Synthesis and Coordination Properties of Pendant Arm Dipyridylmethane Derivatives

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Dipyridylmethane dicarboxylic acids with pendant arms containing pyridine groups were prepared. Cu(II) was shown to form square pyramidal complexes with the ligands. Depending on the structure of the pendant arm, the apical position was occupied either by a water molecule or by a pyridyl group from the same molecule or from a neighboring molecule. The reason for the different behavior of the ligands is suggested to be due to stereoelectronically induced conformational preferences of the ligands.

Introduction

It is well documented that the presence of pendant donor groups may extensively affect the properties of metal complexes of macrocyclic ligands, as illustrated by numerous examples from natural[1] as well as synthetic[2] systems. By apical coordination, it has also proved possible to alter the properties of noncyclic ligands with square planar coordination. For this purpose, pentadentate ligands are particularly attractive, since intramolecular coordination is expected to be favored compared to coordination by an external base. For example, we have been able to demonstrate that the presence of a pendant carbonyl group in polymer-supported bis(6-carboxy-2-pyridyl)methane derivatives influences the metal ion affinity, although we were not able to prove whether the carbonyl group really participated in coordination to the metal ion.[3]

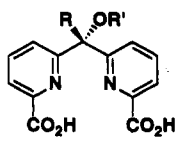
Besides affecting the reactivity of the metal ion, apical coordination also has the effect of blocking one face of the coordination plane, thus leaving only one side for approach of an external ligand. This is expected to be beneficial in asymmetric synthesis involving chiral octahedral metal complexes, since the number of intermediate complexes is reduced. This effect closely resembles that exerted by a tetradentate C_2 symmetric ligand in a square planar complex upon coordination of an additional ligand.[4]

To further study the influence of apical coordination on the properties of metal complexes, we decided to develop methods for the preparation of pentadentate dipyridylmethane dicarboxylic acids. This type of ligand constitutes an attractive model for coordination chemistry studies, since the ligands form stable complexes with a variety of metal ions[5] and since extensive structural variations are possible. Starting from dipyridylmethane derivatives, not only dicarboxylic acids can be prepared, but also macrocyclic ligands[6] and ligands containing chiral groups in the 6-position of the pyridine ring.[7]

In this paper, we present synthetic methods for the introduction of side chains containing a pyridine ring on the central carbon atom of dipyridylmethane. The coordination properties of these new ligands are also discussed.

Results and Discussion

Preparation of Ligands. Two different strategies were followed for the preparation of bis(6-carboxy-2-pyridyl)-methane derivatives 1, in which one substituent (R or R′) has a terminal pyridine ring. One route consisted of *O*-alkylation of a dipyridylcarbinol with an electrophile carrying either the desired functional group or some substituent that subsequently could be transformed into that group. The alkylation could be performed either on the parent alcohol 2 or on a derivative which is substituted in the 6-position of the pyridine rings. However, functionalization of dipyridylmethanes having hydrogen atoms in the 6-position, such as cyanation to yield 6,6′-dicyano derivatives,[8] had to be performed prior to introduction of the pyridine ring in the side chain in order to avoid substitution of this ring. To allow for convenient structural variations, it was desirable to introduce the side chain at a late stage of the reaction sequence. However, further manipulation of the cyano groups sometimes requires protection of the tertiary alcohol, which proved inconvenient. Reaction with either an allyl halide or a benzyl halide proceeded smoothly to yield allyl- and benzyl-protected alcohols, respectively, and allowed subsequent hydrolysis or other manipulations of the cyano groups, but deprotection proved difficult using the common standard methods.[9] Therefore, the most convenient method was found to involve initial cyanation of dipyridylmethanol followed by introduction of the pendant arm.



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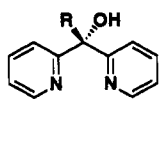

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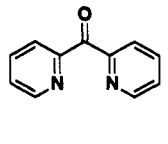

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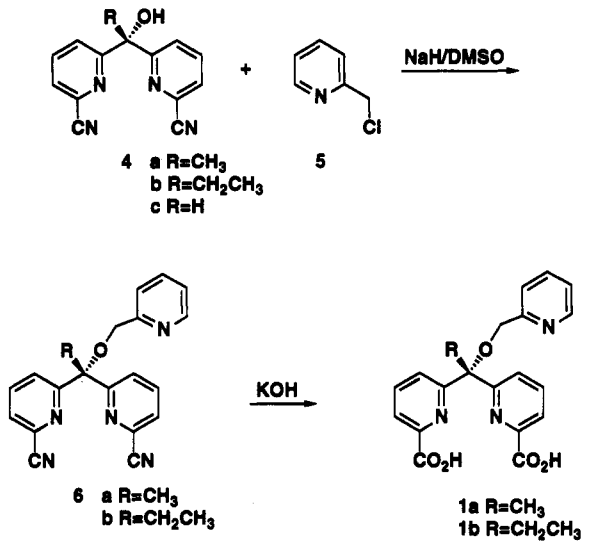
Scheme 1

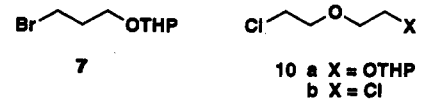


The second strategy for the preparation of **1** employs an electrophilic dipyridylmethane derivative. Reactions of 2,2′-dipyridyl ketone (**3**) with Grignard reagents carrying a functional group which subsequently can be reacted with a pyridine derivative were investigated. The cyano groups were introduced after the Grignard reaction, but, in this case as well, prior to coupling with the side chain containing a pyridine derivative.

Both strategies could be used for the preparation of the desired bis(6-carboxy-2-pyridyl)methane derivatives **1**. However, alkylation of tertiary alkohols **4a** and **4b** proceeded smoothly only with activated electrophiles, so this method was not generally useful. For most derivatives, the method of choice involves initial reaction of 2,2′-dipyridyl ketone with the Grignard reagent prepared from *O*-protected 3-hydroxybromobenzene.

