

Substrate-Binding Ligand Approach in Chemical Modeling of Copper-Containing Monooxygenases, 1 Intramolecular Stereoselective Oxygen Atom Insertion into a Non-Activated C–H Bond

Ingrid Blain,^[a] Michel Giorgi,^[a] Innocenzo De Riggi,^[b] and Marius Réglier*^[a]

Keywords: Copper / Oxygenase / Copper–oxygen radical species / RPY2 ligand / Oxygenation

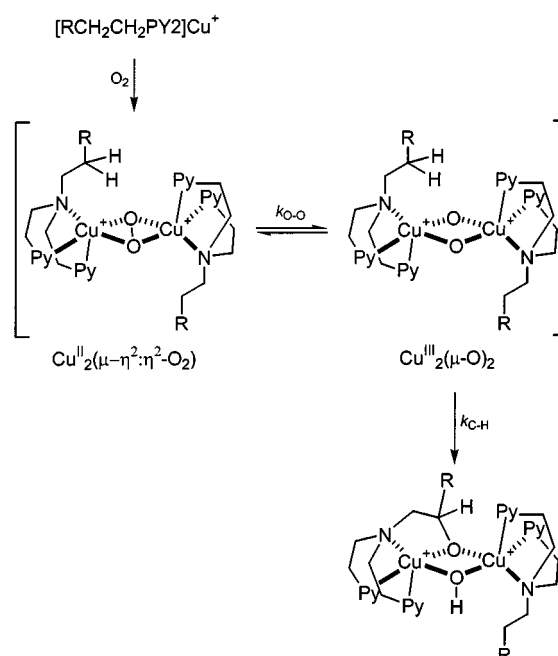
We describe the reactivity of new copper AlkylRPY2 type complexes which react with dioxygen and thus hydroxylate

an aliphatic C–H bond of the ligand in the same manner as copper-containing monooxygenases.

Introduction

Copper-containing monooxygenases^[1] are involved in important biological reactions and copper-dioxygen chemistry has been the subject of important recent investigations.^[2] It has been shown that copper(I) coordinated to tridentate ligands {HB(3,5-*i*Pr₂pz)₃,^[3] RPY2,^[4,5] P(2,4-*i*Pr₂im)₃^[6] and *i*Pr₃tacn^[7] leads to [Cu^I₂(μ-η²:η²-O₂)]²⁺ species upon reaction with dioxygen. More recently, Tolman et al.^[8] reported that these species can exist in equilibrium with a bis(μ-oxo)dicopper species in a formal [Cu^{III}₂(μ-O)₂]²⁺ oxidation state. Whereas the structure of these copper-dioxygen adducts is now well documented, few examples of exogenous substrate oxidation mediated by these species are known.^[4] In some cases, these peroxo species are capable of inserting an oxygen atom into a C–H bond of the ligand.^[5–7,9,10] Taking advantage of this behavior, we described in previous papers,^[10] the *substrate-binding ligand approach*, which involves the study of copper complexes derived from RPY2-type ligands. In these compounds a substrate is covalently bound to the ligand's tertiary amino group in such a way that an intramolecular oxygen-atom transfer from the copper center to the ligand is favored. The chemio-, regio- and stereoselectivities of the oxygen atom transfer, as revealed by the structure of the hydroxylated ligands, are used to gain more information on the nature of the hydroxylating species and the exact oxidation mechanism. When using such complexes, benzylic hydroxylation (DBH functional model)^[5,10c] and hydroxylation at the α-position of the amido group (PHM functional model)^[10a] were described. Herein, we report the reactions of a new RPY2 ligand in which we chose to attach

a propyl or cyclopentyl group as the substrate in order to find out if copper-oxygen species are capable of inserting an oxygen atom into a nonactivated C–H bond.



Scheme 1. Substrate-binding ligand approach

Results and Discussion

The new RPY2 ligands were synthesized from simple organic reactions. Thus, Michael addition of primary amines to freshly distilled 2-vinyl pyridine in a methanol/acetic acid mixture yielded the ligands *n*PrPY2 and *c*PtPY2. The copper(II) complexes [*n*PrPY2]Cu(OTf)₂ and [*c*PtPY2]Cu(OTf)₂ (OTf = OSO₂CF₃) were obtained in methanol in nearly quantitative yields by complexation of the corresponding ligands with Cu(OTf)₂. Recrystallization from dichloromethane using the diethyl ether vapor diffusion technique afforded blue crystals of [*n*PrPY2]Cu(OTf)₂ which were suitable for an X-ray diffraction analysis (Table 1, Figure 1).

