

Shape-Selective Oxidation of Benzylic Alcohols by a Receptor Functionalized with a Dicopper(II) Pyrazole Complex

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Abstract: A novel metallohost containing a substrate-binding site and two copper ions held by two bis-pyrazole ligand sets is described. The cavity of this molecule can bind dihydroxybenzene guests (association constants in chloroform are in the range $K_a = 2000\text{--}3000\text{ M}^{-1}$). In the presence of benzylic alcohols the Cu(II) centers of the metallohost are reduced to Cu(I). During this process the alcohols are oxidized to aldehydes. Benzylic alcohols possessing phenolic hydroxyl functions are extremely effective in the reduction reaction. It is believed that they are bound in the cavity of the metallohost and are oriented in the correct position with respect to the copper centers. This results in a rate enhancement of at least 4 orders of magnitude for the oxidation reaction.

Introduction

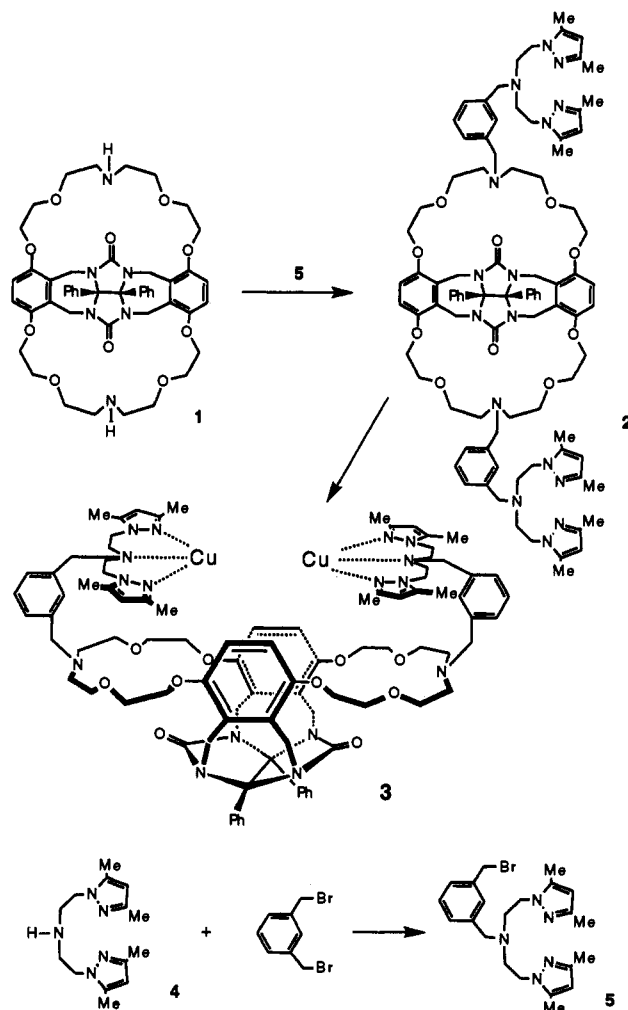
An important theme in the field of homogeneous catalysis is the development of catalysts that display shape selectivity. An enzyme achieves this selectivity by a process of molecular recognition: out of a mixture of substrate molecules one is selected because it has a shape complementary to the pocket of the enzyme. By a multipoint interaction the substrate is bound and oriented in the correct position with respect to a nearby catalytic center. After reaction the enzyme is regenerated because the binding pocket has a lower affinity for the product than for the substrate.

The challenge of mimicking the selectivity of enzymes poses numerous problems to the chemist. A substrate usually possesses diverging binding sites.¹ The enzyme mimic must therefore be a concave molecule with converging binding sites. A molecule that has these properties is receptor molecule **1** (see Scheme 1), which was developed in our group.² It is based on the building block diphenylglycoluril and has the capability of binding neutral molecules. Extensive work has shown that a wide variety of dihydroxybenzenes and other guest molecules can be bound in the cavity of **1** through hydrogen bonding with the carbonyl units of the receptor and $\pi\text{-}\pi$ stacking interactions with the receptor walls.³⁻⁵ In this paper, we describe a derivative of **1** which is functionalized with two bis-pyrazole type of ligands (compound **2**). The ligand arms of **2** can coordinate to two copper centers, yielding a dinuclear metallohost (**3**). We report that this metallohost displays high selectivity in the oxidation of benzylic alcohols.