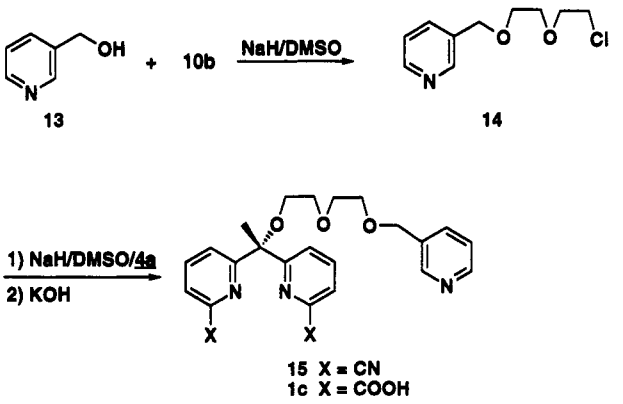
Alkylation of 1,1-Bis(6-cyano-2-pyridyl) alcohols. Alkylation of compounds **4a** and **4b** proceeded smoothly with activated electrophiles in DMSO using sodium hydride as base, whereas only low yields were obtained in THF. Thus, 1,1-bis(6-cyano-2-pyridyl)ethanol (**4a**) and 1,1-bis(6-cyano-2-pyridyl)propanol (**4b**) reacted with 2-(chloromethyl)pyridine (**5**) to yield the expected compounds **6a** and **6b** in 72 and 64% yields, respectively (Scheme 1). Nitriles **6a** and **6b** were hydrolyzed under basic conditions to yield the diacids **1a** and **1b** (64 and 86%, respectively).

In order to allow for the preparation of compounds containing a longer spacer between the two complexing units, initial coupling of the spacer to the dipyridine unit followed by coupling to the monopyridine unit as well as initial coupling of the spacer to the monopyridine unit were investigated. For this purpose, a 3-substituted monopyridine unit was chosen, since this was considered to result in the most favorable angle for apical coordination. Although the secondary alcohol **4c** reacted with 1-(tetrahydropyran-2-yloxy)-3-propyl bromide (**7**) in DMSO to give a high yield (91%)of product **8**, which could then be

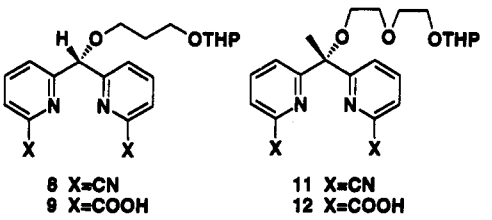


hydrolyzed to afford the diacid **9** (72%), attempted alkylation of *tertiary* dipyridyl alcohols with nonactivated

Scheme 2



halides in THF or DME did not yield the desired products. They were observed only when DMSO was employed, although the yields were poor. Thus, reaction of 1-(tetrahydropyran-2-yloxy)-3-oxo-5-pentyl chloride (**10a**) with 1,1-bis(6-cyano-2-pyridyl)ethanol (**4a**) in DMSO in the presence of sodium hydride gave only 15% of the dinitrile **11**, which was hydrolyzed using KOH to yield the diacid **12** (81%). Since alkylation of the deprotected THP ethers was also inefficient, this route was abandoned.

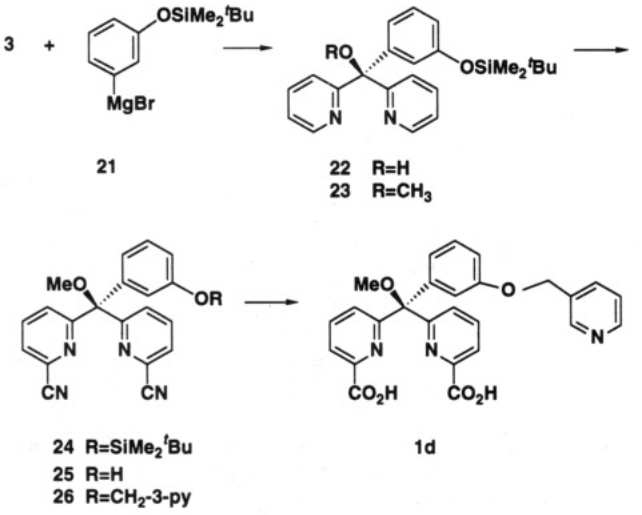


Coupling of the spacer to the monopyridine unit followed by reaction with the tertiary dipyridylcarbinol derivative proved to be slightly better. Alkylation of 3-(hydroxymethyl)pyridine (**13**) with 1,5-dichloro-3-oxopentane (**10b**) yielded the desired product **14**[10] (23% yield, Scheme 2), which was subsequently reacted with 1,1-bis(6-cyano-2-pyridyl)ethanol (**4a**) in DMSO in the presence of sodium hydride to yield the dinitrile **15** (19% yield). Hydrolysis under basic conditions yielded the diacid **1c** (81%). The same compound was obtained via initial coupling with 1-(tetrahydropyran-2-yloxy)-3-oxo-5-pentyl chloride (**10a**). Although coupling with this unsymmetrical spacer was more efficient (45% yield), this route requires more synthetic steps (deprotection of THP ether and tosylation) and did not result in a higher overall yield.

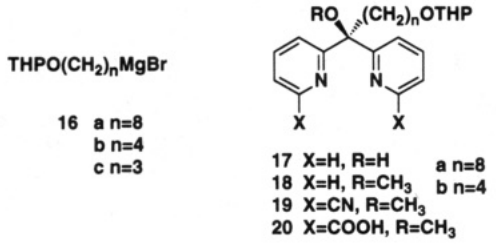
Nucleophilic Additions to 2,2′-Dipyridyl Ketone. Due to the limited applicability of *O*-alkylation reactions, the coupling of 2,2′-dipyridyl ketone with Grignard reagents containing protected alcohols was investigated. Reaction of ketone **3** with 1-(tetrahydropyran-2-yloxy)-8-octyl magnesium bromide (**16a**) has previously been shown to yield **17a**.[3] Analogously, 1-(tetrahydropyran-2-yloxy)-4-butylmagnesium bromide (**16b**) yielded **17b**, whereas reaction with **16c** resulted only in reduction to yield 2,2′-dipyridylmethanol. Adducts **17** could be transformed, via compounds **18** and **19**, into the acids **20** (methylation, cyanation, and hydrolysis of the nitrile groups). However, since the overall yields were quite low

(10) This compound has previously been prepared by a similar method: Niele, F. G. M.; Martens, C. F.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1989**, *111*, 2078.

Scheme 3



and the deprotected alcohols proved unreactive, more efficient methods were chosen.



