subsequent catalytic hydrogenation (H_2, Pd/C) proceeded smoothly furnishing the requisite amine **6** in 70% overall yield. This compound served as a convergence point for the two novel syntheses of ligand **1**.

Scheme 1. First Synthesis of Amine **6**



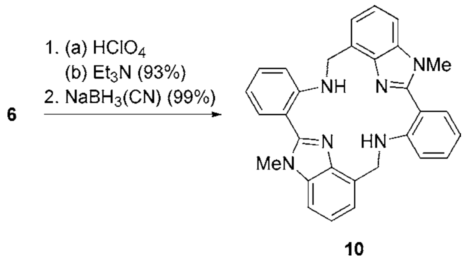
The known benzimidazole **7**[3] was selected as the starting material in an alternative synthesis of the key amine **6** (Scheme 2). Conversion of **7** to benzylic alcohol **8** via a three-step protocol involving catalytic hydrogenation (H_2, Pd/C) of the nitro group, subsequent protection of the resulting amine as its benzyl carbamate, and reduction of the ester function with LAH in THF proceeded uneventfully in 61% overall yield. Sequential oxidation of alcohol **8** with active MnO_2, followed by acetalization (ethylene glycol, *p*TSA), produced benzimidazole **9** in 59% overall yield. Finally, hydrogenolysis of the amino protecting group freed the desired amine **6** in excellent yield.

Scheme 2. Alternative Synthesis of Amine **6**



As the first step in the construction of the primary macrocyclic framework, ligand **1** was prepared according to the known,[2a] high-yielding procedure involving treatment of amine **6** with $HClO_4$ in MeCN, followed by neutralization with Et_3N (Scheme 3). Conversion of ligand **1** to the cyclic amine **10** was achieved by reduction with $NaBH_3(CN)$ in glacial AcOH in excellent yield.

Scheme 3. Synthesis of the Cyclic Amine **10**



Crystals of amine **10** suitable for X-ray analysis were grown by slow evaporation of its $EtOAc/CH_2Cl_2$ solution.[4] Unlike ligands **1**[2a] and **2**,[3] for which the macrocyclic core adopts a well-defined ruffled conformation, amine **10** exhibits a mode of macrocyclic deformation in the solid state that is strikingly different (Figure 2). The two phenylbenzimidazole components are parallel to each other but shifted so that there is no intramolecular π-stacking. When the molecule is viewed along the aryl-heteroaryl axis, the macrocycle creates a

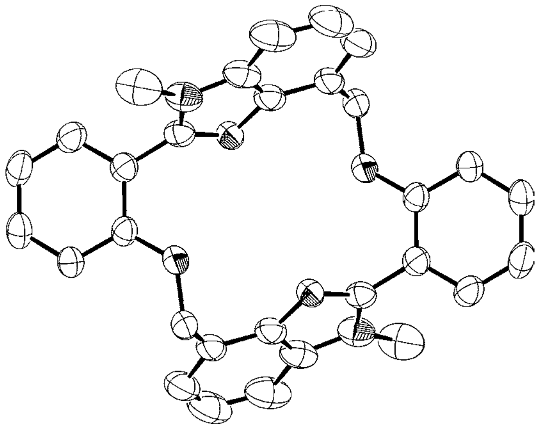


Figure 2. ORTEP view (50% probability thermal ellipsoids) of the cyclic amine **10**. The oxygen and nitrogen atoms are hatched. Hydrogen atoms are omitted for clarity.

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(4) Crystal data for **10**: $C_{30}H_{26}N_6$; $MW = 470.57$; colorless, rhombus-shaped chunk, 0.31 × 0.35 × 0.38 mm; monoclinic; space group $P2_1/n$; $T = 200$ K; $\lambda = 0.71073$ Å; $a = 9.2514(1)$, $b = 7.3897(1)$, $c = 17.7530(3)$ Å; $\beta = 100.5505(5)^\circ$; $V = 1193.17(3)$ Å^3; $Z = 2$; $D_{calc} = 1.310$ Mg/m^3; $F(000) = 496$; μ(Mo K$_\alpha$) $= 0.080$ mm^{-1}; 30 188 reflections collected with $2.71 < \theta < 27.47^\circ$, 2723 of which were independent ($R_{int} = 0.030$); 173 parameters; $R_1 = 0.0460$, w$R_2 = 0.1193$ [for reflections with $I > 2\sigma(I)$]; $R_1 = 0.061$, w$R_2 = 0.1580$ (all data).