Results and Discussion

The synthesis of receptor **2** is outlined in Scheme 1. It involves the reaction of **1**⁶ with ligand **5**,⁷ which is easily accessible from **4**. After purification **2** was obtained in 55% yield. The

Scheme 1



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(1) Kyba, E. P.; Helgeson, R. C.; Madan, K.; Gokel, G. W.; Tarnowski, T. L.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 2564.

(2) Smeets, J. W. H.; Sijbesma, R. P.; Niele, F. G. M.; Spek, A. L.; Smeets, W. J. J.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1987**, *109*, 928.

(3) Sijbesma, R. P. Ph.D. Thesis, University of Nijmegen, 1992.

(4) Sijbesma, R. P.; Nolte, R. J. M. *J. Org. Chem.* **1991**, *56*, 3122.

(5) Sijbesma, R. P.; Kentgens, A. P. M.; Nolte, R. J. M. *J. Org. Chem.* **1991**, *56*, 3199.

(6) Smeets, J. W. H.; Sijbesma, R. P.; van Dalen, L.; Spek, A. L.; Smeets, W. J. J.; Nolte, R. J. M. *J. Org. Chem.* **1989**, *54*, 3710.

(7) Martens, C. F.; Schenning, A. P. H. J.; Klein Gebbink, R. J. M.; Feiters, M. C.; van der Linden, J. G. M.; Heck, J.; Nolte, R. J. M. *J. Chem. Soc., Chem. Commun.* **1993**, 88.

preparation of the dinuclear copper(I) and copper(II) complexes of **2** was achieved by reacting the ligands with 2 molar equiv of the appropriate copper salt. For the copper(I) complex **3a**, this salt was $[\text{Cu(I)}(\text{CH}_3\text{CN})_4]\text{PF}_6$,⁸ and for the Cu(II) complex **3b**,

(8) Kubas, G. J. *Inorg. Synth.* **1979**, *19*, 90.

Table 1. Rate Constants for the Oxidation of Various Benzylic Alcohols by $[\text{Cu}(\text{II})_2\cdot 2](\text{ClO}_4)_4^a$

| alcohol | k_1 ($\text{s}^{-1} \times 10^4$) | K |
|-----------------------------|---------------------------------------|--------------------|
| benzyl alcohol | 2.62 | 2.24 |
| 4-methylbenzyl alcohol | 1.03 | 1.45 |
| 4-fluorobenzyl alcohol | 1.93 | 2.14 |
| 4-chlorobenzyl alcohol | 1.98 | 2.08 |
| 4-bromobenzyl alcohol | 1.48 | 0.98 |
| 4-nitrobenzyl alcohol | 2.50 | 3.23 |
| 4-methoxybenzyl alcohol | 0.785 | 0.66 |
| 3,5-dimethoxybenzyl alcohol | 0.772 | 0.80 |
| 3-methoxybenzyl alcohol | 0.252 | 1.69 |
| 3-hydroxybenzyl alcohol | 47 800 ^b | 7.74 ^b |
| 3,5-dihydroxybenzyl alcohol | >47 800 ^c | >7.74 ^c |

^a Solvent acetonitrile, $T = 30^\circ\text{C}$; estimated error 10%. ^b Calculated from measurements at $T = -30^\circ\text{C}$. ^c Estimated value at -30°C .

the salt was $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$. Complex formation was rapid in all cases, and the products were isolated as yellow (Cu(I)) or green (Cu(II)) powders. The dinuclear Cu(I) complexes display sharp ^1H NMR spectra, as expected for d^{10} species. The ^1H NMR signals of the ligating parts of the molecules are slightly shifted compared to their positions in the free ligand.

In order to get an impression of the binding properties of the free ligand receptor **2** as compared to those of **1**, ^1H NMR titration experiments were carried out in CDCl_3 with resorcinol and floroglucinol (1,3,5-trihydroxybenzene) as the guests molecules. The data were analyzed with a computer program.³ Good fits were obtained assuming 1:1 complexation. In the case of floroglucinol it was necessary to add a small amount of acetonitrile in order to ensure the complete dissolution of the substrate. The association constants for resorcinol and floroglucinol were determined to be $K_a = 2000(\pm 300)$ and $3500(\pm 400) \text{ M}^{-1}$, respectively. These K_a values are similar to those reported previously for **1**,⁴ indicating that the ligand arms have no effect on the binding process.