In order to obtain dipyridylmethane compounds containing more reactive alcohol functions, phenol derivatives were chosen thus allowing for further alkylation employing a mild base such as carbonate. Inspection of molecular models suggested that a ligand derived from a Grignard reagent with a phenolic function in the 3-position, subsequently reacted with a 3-substituted pyridine, would have the most suitable geometry for coordination of the pendant function to the metal ion. Thus, ketone **3** was reacted with [3-[(*tert*-butyldimethylsilyl)oxy]phenyl]-magnesium bromide (**21**) to give a high yield (74%) of the addition product **22**[11] (Scheme 3). This protecting group was chosen since the trimethylsilyl ether is not compatible with the reaction conditions. Furthermore, deprotection of the methyl ether was not possible with dipyridylmethanes substituted in the 6-positions with electron-withdrawing groups using any of the standard methods.[9]

Methylation of alcohol **22** yielded compound **23** (71%), which was transformed to the dinitrile **24** (69%). Deprotection afforded the desired phenol (**25**, 99%), which was reacted with 3-(chloromethyl)pyridine in the presence of potassium carbonate to yield **26** (86%). Hydrolysis under basic conditions afforded the dicarboxylic acid **1d** (80%).

Coordination to Metal Ions. We have previously shown that 1,1-bis(6-carboxy-2-pyridyl)-1-methoxypropane (**1e**) is able to form complexes with a variety of metal ions with either square planar, square pyramidal, or octahedral geometry.[5] The copper(II) complex of this ligand was found by X-ray analysis to be pentacoordinate

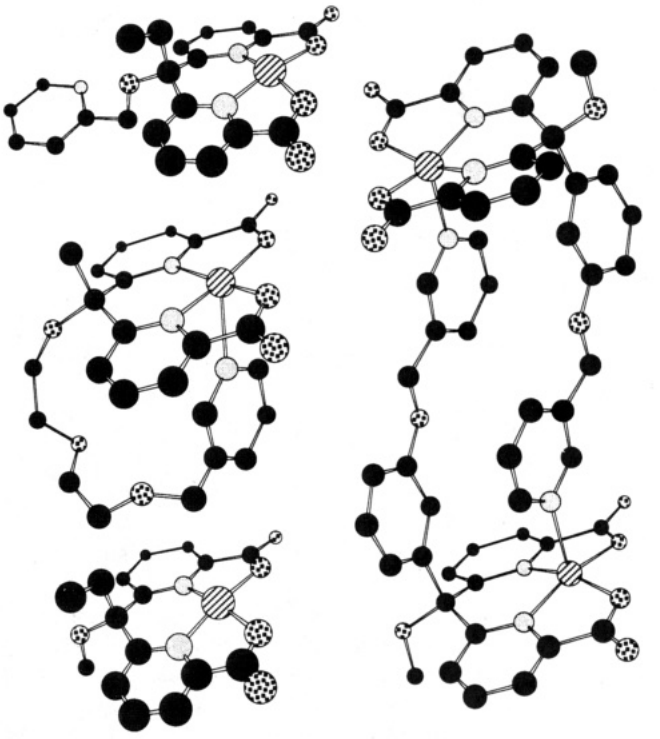


Figure 1. Chem 3D representations of X-ray structures[12] of Cu**1b**-H_2 (left above), Cu**1d**-H_2 (right), Cu**1e**-H_2 (left below), and of assumed structure of Cu**1c**-H_2 (left middle).

with two nitrogen atoms and two carboxylate oxygen atoms coordinating in a plane, and with a water molecule in the apical position.[5] To examine the coordination properties of ligand **1b**, its copper(II) complex was also subjected to X-ray structural analysis.[12] To our surprise, the fifth position in this copper complex was still occupied by a water molecule (Figure 1), even though the pyridine ring of the side chain was thought to be suitably situated for apical coordination, as judged by inspection of molecular models.

In the copper(II) complex of compound **1d**, coordination of the pendant pyridine ring was shown by X-ray crystallography to occur by formation of a dimer (Figure 1).[12] The dimer contains two copper atoms which are held at a fixed distance due to apical coordination. This supramolecular arrangement is probably stabilized by van der Waals interactions between the pendant arms of the two units. Crystals suitable for X-ray analysis of the copper(II) complex of compound **1c** have unfortunately not yet been obtained.

In order to obtain information about the coordinating properties of ligand **1c**, the dark blue copper complexes of **1b**–**1d** were investigated by electron spectroscopy in the range 350–1500 nm.[13] In DMF, the absorption maxima of the three complexes differed only slightly (λ 623–629 nm, Table 1). This suggests that the environment about the metal atom is similar in all complexes, which is possible if a solvent molecule takes part in coordination (in the case of **1d** by displacement of the pyridine ring). In contrast, in the noncoordinating solvent nitromethane, the absorption maxima of the complexes differed considerably (Table 1). Compound Cu**1d**-H_2 was completely insoluble, probably due to the inability of this solvent to

(11) An analogous compound has previously been prepared by reaction of *O*-protected methyl salicylate with 2 equiv of 2-pyridyllithium followed by methylation of the tertiary alcohol: Jameson, D. L.; Hilgen, S. E.; Hummel, C. E.; Pichla, S. L. *Tetrahedron Lett.* **1989**, *30*, 1609.

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(13) Lever, A. B. P. *Inorganic Electronic Spectroscopy*; Elsevier: Amsterdam, 1984.

Table 1. Visible Absorptions of the Cu(II) Complexes (nm)[a]

solvent/ligand	1b	1c	1d	1e
DMF	629 (99)	628 (103)	623 (101)	627 (114)
CH_3NO_2	689 (111)	628 (94)	*b*	588 (106)
CH_3NO_2 + 100 equiv of pyridine	668	656	*b*	629

[a] Molar intensities (in 1 mol^{-1} cm^{-1}) are given in parentheses. [b] Not soluble.

break the dimer. In order to ascertain whether the difference in absorption maxima of Cu1e-H_2 and Cu1c-H_2 was due to coordination of the pendant pyridine of **1c**, the effect of coordination of pyridine to the apical position of Cu1e-H_2 was studied. This was done simply by adding pyridine to the copper complex of **1e** in nitromethane. This caused a gradual shift of the absorption maximum to longer wavelengths. After the addition of 100 equiv, a complex was formed that absorbed at essentially the same wavelength as Cu1c-H_2, supporting the suggestion that the pyridine ring of **1c** does, in fact, take part in coordination to the metal ion (Figure 1). Upon further addition, an isosbestic point was no longer observed, suggesting that some other competing ligand exchange processes occur.