^[a] Chimie, Biologie et Radicaux Libres, UMR-CNRS 6517, case 432, Universités d'Aix-Marseille 1 et 3, Faculté des Sciences et Techniques de Saint Jérôme, av. Escadrille Normandie-Niemen, F-13397 Marseille Cedex 20, France

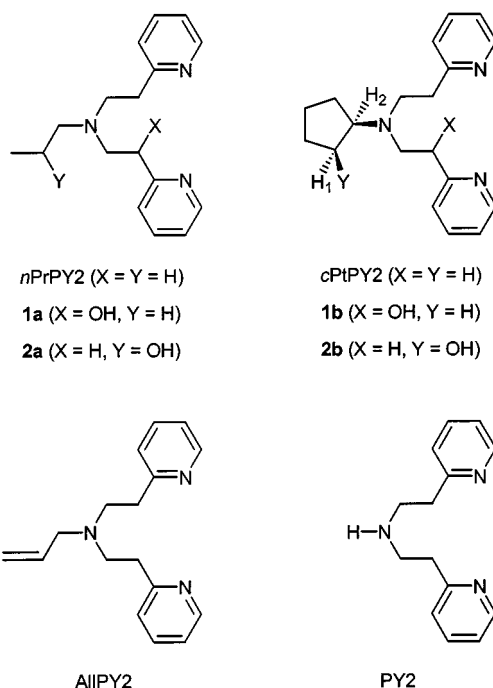
Fax: (internat.) + 33-4/9198-3208
E-mail: marius.reglier@lbs.u-3mrs.fr

^[b] ENSSPICAM, Université d'Aix-Marseille 3, Faculté des Sciences et Techniques de Saint Jérôme, av. Escadrille Normandie-Niemen, F-13397 Marseille Cedex 20, France

Table 1. Crystallographic data for $[n\text{PrPY2}]\text{Cu}(\text{OTf})_2 \cdot 2\text{H}_2\text{O}$

Crystal data	
Formula	$\text{C}_{19}\text{H}_{27}\text{CuF}_6\text{N}_3\text{O}_8\text{S}_2$
M_r	667.09
Crystal system	monoclinic
Space group	$P2_1/n$
a [Å]	8.899(1)
b [Å]	13.726(1)
c [Å]	22.980(1)
α [°]	90.000(1)
β [°]	100.598(1)
γ [°]	90.000(1)
V [Å ³]	2759.1(6)
D_{calc} [g cm ⁻³]	1.62
Z	4
$F(000)$ [e]	1180
μ (Mo- K_α) [mm ⁻¹]	10.299
Data collection	
T [K]	298
Scan mode	
ϕ scans	
Scan width [°]	2
$2\theta_{\text{max}}$ [°]	50–82
Measured refl.	5455
Unique refl.	5265
Refl. used for ref.	3321
Absorption correction	none
Extinction correction	none
Structure refinement	
Ref. parameters	418
H atoms	included not refined
R	0.047
R_w	0.054
w	$1/[\sigma^2 F_0 + 0.03 F_0^2]$
(shift/e.s.d.) _{max}	0.0653
Goodness of fit	1.783
$\Delta\rho_{\text{min}}(\text{max/min})$ [e Å ⁻³]	0.55/–0.59

The copper complex $[n\text{PrPY2}]\text{CuPF}_6$, was prepared in situ by interaction (under argon) of the corresponding ligand $n\text{PrPY2}$ with 1 equiv. of $(\text{CH}_3\text{CN})_4\text{CuPF}_6$ in degassed dichloromethane. When it was placed in a dioxygen atmosphere the clear yellow solution rapidly turned green and a copper(II) complex was obtained. Demetallation with 35% aqueous ammonia and analysis of the organic products indicated the complete recovery of the starting ligand $n\text{PrPY2}$ with no products resulting from an oxygen-atom transfer to the ligand. More interesting were the results obtained by treatment of $[n\text{PrPY2}]\text{Cu}(\text{OTf})_2$ with 2 equiv. of benzoin/ NEt_3 in dichloromethane at 25°C. Under argon, reduction to a copper(I) state by 2 equiv. of benzoin/ NEt_3 occurred in less than two hours. After exposure to a dioxygen atmosphere for 18 hours and demetallation with 35% aqueous ammonia, analysis of the organic products indicated the presence of compounds **1a**, **2a** and AllPY2 in addition to recovered ligand $n\text{PrPY2}$ and small amounts of secondary amine PY2 resulting from an *N*-dealkylation reaction (Table 2, entry 2).^[11] A thorough analysis of the spectral data indicated that the main product **1a** was the result of hydroxylation at the benzylic position of one pyridine ring. This is clearly evident from the ¹³C NMR spectra which show the splitting of all pyridine signals and the appearance of two new signals at $\delta = 61.5$ and 70.8, attributable to the $\text{N}-\text{CH}_2-\text{CHOH}-\text{pyr}$ sequence, and from the ¹H NMR spectra which show a doublet of doublets at $\delta =$