We have reported recently that dinuclear Cu(II) complexes with certain pyrazole ligands can undergo reduction to their dinuclear Cu(I) complexes in the presence of a suitable reductant such as methanol, which is oxidized to formaldehyde.⁵ Since receptor **2** is designed to bind hydroxybenzenes, we tested benzyl alcohol, 3-hydroxybenzyl alcohol, and 3,5-dihydroxybenzyl alcohol as substrates in the oxidation-reduction reaction. All three compounds were found to induce the reduction of the Cu(II) complex **3b**, as was evident by the loss of color in the reaction mixture (indicative of Cu(I)). The formation of benzaldehyde, 3-hydroxybenzaldehyde, and 3,5-dihydroxybenzaldehyde as the oxidation products was confirmed by HPLC and by comparison with authentic samples. Besides the aldehydes, small amounts of the carboxylic acids were also detected. The formation of these acids might be the result of a rapid autoxidation of the aldehyde. To test this, the reactions were carried out under strictly anaerobic conditions and under the exclusion of light. The formation of carboxylic acids was almost completely suppressed, indicating that it is indeed the result of an autoxidation process under aerobic conditions.

We observed that the rates of oxidation of 3-hydroxybenzyl alcohol and 3,5-dihydroxybenzyl alcohol were much faster than the rate of oxidation of benzyl alcohol itself. In order to examine whether this difference is due to a substituent effect or not, a large number of benzylic alcohols were tested as substrates. The alcohol was added to an acetonitrile solution of the dinuclear Cu(II) complex **3b**, and the decrease in the d-d transition of the Cu(II) complex at 700 nm was measured as a function of time at 30°C . The reaction obeyed first-order equilibrium kinetics, in correspondence with our previous studies on Cu(II)-pyrazole systems (see Experimental Section).⁷ The results are presented in Table 1. The oxidation of 3-hydroxybenzyl alcohol could only be accurately determined at -30°C . At this temperature the oxidation of 3,5-dihydroxybenzyl alcohol was still too fast to be

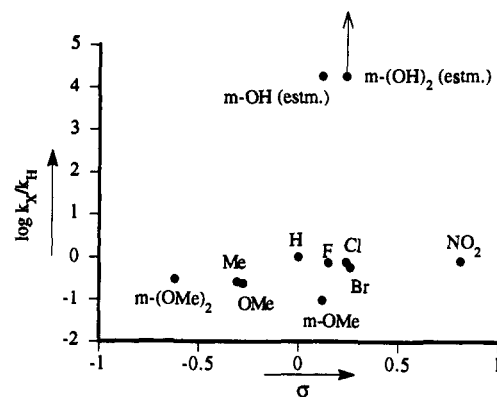


Figure 1. Hammett plot for the oxidation of benzylic alcohols with $[\text{Cu}(\text{II})_2\cdot 2](\text{ClO}_4)_4$ ($T = 30^\circ\text{C}$, except for $m\text{-OH}$ ($T = -30^\circ\text{C}$)).

to measured. Consequently, no exact value can be given, but the conclusion that the rate constant is substantially higher than that of 3-hydroxybenzyl alcohol is justified. The kinetic data from Table 1 are represented as a Hammett plot in Figure 1. As is clear from this plot, the higher rates of reduction of the substrates with OH substituents cannot be explained on the basis of inductive or field effects of the substituent. The kinetic data suggest that metallohost **3b** is capable of selecting substrates for oxidation by the two copper(II) centers. Substrates with a shape complementary to that of the binding site are oxidized at least 4 orders of magnitude faster than substrates which do not have this shape complement. This result is surprising, since it is known that receptors of type **1** have lower binding affinities for dihydroxybenzenes in acetonitrile than in chloroform.^{4,9} Indeed it could be shown by NMR titrations that for **2** binding constants of hydroxy-substituted benzenes also drop by a factor of 20, when going from pure CDCl_3 to 10% $\text{CD}_3\text{CN}/\text{CDCl}_3$ (e.g. for resorcinol $K_a = 109 \pm 15 \text{ M}^{-1}$) whereas in pure CD_3CN only a weak binding ($K_a < 50 \text{ M}^{-1}$) could be observed. The addition of several equivalents of 3,5-dihydroxybenzyl alcohol to a CD_3CN solution of **3a** did not result in large shifts for the aromatic protons of the host and guest. However, an overall sharpening of the signals occurred and the peak patterns became less complex, with the exception of the aromatic wall protons of the host and the methylene signal of the guest, which displayed a broadening, the latter probably due to coordination of the benzylic alcohol function to the Cu(I) centers. This broadening may result from a process in which the guest changes position, i.e. in and out of the cavity, while still being bound to the metal centers with its benzylic alcohol function. Upon addition of a benzyl alcohol without hydroxy substituents, no sharpening of the host and guest signals occurred and no broadening of the aromatic wall protons was visible. On the other hand, the addition of resorcinol to **3a** in CD_3CN did have these effects. These combined observations are suggestive of a multipoint binding interaction of hydroxybenzyl alcohols in metallohosts **3**. Attempts to determine binding constants in acetonitrile by means of a UV-vis titration were unsuccessful, due to overlap of host and guest absorption bands.