It should be noted that a large excess (ca. 100 equiv) of pyridine must be added to the copper complex of ligand **1e** in order to achieve N_3O_2 coordination, i.e. a coordination analogous to that observed in the complexes of ligands **1c** and **1d** in the absence of external base. This clearly demonstrates the efficiency of coordination of the pendant pyridine ring, caused by its proximity to the metal center and a favorable entropy factor.

The reason for the different complexing behavior for the three types of pendant arm ligands seems to be the tendency of the ligands to adopt a conformation in which the alkoxy group is aligned parallel to at least one of the pyridine rings. This phenomenon has previously been observed in a number of X-ray structures of analogous ligands.[6a,6b,14] Upon metal complex formation, this feature could still be observed,[5,6c] except in cases where a five-membered metal chelate is formed by coordination of the oxygen atom of the alcohol group to the metal ion, as for example in (2,2′-dipyridyl)methyl alcohols,[15] the hydrate[16] and hemiacetals[17] of 2,2′-dipyridyl ketone, (2,2′-dipyridyl)dioxolanes,[18] and 2,2′,2″-tripyridylmethanol.[19] Since the phenomenon was also observed in solution,[6a,20] it was not thought to be due to crystal-packing effects. In order to determine whether the reason for this preference is of steric or electronic nature, ab initio and MM2 calculations were performed on model ligand systems.[21] It was found that the conformation observed, in which the C–N and the C–O bonds are in a transoid conformation, represents an energy minimum. This conformation is preferred due to (1) the stabilization caused by an overlap between the antibonding C–O σ orbital and a σ bond of the pyridine ring, an arrangement that resembles the anomeric effect,[22] (2) by an overlap between the same antibonding orbital and the lone pair on nitrogen, and (3) by the absence of a dipole–dipole repulsion of the lone pairs on the heteroatoms. This effect was found to be 12–15 kJ/mol. The consequence of this conformational preference is that the arms of compounds **1a** and **1b** are too short for the pyridine nitrogen to reach the coordination sphere of the metal, whereas that of compound **1d** is too long. This tendency for the ligands to adopt a certain conformation seems to be strong and, therefore, in designing this type of ligand, the requirement of the carbon–ether oxygen bond being parallel to at least one of the pyridine rings should be taken into account. This is achieved in compound **1c**.

Conclusions

Dipyridylmethane dicarboxylic acids containing pendant pyridine rings connected via different spacer arms were prepared. The strong tendency of the ligands to adopt a conformation in which the central carbon–oxygen bond is aligned parallel to a pyridine ring seems to determine whether intra- or intermolecular coordination, or no coordination at all, of the pendant pyridine ring takes place.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise stated. Chemical shifts are reported relative to Me_4Si. Electronic spectra (UV/vis) were recorded in DMF or CH_3NO_2 in the range 350–1500 nm. Chromatography[23] was performed using silica gel (Merck 230–400 mesh). Melting points are uncorrected.

Materials. Di(2-pyridyl)methanol,[24] 1,1-di(2-pyridyl)ethanol,[24] 1,1-bis(6-cyano-2-pyridyl)propanol[5] (**4b**), and 3-[(*tert*-butyldimethylsilyl)oxy]bromobenzene[25] were prepared according to previously described methods. Ethyl acetate, petroleum ether, and CH_2Cl_2 were distilled prior to use. THF was distilled from sodium benzophenone ketyl. Anhydrous DMSO was used as received.

1,1-Bis(6-cyano-2-pyridyl)ethanol (4a). 1,1-Di(2-pyridyl)-ethanol *N,N*′-Dioxide. To a solution of 1,1-di(2-pyridyl)ethanol (3.12 g, 15.6 mmol) in CH_2Cl_2 (50 mL) was added *m*-CPBA (7.07 g 80%, 32.8 mmol) in portions. After 10 d at ambient temperature, additional CH_2Cl_2 (50 mL) was added, and the reaction was terminated by bubbling NH_3 (g) through the reaction mixture for a few min. The ammonium salt which formed was filtered and the filtrate dried. Evaporation of the solvent and thorough drying gave 3.12 g (86%) of the desired bis-*N*-oxide: ^1H NMR (200 MHz) δ 2.10 (s, 3H, CH_3), 7.21 (td, 2H, J = 7 and 2 Hz, 5-pyridyl), 7.44 (td, 2H, J = 7 and 2 Hz, 4-pyridyl), 7.97 (dd, 2H, J = 7 and 2 Hz, 6-pyridyl), 8.00 (dd, 2H, J = 7 and 2 Hz, 3-pyridyl), 8.35 (s, 1H, OH).

(4a). To a solution of the above bis-*N*-oxide (3.12 g, 13.4 mmol) in CH_2Cl_2 (35 mL) was added *N,N*-dimethylcarbamoyl chloride (2.52 mL, 26.9 mmol) and after 2.5 h, trimethylsilyl cyanide (4.41 mL, 32.2 mmol) was added. After 16 d of stirring at ambient temperature, the reaction was terminated by the addition of saturated aqueous NH_4Cl (10 mL) and H_2O (25 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were dried ($MgSO_4$). Evaporation of the solvent gave 4.37 g (99%) of the

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(17) Feller, M. C.; Robson, R. *Aust. J. Chem.* **1970**, *23*, 1997.
(18) Newkome, G. R.; Taylor, H. C. R.; Fronczek, F. R.; Gupta, V. K. *Inorg. Chem.* **1986**, *25*, 1149.
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silylated alcohol 1,1-bis(6-cyano-2-pyridyl)-1-[(trimethylsilyl)oxy]ethane. This compound was desilylated by recrystallization from EtOH/H_2O, to yield 2.5 g (75%) of the desired alcohol **4a**: ^{1}H NMR (200 MHz) δ 1.97 (s, 3H, CH_3), 5.84 (s, 1H, OH), 7.61 (dd, 2H, J = 7.6 and 1 Hz, 5-pyridyl), 7.88 (dd, 2H, J = 8.1 and 7.6 Hz, 4-pyridyl), 8.13 (dd, 2H, J = 8.1 and 1 Hz, 3-pyridyl); ^{13}C NMR (62.9 MHz) δ 29.5, 76.3, 117.0, 124.6, 127.2, 131.7, 138.2, 165.4.