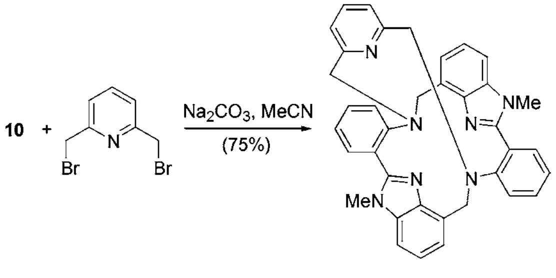
perfectly rhomboidal cavity in the center (the dihedral angle between the joined aryl and heteroaryl components, which corresponds to the smaller angle in the rhomboidal cavity, is equal to 65°).

These results suggest that the dramatic ruffling exhibited by bis(benzimidazole) ligands (e.g., **1** and **2**) is linked, at least in part, to the restricted rotation about the nonbenzimidazole carbon−nitrogen bonds (C_6-N_5 and $C_{14}-N_{13}$, Figure 1). Introduction of a double-bond (e.g., **1**) or double bond-like character (e.g., **2**) at this position likely induces the macrocycle to adopt the more typical and, arguably, more useful conformation.

Modeling studies suggested, however, that an alternative way to promote the desired ruffling might be to join the two nonbenzimidazole nitrogen atoms in **10** with a short, rigid strap. As such structural elements restrict axial binding of external ligands, we chose a strap possessing a nucleophilic center that could coordinate the metal directly. We were also cognizant of the fact that the incorporation of this additional axial ligand would block the face it occupies, leaving only the trans face open for chemistry, a potentially desirable element for future catalytic studies.

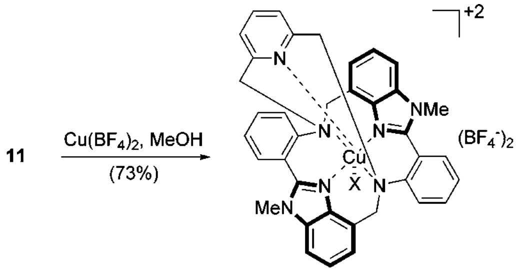
Double alkylation of the cyclic amine **10** with 2,6-bis(bromomethyl)pyridine (Scheme 4) was accomplished by heating the mixture in boiling MeCN in the presence of Na_2CO_3 according to the methodology of Guilard et al.[5] The desired strapped ligand **11** was formed in good yield.[6,7] Importantly, unlike ligands **1** and **2** that are chiral solely due to their inherent nonplanarity, a distortion of the core macrocycle in ligand **11** is not a prerequisite for the handedness of the entire molecular system.

Scheme 4. Synthesis of the Pyridine-Strapped Amine **11**



(±)-**11**

Scheme 5. Metalation of the Strapped, Cyclic Amine **11**



12 (X = MeOH)

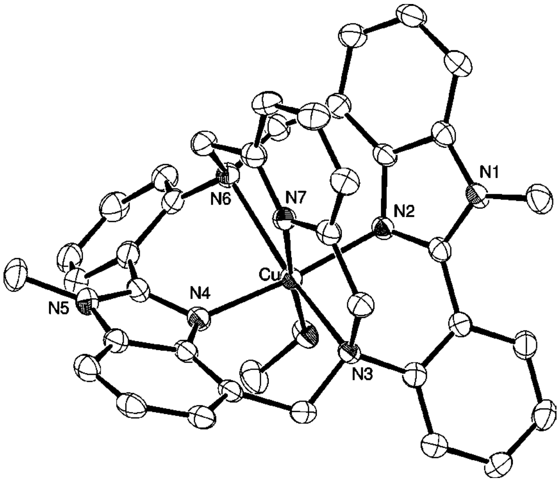


Figure 3. ORTEP view (50% probability thermal ellipsoids) of the Cu(II) complex **12**. The oxygen and nitrogen atoms are hatched. Hydrogen atoms are omitted for clarity.

When a blue solution of ligand **11** and $Cu(BF_4)_2$ in MeOH was kept at reflux (Scheme 5), its color gradually changed to green, and the Cu(II) complex **12** was formed in high yield. Crystals of complex **12** suitable for X-ray analysis were obtained by slow evaporation of its $MeOH/CH_2Cl_2$ solution.[8] The structure reveals a six-coordinate species with a pseudo-octahedral geometry (Figure 3). The four internal nitrogen atoms of the main macrocycle bind in an equatorial fashion to the copper ion, while the two remaining ligands are provided by the nucleophilic centers of methanol and the

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[5] (a) Achmatowicz, M.; Hegedus, L. S.; David, S. *J. Org. Chem*. **2003**, *68*, 7661−7666. (b) Wynn, T.; Hegedus, L. S. *J. Am. Chem. Soc*. **2000**, *122*, 5034−5042. (c) Brandès, S.; Lacour, S.; Denat, F.; Pullumbi, P.; Guilard, R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 639−641. (d) Denat, F.; Lacour, S.; Brandès, S.; Guilard, R. *Tetrahedron Lett*. **1997**, *38*, 4417−4420.