In principle, our mono- and dihydroxy-substituted benzyl alcohol guests can form phenolate complexes with **3**. In the literature a number of such complexes have been described with both pyrazole^{10,11} and pyridine¹²⁻¹⁴ types of ligands. They are characterized by a rather intense phenolate to copper charge-

(9) Reek, J. H. N.; Nolte, R. J. M. To be published.

(10) Sorrell, T. N.; Vankai, V. A. *Inorg. Chem.* **1990**, *29*, 1687.

(11) Sorrell, T. N.; Malachowski, M. R.; Jameson, D. L. *Inorg. Chem.* **1982**, *21*, 3250.

(12) Karlin, K. D.; Hayes, J. C.; Hutchinson, J. P.; Zubieta, J. J. *Chem. Soc., Chem. Commun.* **1983**, 376.

(13) Karlin, K. D.; Farooq, A.; Hayes, J. C.; Cohen, B. I.; Rowe, T. M.; Sinn, E.; Zubieta, J. *Inorg. Chem.* **1987**, *26*, 1271.

(14) Pyrz, J. W.; Karlin, K. D.; Sorrell, T. N.; Vogel, G. C.; Que, L., Jr. *Inorg. Chem.* **1984**, *23*, 4581.

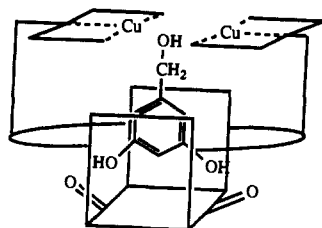
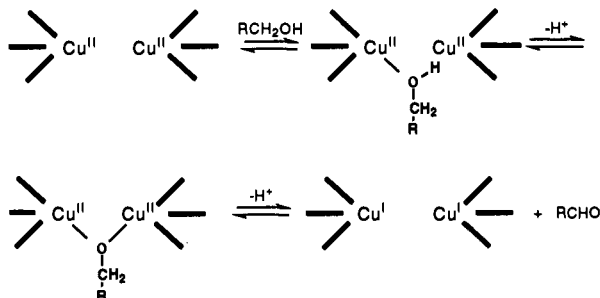


Figure 2. Proposed orientation of 3,5-dihydroxybenzyl alcohol in the cavity of $[\text{Cu}(\text{II})_2](\text{ClO}_4)_4$.

Scheme 2



transfer band around 380 nm. In order to investigate this possibility, we treated the dinuclear Cu(II) complex **3b** with phenol, 3-hydroxybenzyl alcohol, and 3,5-dihydroxybenzyl alcohol and examined the reaction products with UV-vis spectroscopy. When 1 molar equiv of phenol was added, a color change from dark green to brownish yellow was observed. This change was accompanied by the development of an intense UV-vis absorption band at 387 nm. The position of this band corresponds to that reported in the literature.¹¹⁻¹⁵ When 3-hydroxybenzyl alcohol or 3,5-dihydroxybenzyl alcohol was added to **3b**, a color change was also noted. In these cases, however, no absorption band in the 380-nm region was present. On the basis of this result we may conclude that the hydroxybenzyl alcohols are bound to the copper centers through their benzylic alcohol functions instead of through their phenolic functions (see Figure 2).

CPK models indicate that the dihydroxy-substituted benzyl alcohol molecule, while being bound in the receptor, is oriented in such a way that its alcohol function is positioned exactly between the two copper centers. Reaction with the metal center therefore is facilitated. In the case of **3b** this leads to a dinuclear, alkoxo-bridged Cu(II) complex, whose formation is the rate-limiting step in the alcohol oxidation, as we have shown previously for a similar complex without binding site (see Scheme 2).⁷ We therefore propose that the observed rate acceleration in the case of hydroxybenzyl alcohols is the result of shape-selective binding and correct positioning of these substrates in the cavity of metallohost **3b**.