1,1-Bis(6-cyano-2-pyridyl)-1-(2-picolinoxy)ethane (6a). A suspension of sodium hydride (244 mg, 80%, 8.12 mmol) in DMSO (5 mL) was added to a solution of 1,1-bis(6-cyano-2-pyridyl)-ethanol (**4a**, 1.00 g, 4.0 mmol) in DMSO (5 mL) under nitrogen at ambient temperature. After 3 h, when the evolution of hydrogen gas had ceased, the resulting dark brown solution was transferred to a solution of 2-picolyl chloride (**5**, 1.05 g, 8.21 mmol) in DMSO (5 mL). The reaction mixture was stirred at ambient temperature for 3.5 d, and the reaction was terminated by the addition of saturated aqueous NH_4Cl (40 mL). Extraction with CH_2Cl_2 (4 × 40 mL) followed by washing of the organic phase with saturated aqueous NH_4Cl (40 mL), drying ($MgSO_4$), and evaporation of the solvent gave a crude product which was chromatographed (column 2 × 14 cm) with EtOAc:petroleum ether 1:1 (600 mL) to give 529 mg (39%) of **6a**: R_f 0.35 (EtOAc); ^{1}H NMR (200 MHz) δ 2.15 (s, 3H, CH_3), 4.55 (s, 2H, CH_2), 7.21 (ddd, 1H, J = 7.5, 4.9, and 1.3 Hz, 5-picolyl), 7.59 (dd, 2H, J = 7.2 and 1.4 Hz, 5-pyridyl), 7.59 (dd hidden, 1H, J = 7.5 and 1.3 Hz, 3-picolyl), 7.75 (td, 1H, J = 7.5 and 1.8 Hz, 4-picolyl), 7.84 (dd, 2H, J = 8.1 and 7.2 Hz, 4-pyridyl), 7.92 (dd, 2H, J = 8.1 and 1.4 Hz, 3-pyridyl), 8.52 (ddd, 1H, J = 4.9, 1.8 and 1.0 Hz, 6-picolyl).

1,1-Bis(6-carboxy-2-pyridyl)-1-(2-picolinoxy)ethane (1a). 1,1-Bis(6-cyano-2-pyridyl)-1-(2-picolinoxy)ethane (**6a**, 485 mg, 1.42 mmol) was dissolved in EtOH/H_2O (6:1, 28 mL). KOH (832 mg, 14.8 mmol) was added and the reaction mixture was refluxed for 16 h. After the mixture had cooled, the pH was adjusted to 4 with 1 M HCl. Extraction with CH_2Cl_2 (3 × 50 mL), drying ($MgSO_4$), and evaporation of the solvent gave 273 mg of product. Further continuous extraction at pH = 5 gave another 60 mg of product. Total yield: 333 mg (64%) of **1a**. The product was purified by recrystallization from EtOH to give white crystals: mp 105 °C; ^{1}H NMR (400 MHz) δ 2.24 (s, 3H, CH_3), 4.66 (s, 2H, CH_2), 7.32 (ddd, 1H, J = 7.7, 5.0 and 1.1 Hz, 5-picolyl), 7.49 (br d, 1H, J = 7.7 Hz, 3-picolyl), 7.6 (br, 2H, COOH), 7.79 (td, 1H, J = 7.7 and 1.8 Hz, 4-picolyl), 7.88 (dd, 2H, J = 8.0 and 1.1 Hz, 3-pyridyl), 7.95 (dd, 2H, J = 8.0 and 7.5 Hz, 4-pyridyl), 8.14 (dd, 2H, J = 7.5 and 1.1 Hz, 5-pyridyl), 8.68 (ddd, 1H, J = 5.0, 1.8 and 0.9 Hz, 6-picolyl); ^{13}C NMR (100.6 MHz) δ 23.7, 67.6, 82.8, 122.9, 123.0, 123.3, 126.0, 137.4, 139.3, 145.6, 149.5, 156.8, 161.5, 164.3. Anal. Calcd for $C_{20}H_{17}N_3O_5 \cdot H_2O$: C, 60.45; H, 4.82; N, 10.57. Found: C, 60.18; H, 4.93; N, 10.42.

1,1-Bis(6-carboxy-2-pyridyl)-1-(2-picolinoxy)propane (1b). This ligand was prepared in a manner analogous to that of **1a**, starting from 1,1-bis(6-cyano-2-pyridyl)propanol (**4b**). Reaction of **4b** with 2-picolyl chloride (**5**) gave 1,1-bis(6-cyano-2-pyridyl)-1-(2-picolinoxy)propane (**6b**, 72%) which was hydrolyzed to **1b** (86%). The product was recrystallized from EtOH to give white crystals: mp 210 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.64 (t, 3H, J = 7.3 Hz, CH_3), 2.83 (q, 2H, J = 7.3 Hz, CH_2CH_3), 4.31 (s, 2H, CH_2O), 7.29 (dd, 1H, J = 7.0 and 4.9 Hz, 5-picolyl), 7.70 (d, 1H, J = 7.8 Hz, 3-picolyl), 7.83 (dd, 2H, J = 7.7 and 1.1 Hz, 3-pyridyl), 7.83 (dd hidden, 1H, J = 7.8 and 7.0 Hz, 4-picolyl), 7.91 (dd, 2H, J = 7.7 and 1.1 Hz, 5-pyridyl), 7.96 (t, 2H, J = 7.7 Hz, 4-pyridyl), 8.46 (d, 1H, J = 4.9 Hz, 6-picolyl); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 7.0, 25.0, 65.5, 85.6, 121.4, 122.6, 123.3, 125.2, 136.8, 137.9, 147.3, 148.6, 157.8, 162.0, 165.9. Anal. Calcd for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 63.95; H, 4.86; N, 10.59.