[6] Although in the literature, the terms “capping” and “strapping” are very often regarded as synonymous, with the former frequently covering all of the possible topologies, we intentionally differentiate between them, in particular when aromatic rings or similar components are used to block one of the macrocyclic faces. When the aromatic ring is, more or less, parallel to the averaged macrocyclic plane, the former serves as a cap. In contrast, when the aromatic ring is approximately perpendicular to the averaged macrocyclic plane, it acts as a strap.

[7] As the crude reaction product is spectroscopically different (^1H NMR) from the purified amine **11**, it is postulated that the crude reaction mixture contains a sodium complex of the capped amine **11**. The cation may serve as a template on which strapping takes place. However, as a reviewer pointed out, other phenomena (partial protonation, hydration, kinetic alkylation, etc.) might be responsible for the observed spectroscopic discrepancies.

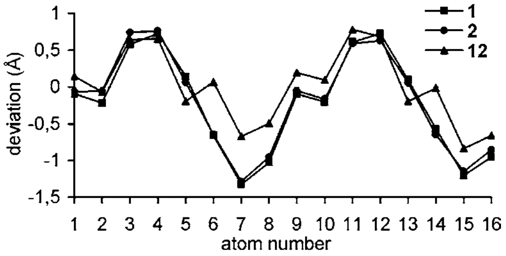
[8] Crystal data for **12**: $C_{39}H_{39}B_2CuF_8N_7O_2$; $MW = 874.93$; green, rectangular plate, $0.04 \times 0.27 \times 0.35$ mm; monoclinic; space group $P2_1/c$; $T = 150$ K; $\lambda = 0.71073$ Å; $a = 1.595(1)$, $b = 16.922(2)$, $c = 19.919(3)$ Å; $\beta = 106.12(1)°$; $V = 3754.7(7)$ Å^3; $Z = 4$; $D_{calc} = 1.548$ Mg/m^3; $F(000) = 1796$; $\mu(\text{Mo K}_\alpha) = 0.669$ mm^{-1}; 55 721 reflections collected with $2.13 < \theta < 24.99°$, 6608 of which were independent ($R_{int} = 0.038$); 538 parameters; $R_1 = 0.0515$, w$R_2 = 0.1252$ [for reflections with $I > 2\sigma(I)$]; $R_1 = 0.0667$, w$R_2 = 0.1367$ (all data).

strap-incorporated pyridine. The Cu−O(methanol) and Cu−N(pyridine) distances are equal 1.98 and 1.99 Å, respectively, and the central metal ion exhibits some doming (0.31 Å relative to the mean 4N-plane) in the direction of the axially bound MeOH.

The two sets of Cu−N bonds within the primary macrocyclic ring are markedly different. The average length of the Cu−N(benzimidazole) bond is 2.00 Å, which is common for a Cu−N bond in other complexes of polyazamacrocyclic ligands. In contrast, the average length of the Cu−N(aniline) bond is 2.45 Å, presumably reflecting a Jahn−Teller (JT) distortion.[9,10] While such bond elongations are fairly common in octahedral Cu(II) complexes, their orientation within the macrocyclic 4N-plane is unusual.[2c,5b,11−12] For example, in the structure of Cu(II)·**1**·$(ClO_4)_2$, the JT distortion is perpendicular to the 4N-plane, with the perchlorate ions having long, 2.6 Å, interactions with the open axial sites of the copper ion.[2c]

In addition to the JT distortions at the metal center, as anticipated, the macrocyclic core of **12** is highly nonplanar with the two benzimidazole subunits located syn to the strap relative to the average macrocyclic plane.[12] The level of distortion for the core 16 atoms in complex **12**, however, is significantly lower than that observed for highly ruffled ligands **1** and **2**, arguably the most distorted polyazamacrocyclic ligands reported to date[2a,3] (Figure 4; see Figure 1 for numbering system). The maximum distortion for **12** reaches 0.84 Å (1.15 and 1.29 Å for ligands **1**·$(HClO_4)_2$[2a] and **2**,[3] respectively). The average distortion for the core 16 atoms in **12** is 0.40 Å, compared to 0.58 and 0.54 Å for **1**·$(HClO_4)_2$ and **2**, respectively. Analogously, the average distortion for the four *meso* carbons (i.e., atoms 3, 7, 11, and 15) in **12** is 0.73 Å, compared to 0.93 and 0.94 Å for **1**·$(HClO_4)_2$ and **2**, respectively.