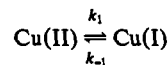
In summary, we have synthesized a novel receptor functionalized with pyrazole ligands which is capable of forming dinuclear copper complexes. The copper(II) receptor can select hydroxy-substituted benzylic alcohols and rapidly convert them into the corresponding aldehydes in a stoichiometric reaction. To our knowledge no examples of metallohosts have been reported in the literature which display rate enhancements $>5 \times 10^4$ as reported here. Current research is aimed at the development of a catalytic system which uses molecular oxygen as the oxidant.

Experimental Section

Materials and Methods. All reagents and chemicals were obtained from commercial sources. Solvents were dried and distilled prior to use. Diethyl ether was distilled from sodium; dichloromethane and acetonitrile were distilled from calcium hydride. DMF was stored over 4-Å molecular sieves and distilled at reduced pressure. Solvents used during the synthesis

or handling of the Cu(I) complexes were deoxygenated by three freeze-pump-thaw cycles. $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ was purchased from Janssen Chimica. TLC analyses were performed on Merck precoated silica gel 60 F-254 plates. R_f values for the receptor molecules were determined on silica F-254 plates that were impregnated by soaking them for a short time in a 10% aqueous solution of NaBr. Subsequently the plates were air-dried and activated overnight at 130 °C. Flash chromatography was carried out using Merck silica 60H. FAB mass spectra were recorded using 3-nitrobenzyl alcohol as a matrix. HPLC analyses were performed on a LKB HPLC apparatus, equipped with a Waters RCN 8 × 10 column using $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ (1:1, v/v) as the eluent and a pressure of 28 bar.

Oxidation of Alcohols. In a quartz cuvette 4.5 mg (2.81×10^{-3} mmol) of **2** was dissolved in 1.5 mL of acetonitrile. To this solution was added 2.1 mg (5.86×10^{-3} mmol) of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ dissolved in 0.5 mL of CH_3CN and 5 molar equiv (1.41×10^{-2} mmol) of a benzylic alcohol. The decrease in the intensity of the d-d transition at 700 nm was subsequently followed as a function of time at a temperature of 30 °C. The rate constants k_1 and k_{-1} for the reaction



follow from the equilibrium constant $K = k_1/k_{-1}$ and from $k = k_1 + k_{-1}$. The latter k is obtained by fitting absorbance (A) versus time (t) data points to the equation $A_t = (A_{t=0}/(K+1))(1 + (K \exp(-kt)))$.¹⁵ The constants presented in Table 1 are forward rate constants (k_1) and equilibrium constants (K). Simple Cu(II) salts of pyrazole, e.g. $[\text{Cu}(\text{II})_4](\text{ClO}_4)_2$, do not catalyze the oxidation of the benzylic alcohols, as we checked separately.

Product Determination. To a solution containing 25 mg (1.56×10^{-2} mmol) of **2** in 10 mL of $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ (1:1 v/v) were added under a dinitrogen atmosphere 2 molar equiv (3.11×10^{-2} mmol) of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$. Subsequently, 5 molar equiv of a benzylic alcohol was added. Product formation was followed by HPLC, and identification was carried out with the aid of authentic samples. In the case of 3,5-dihydroxybenzyl alcohol and 3,5-dihydroxybenzaldehyde, a small amount of acetone was added to the reaction mixture to ensure the complete dissolution of the substrate and the product.

α -Bromo- α' -[bis[2-(3,5-dimethyl-1-pyrazolyl)ethyl]amino]-*m*-xylene (5). This compound was synthesized according to a procedure described previously.⁵

Compound 1. This compound was prepared using a procedure published previously by us.⁶