5-Chloro-3-oxo-1-(3-picolinoxy)pentane (14).[11] To a suspension of sodium hydride (750 mg, 80%, 25 mmol) in DMSO (20 mL) was added (3-pyridyl)methanol (**13**, 2.18 g, 20 mmol) in DMSO (5 mL) under nitrogen at ambient temperature. After 20 min, bis(2-chloroethyl) ether (**10**, 5.72 g, 40 mmol) was added to the dark blue alkoxide solution. The reaction was terminated after 5 d by the addition of H_2O (40 mL), followed by extraction with CH_2Cl_2 (3 × 50 mL). The organic phase was washed with H_2O (50 mL) and dried ($MgSO_4$) and the solvent was evaporated. The crude product was chromatographed (column 4 × 15 cm) with EtOAc/EtOH (9:1 and 4:1, 250 mL of each) to yield 980 mg (23%) of **14** as a pale yellow oil: R_f 0.2 (EtOAc); ^{1}H NMR (250 MHz) δ 3.62–3.79 (m, 8H), 4.59 (s, 2H, CH_2-py), 7.28 (ddd, 1H, J = 7.8, 4.8, and 0.6 Hz, 5-pyridyl), 7.70 (ddd, 1H, J = 7.8, 2.2, and 1.7 Hz, 4-pyridyl), 8.54 (dd, 1H, J = 4.8 and 1.7 Hz, 6-pyridyl), 8.58 (dd, 1H, J = 2.2 and 0.6 Hz, 2-pyridyl); ^{13}C NMR (62.9 MHz) δ 42.6, 69.6, 70.5, 70.6, 71.2, 123.2, 133.4, 135.3, 147.0.

2,2-Bis(6-cyano-2-pyridyl)-3,5-dioxo-8-(3-picolinoxy)octane (15). To a suspension of sodium hydride (63 mg, 80%, 2.09 mmol) in DMSO (6 mL) was added 1,1-bis(6-cyano-2-pyridyl)-ethanol (**4a**, 418 mg, 1.67 mmol) dissolved in DMSO (5 mL). When the hydrogen gas evolution had ceased after approximately 30 min, **14** (720 mg, 3.34 mmol) was added. The reaction was quenched after 4 d at ambient temperature by the addition of saturated aqueous NH_4Cl (40 mL), extracted with CH_2Cl_2 (3 × 50 mL), washed with saturated aqueous NH_4Cl (70 mL), and dried ($MgSO_4$). Evaporation of the solvent gave a crude product mixture which after chromatography (column 2.5 × 10 cm, eluent: 800 mL of EtOAc) yielded 121 mg of **15** (17%) as a pale yellow oil: R_f 0.1 (EtOAc); ^{1}H NMR (250 MHz) δ 2.01 (s, 3H, CH_3), 3.48 (t, 2H, J = 4.9 Hz, CH_2), 3.65–3.71 (m, 6H, CH_2), 4.58 (s, 2H, CH_2), 7.25 (dd, 1H, J = 7.8 and 4.8 Hz, 5-picolyl), 7.54 (dd, 2H, J = 7.8 and 1.3 Hz, 5-pyridyl), 7.67 (ddd, 1H, J = 7.8, 1.9 and 1.5 Hz, 4-picolyl), 7.75 (t, 2H, J = 7.8 Hz, 4-pyridyl), 7.83 (dd, 2H, J = 7.8 and 1.3 Hz, 3-pyridyl), 8.52 (dd, 1H, J = 4.8 and 1.5 Hz, 6-picolyl), 8.56 (d, 1H, J = 1.9 Hz, 2-picolyl); ^{13}C NMR (62.9 MHz) δ 22.5, 63.0, 69.9, 70.6, 70.6, 70.8, 83.2, 117.2, 123.4, 125.0, 127.2, 132.5, 133.6, 135.4, 137.5, 149.1 (2C), 164.9.

2,2-Bis(6-carboxy-2-pyridyl)-3,5-dioxo-8-(3-picolinoxy)octane (1c). To compound **15** (224 mg, 0.52 mmol) in EtOH/H_2O (6:1, 7 mL) was added KOH (290 mg, 5.2 mmol). The solution was refluxed for 24 h and after cooling the pH was adjusted to 4.5 with 1 M HCl. Extraction with CH_2Cl_2 (4 × 15 mL), drying ($MgSO_4$), and evaporation of the solvent gave 224 mg (92%) of **1c**. Recrystallization from EtOAc gave pale yellow crystals: mp 101–103 °C; ^{1}H NMR (400 MHz) δ 2.12 (s, 3H, CH_3), 3.58–3.78 (m, 8H, CH_2), 4.62 (s, 2H, CH_2), 6.25 (br, 2H, OH), 7.31 (ddd, 1H, J = 7.8, 4.9, and 0.7 Hz, 5-picolyl), 7.73 (br d, 1H, J = 7.8 Hz, 4-picolyl) 7.86–7.91 (m, 4H, 4- and 5-pyridyl), 8.08 (dd, 2H, J = 6.3 and 2.5 Hz, 3-pyridyl), 8.55 (dd, 1H, J = 4.9 and 1.6 Hz, 6-picolyl), 8.62 (dd, 1H, J = 2.2 and 0.7 Hz, 2-picolyl); ^{13}C NMR (100.6 MHz) δ 22.92, 63.42, 70.06, 70.74, 70.80, 82.46, 102.19, 122.85, 123.74, 125.57, 134.00, 136.18, 139.06, 145.74, 148.41, 148.46, 162.06, 164.52. Anal. Calcd for $C_{24}H_{25}N_3O_7 \cdot H_2O$: C, 59.38; H, 5.61; N, 8.66. Found: C, 59.39; H, 5.50; N, 8.65.

1,1-Di(2-pyridyl)-1-[3-[(*tert*-butyldimethylsilyl)oxy]-phenyl]methanol (22). A Grignard reagent (**21**) was prepared from freshly distilled 3-[(*tert*-butyldimethylsilyl)oxy]-1-bromobenzene (4.68 g, 16.3 mmol) and magnesium (467 mg, 19.6 mmol) in THF (30 mL). 1,2-Dibromoethane (250 μL) was added as an initiator. 2,2-Dipyridyl ketone (**3**, 3.0 g, 16.3 mmol) in THF (20 mL) was added to the Grignard reagent, and the resulting dark blue solution was stirred at ambient temperature for 16 h. The reaction was terminated by the addition of 10% aqueous $NaHCO_3$ (25 mL), THF was evaporated, and the water phase was extracted with CH_2Cl_2 (3 × 50 mL). Drying ($MgSO_4$) and evaporation of the solvent gave a crude product, which after chromatography (column 5 × 10 cm, eluent: 400 mL hexane:EtOAc 9:1 and 400 mL of hexane:EtOAc 1:1) yielded 4.73 g (74%) of **22** as white crystals: mp 87 °C; R_f 0.44 (EtOAc); ^{1}H NMR (250 MHz) δ 0.09 (s, 6H, CH_3), 0.90 (s, 9H, CH_3), 6.72 (dd, 1H, J = 7.8 and 2.0 Hz, 4- or 6-phenyl), 6.76 (d, 1H, J = 2.0 Hz, 2-phenyl), 6.85 (br, 1H, OH), 6.87 (d, 1H, J = 7.8 Hz, 4- or 6-phenyl), 7.13 (t, 1H, J = 7.8 Hz, 5-phenyl), 7.19 (ddd, 2H, J = 7.5, 4.9 and 1.3 Hz, 5-pyridyl), 7.68 (td, 2H, J = 7.5 and 1.8 Hz, 4-pyridyl), 7.77 (br d, 2H, J = 7.5 Hz, 3-pyridyl), 8.53 (br d, 2H, J = 4.9 Hz, 6-pyridyl).