Scheme 2

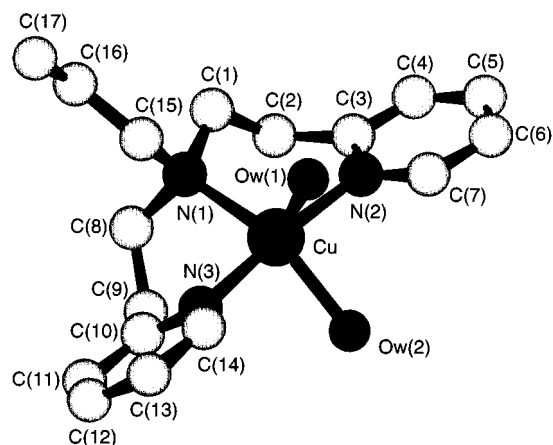


Figure 1. Perspective view of the copper(II) complex $[n\text{PrPY2}]\text{Cu}(\text{OTf})_2$ emphasizing the central coordination sphere; selected bond distances (Å): Cu–Ow(1), 2.224 (3), Cu–Ow(2), 2.045 (3), Cu–N(1), 2.088 (3), Cu–N(2), 1.994 (3), Cu–N(3), 1.990 (4); bond angles (°): Ow(1)–Cu–Ow(2), 102.8 (1), Ow(1)–Cu–N(2), 86.9 (2), Ow(1)–Cu–N(1), 106.8 (2), Ow(1)–Cu–N(3), 93.5 (2), Ow(2)–Cu–N(2), 87.8 (2), Ow(2)–Cu–N(1), 150.2 (2), Ow(2)–Cu–N(3), 86.4 (2), N(2)–Cu–N(1), 96.4 (2), N(2)–Cu–N(3), 174.1 (2), N(1)–Cu–N(3), 89.1 (2).

4.75 corresponding to $\text{N}-\text{CH}_2-\text{CHOH}-\text{pyr}$. Compound **2a** as revealed by NMR analysis and confirmed by comparison with an authentic sample was the result of a β -hydroxylation of the *n*-propyl group.^[12]

In order to study the stereoselectivity of the oxygen-atom transfer to the alkyl part of the ligand, we then studied the reactivity of $c\text{PtPY2}$ -derived copper complexes. As already mentioned for $[n\text{PrPY2}]\text{CuPF}_6$, we did not observe any hydroxylation products by reaction of $[c\text{PtPY2}]\text{CuPF}_6$, prepared in situ, with dioxygen. However two equiv. of

Table 2. Reactions of [RPY2]Cu(OTf)₂ complexes with O₂/Benzoin/NEt₃ in CH₂Cl₂

Entries	Ligands	Ratios Cu/Benzoin/NEt ₃	Product Distributions ^[a]
1	<i>n</i> PrPY2	1/0/2	<i>n</i> PrPY2 (98%) + PY2 (2%)
2	<i>n</i> PrPY2	1/2/2	<i>n</i> PrPY2 (44%) + 1a (37%) + 2a (8%) + AllPY2 (2%) + PY2 (9%)
3	<i>n</i> PrPY2	1/2/4	<i>n</i> PrPY2 (37%) + 1a (36%) + 2a (6%) + AllPY2 (3%) + PY2 (18%)
4	<i>n</i> PrPY2	1/4/4	1a (64%) + 2a (10%) + AllPY2 (6%) + PY2 (12%)
5	<i>c</i> PtPY2	1/2/2	<i>c</i> PtPY2 (35%) + 1b (42%) + 2b (13%) + PY2 (5%)

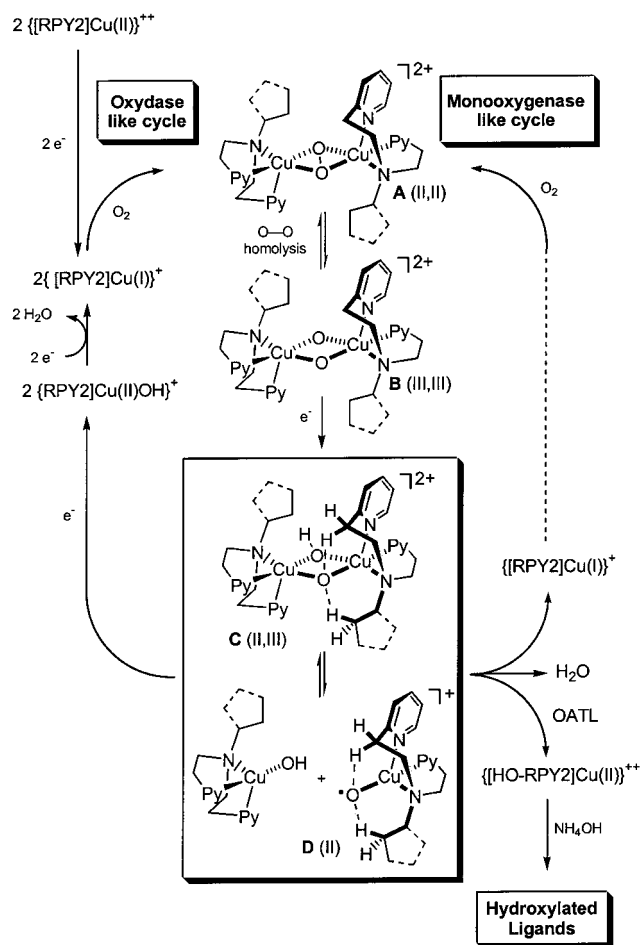
^[a] Determined by HPLC (Ultrasphere C18 column, Beckmann) using H₂O/CH₃CN 90/10 containing 1% TFA as mobile phase, detection at 270 nm using diode array detector.