Compound 2. To a suspension of 888 mg (1.02 mmol) of **1** in 20 mL of DMF was added 900 mg (2.03 mmol) of **5**. An excess of K_2CO_3 was used as a base for the reaction. Upon addition of **5** the originally cloudy DMF solution turned clear within 1 min. A sample taken from the crude reaction mixture showed the complete disappearance of **1** after 30 min (TLC, silica 60H, impregnated with NaBr, 10% methanol in chloroform as the eluent). The reaction was stirred at ambient temperature for 18 h. Then 50 mL of dichloromethane was added, and the organic layer was washed (2×) with brine, separated, dried (MgSO_4), and concentrated. The residue was subjected to column chromatography (silica 60H, eluent 5% methanol, 1% triethylamine, 94% chloroform) to yield **2** as a white solid: $^1\text{H NMR}$ (200 MHz, CD_3CN , 298 K) δ 2.07 (s, 12H, CH_3), 2.16 (s, 12H, CH_3), 2.80 (m, 16H, $\text{ArCH}_2\text{NCH}_2$, $\text{OCH}_2\text{CH}_2\text{N}$), 3.62–4.16 (m, 44H, $\text{OCH}_2\text{CH}_2\text{OCH}_2$, ArCH_2 , NCHH , $\text{NCH}_2\text{CH}_2\text{N}$), 5.52 (d, 4H, NCHH), 5.71 (s, 4H, PyrazH), 6.75 (s, 4H, XyH), 7.12–7.35 (m, 18H, ArH , XyH); FAB-MS (m/z) 1627 ($\text{M} + \text{Na}^+$). Anal. Calcd for $\text{C}_{92}\text{H}_{114}\text{N}_{16}\text{O}_{10} \cdot 2\text{CHCl}_3$: C, 61.27; H, 6.34; N, 12.16. Found: C, 61.27; H, 6.26; N, 11.33.

$[\text{Cu}(\text{I})_2](\text{PF}_6)_2$ (3a). This compound was prepared by adding under a dinitrogen atmosphere 14.2 mg (3.81×10^{-5} mol) of solid $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ to a dichloromethane solution containing 30.5 mg (1.9×10^{-5} mol) of **2**. The solution was stirred for 30 min at ambient temperature, whereafter the solvent was removed to leave the dinuclear Cu(I) complex as a yellow-orange solid: $^1\text{H NMR}$ (90 MHz, CDCl_3 , 298 K) δ 2.27 (s, 12H, CH_3), 2.31 (s, 12H, CH_3), 2.81 (m, 8H, $\text{ArCH}_2\text{NCH}_2$), 3.21 (m, 8H, $\text{OCH}_2\text{CH}_2\text{N}$), 3.43–4.40 (m, 44H, $\text{OCH}_2\text{CH}_2\text{OCH}_2$, ArCH_2 , NCHH , $\text{NCH}_2\text{CH}_2\text{N}$), 5.73 (d, 4H, NCHH), 5.92 (s, 4H, PyrazH), 6.78 (s, 4H, XyH), 7.07–7.29 (m, 18H, ArH , XyH). FAB-MS (m/z) 1874 ($2 + 2\text{Cu} + \text{PF}_6$), 865 ($[2 + 2\text{Cu}]/2$). Anal. Calcd for $\text{C}_{92}\text{H}_{114}\text{N}_{16}\text{O}_{12}\text{P}_2\text{F}_{12}\text{Cu}_2$: C, 53.82; H, 5.60; N, 10.92. Found: C, 54.07; H, 5.60; N, 10.63.

[Cu(II)₂·2](ClO₄)₄ (3b). This compound was prepared by adding 18.4 mg (5×10^{-2} mmol) of Cu(ClO₄)₂·6H₂O to a solution containing 40 mg (2.5×10^{-2} mmol) of 2 in 20 mL of acetonitrile. The solution was stirred for 30 min, and the solvent was subsequently removed *in vacuo*: Mp = 235 °C; UV-vis (CH₃CN) λ (nm) (ε (mol L⁻¹)) 223.6 (50 500), 293.7 (11 000), 700 (50); IR (KBr) 2924 (CH₂), 1685 (C=O), 1552 (pyrazole), 1471 (C=C), 1352, 1309, and 1261 (CH₂O), 1090 and 624 (ClO₄⁻).

Anal. Calcd for C₉₂H₁₁₄N₁₆O₂₂Cl₂Cu₂·4H₂O: C, 50.21; H, 5.59; N, 10.18. Found: C, 50.47; H, 5.39; N, 10.12.

Preparation of Benzylic Alcohols. General Procedure. All alcohols were prepared according to standard procedures and fully characterized by spectroscopic techniques and elemental analysis.^{4,16}

(16) Adams, R.; Harfenist, M.; Loewe, S. *J. Am. Chem. Soc.* **1949**, *71*, 1624.