1,1-Di(2-pyridyl)-1-methoxy-1-[3-[(*tert*-butyldimethylsilyl)oxy]phenyl]methane (23). To a suspension of sodium hydride (434 mg, 14.5 mmol) in THF (10 mL) was added a solution of the alcohol **22** (4.73 g, 12.1 mmol) in THF (40 mL). After 1 h at ambient temperature, methyl iodide (900 μL, 14.5 mmol) was added and after a further 15 h, the reaction was quenched by the addition of 10% aqueous $NaHCO_3$ (30 mL). THF was evaporated and the resulting water phase was extracted with CH_2Cl_2 (3 × 25 mL). The organic phase was dried ($MgSO_4$) and

the solvent was evaporated. The crude product was purified by chromatography (column 5 × 10 cm) with EtOAc (600 mL) as eluent to give 3.51 g (71%) of **23** as a pale yellow oil: R_f 0.62 (EtOAc); ^{1}H NMR (250 MHz) δ 0.11 (s, 6H, CH_3), 0.92 (s, 9H, CH_3), 3.20 (s, 3H, OCH_3), 6.73 (d, 1H, J = 7.6 Hz, 4- or 6-phenyl), 6.95 (t, 1H, J = 2 Hz, 2-phenyl), 7.09–7.20 (m, 4H, 4- or 6-phenyl, 5-phenyl and 5-pyridyl), 7.65 (m, 4H, 3- and 4-pyridyl), 8.58 (d, 2H, J = 4.8 Hz, 6-pyridyl); ^{13}C NMR (100.6 MHz) δ −4.5, 18.1, 25.7, 52.8, 87.6, 119.1, 121.1, 121.9, 122.1, 123.2, 128.5, 136.1, 143.3, 148.4, 155.0, 162.3.

1,1-Bis(6-cyano-2-pyridyl)-1-methoxy-1-[3-[(*tert*-butyldimethylsilyl)oxy]phenyl]methane (24). To compound **23** (3.51 g, 8.62 mmol) in CH_2Cl_2 (100 mL) was added *m*-CPBA (4.83 g, 22.4 mmol) in portions. After 2 d stirring at ambient temperature, another portion of CH_2Cl_2 (150 mL) was added and NH_3 (g) was bubbled through the solution for 5 min. The ammonium salt formed was filtered and the filtrate dried ($MgSO_4$). Evaporation of the solvent gave 3.26 g (86%) of 1,1-di(2-pyridyl)-1-methoxy-1-[3-[(*tert*-butyldimethylsilyl)oxy]-phenyl]methane *N,N'*-dioxide. To a solution of the bis-*N*-oxide (3.26 g, 7.4 mmol) in CH_2Cl_2 (70 mL) was added *N,N*-dimethylcarbamoyl chloride (2.04 mL, 22.3 mmol), followed after 4 h by trimethylsilyl cyanide (3.0 mL, 22.3 mmol). The reaction mixture was stirred at ambient temperature for 2 d, refluxed for 24 h, and then another addition of *N,N*-dimethylcarbamoyl chloride (0.68 mL, 7.4 mmol) and trimethylsilyl cyanide (1 mL, 7.4 mmol) was made. After 7 d, the reaction was terminated by the addition of 10% aqueous $NaHCO_3$ (20 mL), the mixture extracted with CH_2Cl_2 (3 × 25 mL), and the organic phase dried ($MgSO_4$). Evaporation of the solvent gave a crude product which was chromatographed (column 5 × 10 cm) with hexane:EtOAc 9:1 (600 mL) and hexane:EtOAc 1:1 (400 mL) as eluent, to yield 2.34 g (69%) of compound **24** as white crystals: mp 126 °C; R_f 0.7 (EtOAc); ^{1}H NMR (250 MHz) δ 0.14 (s, 6H, CH_3), 0.94 (s, 9H, CH_3), 3.20 (s, 3H, OCH_3), 6.79 (ddd, 1H, J = 7.9, 2.5 and 1.0 Hz, 4- or 6-phenyl), 6.87 (br d, 1H, J = 2.5 Hz, 2-phenyl), 7.00 (ddd, 1H, J = 7.9, 1.7 and 1.0 Hz, 4- or 6-phenyl), 7.20 (t, 1H, J = 7.9 Hz, 5-phenyl), 7.60 (dd, 2H, J = 7.7 and 1.4 Hz, 5-pyridyl), 7.83 (t, 2H, J = 7.7 Hz, 4-pyridyl), 7.90 (dd, 2H, J = 7.7 and 1.4 Hz, 3-pyridyl); ^{13}C NMR (100.6 MHz) δ −4.4, 18.2, 25.6, 53.2, 87.3, 117.1, 119.9, 120.8, 121.2, 126.8, 127.1, 129.0, 132.5, 137.1, 141.4, 155.4, 163.8.

1,1-Bis(6-cyano-2-pyridyl)-1-methoxy-1-(3-hydroxyphenyl)-methane (25). The protected phenol **24** was dissolved in 1% HCl in EtOH (10 mL) and left with stirring at ambient temperature for 17 h. The solvent was evaporated, saturated aqueous Na_2CO_3 was added to the residue to attain pH = 8.5, and the water phase was extracted with CH_2Cl_2 (3 × 15 mL). Drying ($MgSO_4$) and evaporation of the solvent gave 370 mg (99%) of the phenol **25** as a yellow oil: ^{1}H NMR (250 MHz) δ 3.20 (s, 3H, OCH_3), 5.40 (br, 1H, OH), 6.78 (ddd, 1H, J = 7.9, 2.5 and 1.0 Hz, 4- or 6-phenyl), 6.92 (br d, 1H, J = 2.5 Hz, 2-phenyl), 6.96 (br d, 1H, J = 7.9 Hz, 4- or 6-phenyl), 7.21 (t, 1H, J = 7.9 Hz, 5-phenyl), 7.60 (dd, 2H, J = 7.7 and 1.4 Hz, 5-pyridyl), 7.83 (t, 2H, J = 7.7 Hz, 4-pyridyl), 7.90 (dd, 2H, J = 7.7 and 1.4 Hz, 3-pyridyl); ^{13}C NMR (100.6 MHz) δ 53.2, 87.2, 115.1, 115.7, 117.1, 120.9, 126.9, 127.2, 129.4, 132.5, 137.3, 141.9, 155.5, 163.6.