benzoin/NEt₃ in dichloromethane at 25°C transformed [*c*PtPY2]Cu(OTf)₂ into the hydroxylated compounds **1b** and **2b** (Table 2, entry 5). Compound **1b**, which showed the same spectroscopic features as **1a** (¹³C NMR: splitting of all pyridine signals and appearance of two new signals at δ = 71 and 59; ¹H NMR: dd at δ = 4.76), was the result of a hydroxylation at a benzylic position. An NMR structural analysis of compound **2b** revealed that it was the result of a β-*cis* hydroxylation of the cyclopentane ring. The *cis* stereochemistry could be assigned by a two dimensional NOESY sequence showing a Nuclear Overhauser Effect (NOE) between protons H-2 and H-1.^[13]

In one of our previous papers the higher deuterium kinetic isotope effect observed for reaction of [IndPY2]CuPF₆/O₂ relative to that of [IndPY2]Cu(OTf)₂/benzoin/NEt₃/O₂ (11 vs. 7.6) was rationalized as being due to the occurrence of two different copper-oxygen intermediates.^[10c] The absence of Oxygen Atom Transfer to the Ligand (OATL) during the reaction of [RPY2]CuPF₆ with dioxygen confirms this suggestion. At this time it is difficult to provide any evidence for the oxygenated copper species responsible for the hydroxylation. Nevertheless, on the basis of the observed products we can formulate several hypotheses concerning the structure of the active oxygen species. Itho,^[5] and more recently Karlin,^[4a] with [PhenPY2]CuPF₆ and [MePY2]CuPF₆ complexes, respectively, have shown that such complexes lead to {[RPY2]Cu^{II}₂(μ-η²:η²-O₂)}²⁺ by oxygenation, and that a homolytic cleavage of the peroxy bond occurs (at least partially) to give, in the first step of the reaction, a {[RPY2]Cu^{III}₂(μ-O₂)}²⁺ species (Scheme 3). In this context, it is reasonable to assume the formation of species **A** and/or **B** upon reaction with dioxygen (Scheme 3). Except with complexes derived from PhenPY2 and IndPY2 ligands where activated benzylic hydrogen are present, such species do not transfer an oxygen atom to the AlkylPY2 ligand. In a recent study on pMMO, Chan et al. proposed that a Cu^{III}₂(μ-O₂)²⁺ species is not reactive enough to abstract a hydrogen atom from methane.^[14] Nevertheless, these authors suggested that transfer of an additional electron, probably from another copper atom, and the occurrence of the mixed valence Cu^{II}Cu^{III}(μ-O₂)²⁺ species,^[14] may enhance the reactivity of the copper-oxygen core. This hypothesis is very attractive for the hydroxylation of complexes derived from an AlkylPY2 ligand, which only occurs when benzoin is present. Thus, we propose that benzoin acts in the monoelectronic reduction of **A** and/or

B to give a mixed valence species **C** which, as suggested by Chan, could be active in transferring one oxygen atom to the ligand to give {[HORPY2]Cu^{II}}²⁺. This process is accompanied by the formation of a copper(I) complex, which can participate again after reaction with dioxygen in a monooxygenase-like cycle.^[15] According to this mechanism, the transformation of copper(II) complexes [RPY2]Cu(OTf)₂ in such a cycle needs two electrons (one equiv. of benzoin). We observed that the transformation of the original copper(II) complexes into the observed products consumed a four-fold excess of benzoin (Table 2, entry 4). Benzoin is a strong reducing agent that can participate in a second electron addition to **C** (and/or **D**) in a competitive reaction to give a different copper(II) species which is unreactive in the hydroxylation reaction (oxydase like cycle). The two competitive processes (oxydase vs. monooxygenase) may explain why the complete transformation of [RPY2]Cu(OTf)₂ needs more than one equiv. of benzoin.