As there is no spectroscopic evidence (^{1}H and ^{13}C NMR) that ligand **11** consists of a mixture of diastereomers due to macrocyclic inversion of the bis(benzimidazole) core, it is possible that its geometry is well-defined and analogous to that of complex **12** (with the two benzimidazole subunits located syn to the strap relative to the averaged macrocyclic plane). However, at this stage we cannot rule out very fast interconversion (relative to the NMR time-scale) of the two possible diastereomeric species that could also account for the simplicity of the NMR spectra.



	distortion/Å		
atom	1·$(HClO_4)_2$	2	12
1	-0.10	-0.06	0.15
2	-0.22	-0.06	-0.07
3	**0.58**	**0.74**	**0.65**
4	0.73	0.76	0.65
5	0.14	0.06	-0.19
6	-0.66	-0.65	0.07
7	**-1.32**	**-1.29**	**-0.67**
8	-1.03	-0.96	-0.50
9	-0.10	-0.05	0.20
10	-0.20	-0.17	0.10
11	**0.61**	**0.59**	**0.78**
12	0.73	0.63	0.69
13	0.10	0.06	-0.20
14	-0.57	-0.65	-0.02
15	**-1.20**	**-1.15**	**-0.84**
16	-0.95	-0.85	-0.66

Figure 4. Deviation from planarity (Å) relative to the mean 4N-plane for the core 16 atoms in ligands **1**·$(HClO_4)_2$ and **2** and the Cu(II) complex **12**. For the atom numbering system, see Figure 1. The values of distortion for the *meso* carbons are shown in bold font.

In conclusion, a synthesis of the pyridine-strapped, benzimidazole-based cyclic ligand **11** and its Cu(II) complex **12** has been developed. The core macrocycle in **12** has been shown to adopt a significantly ruffled, well-defined conformation. Work is currently underway to prepare enantioenriched samples of **11** and to develop asymmetric syntheses of its analogues in order to use them as ligands in transition-metal-catalyzed enantioselective transformations.[13]

Acknowledgment. This work was supported by the National Science Foundation (CAREER Award No. 9984071).

Supporting Information Available: Synthetic procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds and crystallographic details for **10** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Jahn, H. A.; Teller, E. *Proc. R. Soc. London* **1937**, *161*, 220−235.

(10) For reviews on the Jahn−Teller effect in Cu(II) complexes, see: (a) Bersuker, I. B. *Chem. Rev.* **2001**, *101*, 1067−1114. (b) *The Jahn−Teller Effect. A Bibliographic Review*; Bersuker, I. B., Ed.; IFI/Plenum: New York, 1984; pp 1−590. (c) Hathaway, B. J. *Struct. Bonding (Berlin)* **1984**, *57*, 55−118. (d) Bersuker, I. B. *Coord. Chem. Rev.* **1975**, *14*, 357−412.

(11) For representative structures of Cu(II) bound to 4N-macrocyclic amine ligands, see: (a) Curtis, N. F.; Gladkikh, O. P. *Aust. J. Chem.* **2000**, *53*, 727−741. (b) Goeta, A. E.; Howard, J. A. K.; Maffeo, D.; Puschmann, H.; Williams, J. A. G.; Yufit, D. S. *J. Chem. Soc., Dalton Trans.* **2000**, 1873−1880. (c) Kim, J. C.; Fettinger, J. C.; Kim, Y. I. *Inorg. Chim. Acta* **1999**, *286*, 67−73. (d) Kang, S.-G.; Kim, S.-J.; Jeong, J. H. *Polyhedron* **1998**, *17*, 3227−3234. (e) Lancashire, R. J.; Newman, P. D.; Stephens, F. S.; Vagg, R. S.; Williams, P. A. *J. Coord. Chem.* **1995**, *34*, 345−350. (f) Bu, X. H.; An, D. L.; Chen, Y. T.; Shionoza, M.; Kimura, E. *J. Chem. Soc., Dalton Trans.* **1995**, 2289−2295. (g) Pattrick, G.; Hancock, R. D. *Inorg. Chem.* **1991**, *30*, 1419−1422. (h) Comba, P.; Curtis, N. F.; Lawrance, G. A.; O'Leary, M. A. *J. Chem. Soc., Dalton Trans.* **1988**, 2145−2152.

(12) For reviews on nonplanar distortions in other classes of polyazamacrocyclic ligands, see: (a) Senge, M. O. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 1, Chapter 6, pp 239−347. (b) Shelnutt, J. A.; Song, X.-Z.; Ma, J.-G.; Jia, S.-L.; Jentzen, W.; Medforth, C. J. *Chem. Soc. Rev.* **1998**, *27*, 31−41.

(13) Preliminary studies indicate that the molecule of methanol in the Cu(II) complex **12** is not tightly bound to the central metal atom. As a result, **12** can potentially serve as a Lewis acid and activator in a host of important transformations. For instance, it catalyzes the hydrolytic epoxide ring opening in 1,2-epoxypropane. Therefore, the hydrolytic kinetic resolution of racemic oxiranes catalyzed by enantioenriched samples of **12** and its analogues should be possible. For a recent report on the $Cu(BF_4)_2$-catalyzed epoxide-ring opening, see: Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *Org. Lett.* **2002**, *4*, 2817−2819.