1,1-Bis(6-cyano-2-pyridyl)-1-methoxy-1-(3-picolinoxyphenyl)methane (26). To the phenol **25** (500 mg, 1.45 mmol) in DMF (11 mL) was added potassium carbonate (6 g, 43.6 mmol) and 3-picolyl chloride hydrochloride (238 mg, 1.45 mmol). After 19 h at ambient temperature, the reaction was terminated by the addition of H_2O (10 mL). Extraction with CH_2Cl_2 (3 × 25 mL), drying ($MgSO_4$) of the organic phase, and evaporation of the solvent gave a crude product mixture. Chromatography (column 2 × 12 cm) with EtOAc (270 mL) gave 544 mg (86%) of **26** as a pale yellow oil: R_f 0.3 (EtOAc); ^{1}H NMR (250 MHz) δ 3.18 (s, 3H, OCH_3), 5.04 (s, 2H, CH_2), 6.91 (ddd, 1H, J = 8.2, 2.5, and 1.0 Hz, 4- or 6-phenyl), 7.01–7.08 (m, 2H, 2- and 4- or 6-phenyl), 7.24–7.34 (m, 2H, 5-phenyl and 5-picolyl), 7.59 (dd, 2H, J = 7.5 and 2.0 Hz, 5-pyridyl), 7.75 (td, 1H, J = 7.9 and 2.0 Hz, 4-picolyl), 7.82 (t, 2H, J = 7.5 Hz, 4-pyridyl), 7.86 (dd, 2H, J = 7.5 and 2.0 Hz, 3-pyridyl), 8.57 (dd, 1H, J = 4.8 and 2.0 Hz, 6-picolyl), 8.64 (d, 1H, J = 2.0 Hz, 2-picolyl); ^{13}C NMR (100.6 MHz) δ 53.2, 67.5, 87.3, 114.2, 115.4, 117.2, 121.7, 123.8, 126.8, 127.2, 129.3, 132.6, 132.6, 136.0, 137.3, 141.9, 148.2, 148.7, 158.0, 163.6.

1,1-Bis(6-carboxy-2-pyridyl)-1-methoxy-1-(3-picolinoxyphenyl)methane (1d). To the dinitrile **26** (85 mg, 0.2 mmol) in EtOH/H_2O (6:1, 8 mL) was added KOH (109 mg, 1.95 mmol) and the solution was refluxed for 20 h. When the reaction mixture had cooled it was diluted with H_2O and the pH was adjusted to 5.5 with 1 M HCl. Extraction with CH_2Cl_2 (3 × 25 mL), adjustment of pH to 5, and further extraction with CH_2Cl_2 (2 × 25 mL) yielded, after drying ($MgSO_4$) and evaporation of the solvent, 69 mg (80%) of **1d**. The product was recrystallized from EtOH to give white crystals: mp 189 °C; ^{1}H NMR (400 MHz) for **1d** δ 3.18 (s, 3H, CH_3), 5.06 (s, 2H, CH_2), 6.92 (ddd, 1H, J = 8.0, 2.4, and 0.9 Hz, 4- or 6-phenyl), 7.05 (ddd, 1H, J = 8.0, 1.7, and 0.9 Hz, 4- or 6-phenyl), 7.12 (br s, 1H, 2-phenyl), 7.29 (t, 1H, J = 8.0 Hz, 5-phenyl), 7.36 (dd, 1H, J = 7.9 and 4.9 Hz, 5-picolyl), 7.7–8.2 (br, 2H, OH), 7.81 (br d, 1H, J = 7.9 Hz, 4-picolyl), 7.91 (dd, 2H, J = 7.7 and 1.2 Hz, 5-pyridyl), 7.97 (t, 2H, J = 7.7 Hz, 4-pyridyl), 8.13 (dd, 2H, J = 7.7 and 1.2 Hz, 3-pyridyl), 8.58 (dd, 1H, J = 4.9 and 1.6 Hz, 6-picolyl), 8.67 (d, 1H, J = 1.9 Hz, 2-picolyl); ^{13}C NMR (100.6 MHz) for **1d** δ 53.1, 67.5, 87.1, 114.3, 115.7, 121.7, 122.9, 124.0, 127.1, 129.4, 133.0, 136.4, 139.0, 142.0, 145.6, 147.8, 148.4, 158.1, 160.7, 164.2. Anal. Calcd for $C_{26}H_{21}N_3O_6$: C, 66.24; H, 4.49; N, 8.91. Found: C, 66.01; H, 4.82; N, 8.74.

Preparation of Metal Complexes. General method for the preparation of Cu(II) complexes of ligands **1a–d**. To the ligand in EtOH (2 mL) was added an aqueous solution of the metal acetate (1 equiv). The solutions turned bright blue and the complexes precipitated when left standing. The complexes were purified by recrystallization from MeCN (Cu**1a**-H_2 and Cu**1b**-H_2) and EtOH (Cu**1c**-H_2 and Cu**1d**-H_2). Anal. Calcd for Cu**1b**·H_2O-H_2, $C_{21}H_{17}N_3O_5Cu·H_2O$: C, 53.33; H, 4.05; N, 8.88. Found: C, 53.05; H, 4.02; N, 8.77. Anal. Calcd for Cu**1d**·$0.5H_2O$-H_2, $[C_{26}H_{19}N_3O_6Cu]_2·H_2O$: C, 57.62; H, 3.72; N, 7.75. Found: C, 57.46; H, 3.82; N, 7.84.

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Supplementary Material Available: Experimental procedure for the preparation of compounds **8**, **9**, **10a**, **11**, **12**, **17b**, **18b**, **19**, and **20**, characterization of compound **6b**, and ^{1}H and ^{13}C NMR spectra of compounds **1a–d** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.