The OATL mechanism needs some comments. Scheme 4 illustrates possible pathways whereby hydroxylation can occur *via* the dimeric species **C** (or monomer **D**). The first explanation for the formation of **1a** or **1b** is to consider that the electrophilic Cu^{III} core in **B** (or **C**) increases the acidity of the benzylic hydrogen of pyridine, thus facilitating the deprotonation with triethylamine (path *d*). This mechanism can be dismissed as increasing the amount of triethylamine did not increase the amount of **1a** in the [*n*PrPY2]Cu(OTf)₂/Benzoin/O₂ reaction (Table 2, entry 3). From our results two observations are in favor of a mechanism occurring in the coordination sphere of the copper core: (1) hydroxylation exclusively in the β position of the tertiary amino group, and (2) exclusive *cis* hydroxylation of the aminocyclopentane moieties of [*c*PtPY2]Cu(OTf)₂. While we cannot definitively exclude a concerted mechanism, several examples in the literature are in favor of a two step mechanism where the abstraction of a β hydrogen atom occurs in the partially rate determining step. Since AllPY2 is not the result of the dehydration of a copper(II) complex of [**2a**],^[16] the isolation of AllPY2 can be considered as being indicative of a two-step mechanism where a carbenium ion is formed. The question which arises now is to know if this intermediate is formed directly by abstraction of a H⁺ by an electrophilic oxygen (path *c*) or by oxidation of the radical **E** (path *f*). At the moment, it is difficult to answer this fundamental question. More experiments are needed, notably using a radical clock fixed on the tertiary amino group



Scheme 3. Oxydase vs. monooxygenase-like cycles

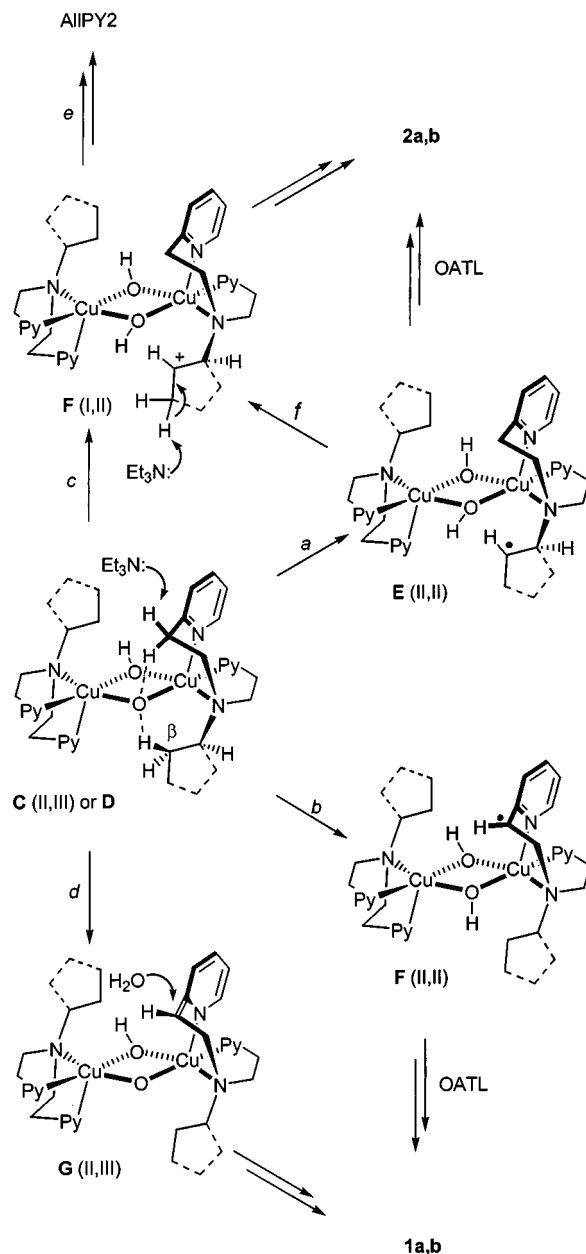
of the ligand. However, initial radical formation from a hydrogen atom abstraction by the Cu–O core seems to be more reasonable since Mayer has recently shown that metal-oxo complexes oxidize hydrocarbons by a hydrogen-atom abstraction mechanism which is attributed to their thermodynamic affinity for a hydrogen atom ($\equiv \text{H}^+ + \text{e}^-$).^[17]

Conclusion

While benzylic hydroxylation is the easier process, we have now demonstrated that copper-oxygen species are able to functionalise aliphatic C–H bonds probably *via* a two-step process. Once again, it is possible to show that the substrate binding ligand approach gives valuable information about the active species involved in the copper-dioxygen activation. This organic chemistry approach is complementary to that of inorganic chemists who are more interested in the structural study of copper-oxygen species

Experimental Section

General: Solvents were freshly distilled under argon: MeOH from Mg, Et₂O from sodium benzophenone ketyl and CH₂Cl₂ from

Scheme 4. Mechanism proposed for β -hydroxylations

P₂O₅. Deoxygenation of solvents and solutions was carried out by three vacuum/purge cycles. Standard Schlenk techniques were used in the preparation and handling of air-sensitive compounds. Commercial starting materials were used without further purification, except for 2-vinylpyridine, which was distilled prior to use. NMR spectra were recorded on Bruker AC-200 or AMX-400 spectrometers. Chemical shifts are reported in ppm as δ values downfield from an internal standard (TMS). Elemental analyses were obtained on a CHN Technicon microanalyser.

RPY2: To absolute MeOH were added freshly distilled 2-vinylpyridine, the primary amine and acetic acid. After refluxing for 2–5 days, MeOH and the excess 2-vinylpyridine were evaporated under vacuum. The crude product was dissolved in CH₂Cl₂, washed with a saturated solution of NaHCO₃ and dried over Na₂SO₄. Evaporation of CH₂Cl₂ under reduced pressure (18 Torr) and flash chro-

matography (Silica gel, CH₂Cl₂/MeOH 85/15) afforded ligands RPY2.

nPrPY2: Yield: 610 mg (2.3 mmol, 38%) [from *n*-propylamine (354 mg, 6 mmol), 2-vinylpyridine (3.88 mL, 36 mmol), CH₃COOH (420 mL, 7.5 mmol), MeOH (8 mL), 2 day reflux]. – ¹H NMR (200 MHz, CDCl₃): δ = 0.83 (t, *J* = 7.5 Hz, 3 H), 1.52 (hex, *J* = 7.5 Hz, 2 H), 2.63–2.56 (m, 2 H), 3.00 (s, 8 H), 7.16–7.07 (m, 4 H), 7.57 (td, *J* = 7.5 and 1.7 Hz, 2 H), 8.51 (ddd, *J* = 4.8, 1.7 and 1 Hz, 2 H). – ¹³C NMR (50.32 MHz, CDCl₃): δ = 11.47 (CH₃), 19.64 (CH₂), 34.99 (CH₂), 53.48 (CH₂), 55.46 (CH₂), 120.96 (CH), 123.18 (CH), 136.10 (CH), 148.82 (CH), and 159.86 (C).

cPtPY2: Yield: 1.18 g (4 mmol, 40%) [*c*-pentylamine (850 mg, 10 mmol), 2-vinylpyridine (10 mL, 0.1 mol), CH₃COOH (2.3 mL, 40 mmol), MeOH (10 mL), 5 day reflux]. – ¹H NMR (200 MHz, CDCl₃): δ = 1.32–1.74 (m, 6 H), 1.75–1.85 (m, 2 H), 2.90–3.10 (m, 9 H), 7.00–7.10 (m, 4 H), 7.52 (td, *J* = 7.7 and 1.8 Hz, 2 H), 8.46 (dd, *J* = 4.8 and 0.9 Hz, 2 H). – ¹³C NMR (50.32 MHz, CDCl₃): δ = 23.93 (CH₂), 30.10 (CH₂), 35.71 (CH₂), 51.80 (CH₂), 63.71 (CH), 121.11 (CH), 123.38 (CH), 136.27 (CH), 149.13 (CH), and 160.70 (C).

[RPY2]Cu(OTf)₂: To a solution of Cu(OTf)₂ (694 mg, 1.9 mmol) in CH₂Cl₂ (5 mL) was added dropwise a solution of ligand RPY2 (1.9 mmol) in CH₂Cl₂ (5 mL). The mixture was allowed to stir for 2 h, and Et₂O was added until precipitation. The precipitate obtained was centrifuged, washed with Et₂O and dried in vacuo to give [RPY2]Cu(OTf)₂.

[nPrPY2]Cu(OTf)₂: blue solid. – Yield: 1.10 g (1.66 mmol, 87%) – C₁₉H₂₃CuF₆N₃O₆S₂ (631.06): calcd. C 36.16, H 3.67, N 6.66; found C 35.16, H 3.88, N 6.47.

[cPtPY2]Cu(OTf)₂: blue solid. – Yield 1.23 g (1.78 mmol, 94%) – C₂₁H₂₅CuF₆N₃O₆S₂ (657.10): calcd. C 38.39, H 3.83, N 6.39; found C 37.36, H 4.03, N 6.22.

Oxidation of [RPY2]CuPF₆ With O₂: To a solution of [CH₃CN]₄CuPF₆ (0.1 mmol) in degassed CH₂Cl₂ (50 mL), was added dropwise a solution of RPY2 (0.1 mmol) in CH₂Cl₂ (50 mL). The mixture was stirred under argon for 1 h, and then exposed to an O₂ atmosphere for 24 h. The CH₂Cl₂ was subsequently evaporated in vacuo, Et₂O (50 mL) was added, and the precipitate thus obtained was filtered off, washed with Et₂O, and dried in vacuo to give a mixture of copper(II) complexes. This mixture was dissolved in CH₂Cl₂ (20 mL), washed with 35% NH₄OH (5 mL) and brine (3 × 5 mL), and dried over Na₂SO₄. Evaporation of the CH₂Cl₂ under reduced pressure (18 Torr) gave the crude product. Flash chromatography (SiO₂, CH₂Cl₂/MeOH, 90:10) afforded the recovered ligands RPY2.

Oxidation of [RPY2]Cu(OTf)₂ With O₂ in the Presence of Benzoin: To a solution of [RPY2]Cu(OTf)₂ in degassed CH₂Cl₂ were added benzoin (1 equiv.) and NEt₃ (1 equiv.). This mixture was stirred under argon for 2 h and then exposed to an O₂ atmosphere for 24 h. The CH₂Cl₂ was subsequently evaporated in vacuo and Et₂O was added. The precipitate thus obtained was filtered off, washed with Et₂O, dissolved in CH₂Cl₂, washed with 35% NH₄OH and brine, and dried over Na₂SO₄. Evaporation of the CH₂Cl₂ under reduced pressure (18 Torr) gave a mixture of recovered ligands RPY2 and compounds **1a**, **b**, **2a**, **b** and AllPY2 which were separated by flash chromatography (SiO₂, CH₂Cl₂/MeOH, 90:10).

1a: ¹H NMR (200 MHz, CDCl₃): δ = 0.75 (t, *J* = 7 Hz, 3 H), 1.4 (m, 2 H), 2.4–2.7 (m, 3 H), 3.1–2.85 (m, 5 H), 4.75 (dd, *J* = 9 and 3.4 Hz, 1 H), 6.95 (d, *J* = 7.5 Hz, 1 H), 7.2–7.05 (m, 4 H), 7.4–7.7 (m, 3 H), 8.50 (m, 2 H). – ¹³C NMR (50.32 MHz, CDCl₃):

δ = 11.6 (CH₃), 20.0 (CH₂), 35.6 (CH₂), 54.1 (CH₂), 56.2 (CH₂), 61.5 (CH₂), 70.8 (CH), 121.4 (CH), 120.5 (CH), 123.4 (CH), 122.2 (CH), 136.7 (CH), 136.6 (CH), 149.1 (CH), 148.6 (CH), 162.1 (C), 160.2 (C).

1b: ¹H NMR (200 MHz, CDCl₃): δ = 1.20–1.80 (m, 8 H), 2.60 (dd, *J* = 13 and 10 Hz, 1 H), 2.90–3.08 (m, 5 H), 3.14–3.32 (m, 1 H), 4.76 (dd, *J* = 10 and 3 Hz, 1 H), 7.05–7.20 (m, 3 H), 7.50–7.72 (m, 3 H), 8.50 (m, 2 H). – ¹³C NMR (50.32 MHz, CDCl₃): δ = 29.8 (CH₂), 27.6 (CH₂), 24.0 (CH₂), 23.9 (CH₂), 36.2 (CH₂), 52.3 (CH₂), 59.0 (CH₂), 63.5 (CH), 71.0 (CH), 121.3 (CH), 120.4 (CH), 123.4 (CH), 122.2 (CH), 136.7 (CH), 136.5 (CH), 149.0 (CH), 148.6 (CH), 162.4 (C), 160.3 (C).

2a: ¹H NMR (200 MHz, CDCl₃): δ = 1.08 (d, *J* = 6.2 Hz, 3 H), 2.35 (dd, *J* = 12.9 and 9.9 Hz, 1 H), 2.48 (dd, *J* = 12.9 and 3.1 Hz, 1 H), 2.70–3.10 (m, 8 H), 3.66 (dq, *J* = 9.9, 6.2 and 3.1 Hz, 1 H), 4.09 (br. s, 1 H), 6.97 (d, *J* = 7.5 Hz, 2 H), 7.07 (ddd, *J* = 7.5, 5.1 and 1.0 Hz, 2 H), 7.51 (td, *J* = 7.5 and 1.7 Hz, 2 H), 8.48 (ddd, *J* = 5.1, 1.7 and 1.0 Hz, 2 H). – ¹³C NMR (50.32 MHz, CDCl₃): δ = 19.5 (CH₃), 35.6 (CH₂), 53.9 (CH₂), 62.1 (CH₂), 63.5 (CH), 120.8 (CH), 123.9 (CH), 135.9 (CH), 148.7 (CH), 160.0 (C).

2b: ¹H NMR (200 MHz, CDCl₃): δ = 1.53–1.62 (m, 1 H), 1.78–1.90 (m, 4 H), 1.95 (br. t, *J* = 10 Hz, 1 H), 3.05–3.19 (m, 4 H), 3.23 (br. s, 1 H), 3.41–3.50 (m, 4 H), 4.35 (br. s, 1 H), 7.10 (ddd, *J* = 8, 5 and 2 Hz, 2 H), 7.58 (td, *J* = 8 and 2 Hz, 2 H), 7.16 (d, *J* = 8 Hz, 2 H), 8.38 (br. d, *J* = 5 Hz, 2 H). – ¹³C NMR (50.32 MHz, CDCl₃): δ = 20.7 (CH₂), 26.6 (CH₂), 31.8 (CH₂), 32.5 (CH₂), 68.3 (CH), 51.0 (CH₂), 70.4 (CH), 121.9 (CH), 123.7 (CH), 137.0 (CH), 149.0 (CH), 158.5 (C). Two-dimensional NMR experiments were carried out on an AMX Bruker 400 MHz spectrometer. COSY gradient, HMQC and HMBC experiments were performed with 5 mm inverse broadband probehead incorporating a shielded z-gradient coil. These correlations allowed the total assignment of all the protons and carbon atoms of the compound **3b**. A 5 mm DUAL ¹H/¹³C probehead was used to acquire the 2D phase-sensitive NOESY data.

AllPY2: ¹H NMR (200 MHz, CDCl₃): δ = 2.90 (br. s, 8 H), 3.25 (d, *J* = 6 Hz, 2 H), 5.10 (br. d, *J* = 10 Hz, 1 H), 5.18 (br. d, *J* = 17 Hz, 1 H), 5.80 (ddt, *J* = 17, 10 and 6 Hz, 1 H), 7.10–6.90 (m, 4 H), 7.50 (td, *J* = 8 and 2 Hz, 2 H), 8.50 (dt, *J* = 5 and 1 Hz, 2 H). – ¹³C NMR (50.32 MHz, CDCl₃): δ = 35.7 (CH₂), 53.3 (CH₂), 58.8 (CH₂), 116.9 (CH₂), 120.7 (CH), 123.0 (CH), 135.5 (CH), 135.8 (CH), 146.8 (CH), 160.3 (C).

X-ray Structure Analysis: Crystal data for [nPrPY2]Cu(OTf)₂ together with details of the X-ray diffraction experiment, are reported in Table 1. Crystallographic data for the structure reported in this paper has been deposited at the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 113535. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033, E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

This research was supported by the CNRS and the French Ministry of Universities. The authors are grateful to Dr. A. Heumann for a number of enlightening discussions.

[1] [1a] General references on copper-containing enzymes: J. P. Klinman, *Chem. Rev.* **1996**, *96*, 2541–2561; W. Kaim, J. Rall, *Angew. Chem.* **1996**, *108*, 47–64; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 43–60. – [1b] Dopamine β-hydroxylase (DBH),

- benzylic hydroxylation of dopamine into noradrenaline: L. C. Stewart, J. P. Klinman, *Ann. Rev. Biochem.* **1988**, *57*, 551–592. — ^[1c] Peptidylglycine α -hydroxylating monooxygenase (PHM), neuropeptide amidation: S. T. Pridge, A. S. Kolhenar, B. A. Eipper, R. E. Mains, L. M. Amzel, *Science* **1997**, *278*, 1300–1305. — ^[1d] Particulate methane monooxygenase (pMMO), methane hydroxylation into methanol: S. J. Eliot, M. Zhu, L. Tso, H.-H. T. Nguyen, J. H.-K. Yip, S. I. Chan, *J. Am. Chem. Soc.* **1997**, *119*, 9949–9955.
- [2] ^[2a] K. D. Karlin, S. Kaderli, A. D. Zuberbühler, *Acc. Chem. Res.* **1997**, *30*, 139–147. — ^[2b] W. B. Tolman, *Acc. Chem. Res.* **1997**, *30*, 227–237. — ^[2c] N. Kitajima, Y. Moro-Oka, *Chem. Rev.* **1994**, *94*, 737–757.
- [3] N. Kitajima, K. Fujisawa, Y. Moro-Oka, K. Toriumi, *J. Am. Chem. Soc.* **1989**, *111*, 8975–8976.
- [4] ^[4a] H. V. Obias, Y. Lin, N. N. Murthy, E. Pidcock, E. I. Solomon, M. Ralle, N. J. Blackburn, Y.-M. Neuhold, A. D. Zuberbühler, K. D. Karlin, *J. Am. Chem. Soc.* **1998**, *120*, 12960–12961. — ^[4b] M. A. Lockwood, T. J. Blubaugh, M. Coler, S. Lovell, J. M. Mayer, *Angew. Chem. Int. Ed.* **1999**, *38*, 225–227.
- [5] S. Itho, T. Kondo, M. Komatsu, Y. Ohshiro, C. Li, N. Kanehisa, Y. Kai, S. Fukuzumi, *J. Am. Chem. Soc.* **1995**, *117*, 4714–4715; S. Itho, H. Nakao, L. M. Berreau, T. Kondo, M. Komatsu, S. Fukuzumi, *J. Am. Chem. Soc.* **1998**, *120*, 2890–2899.
- [6] T. N. Sorrel, W. E. Allen, P. S. White, *Inorg. Chem.* **1995**, *34*, 952–960; W. E. Allen, T. N. Sorrell, *Inorg. Chem.* **1997**, *36*, 1732–1734.
- [7] ^[7a] S. Mahapatra, J. A. Halfen, E. C. Wilkinson, L. Que, Jr., W. B. Tolman, *J. Am. Chem. Soc.* **1994**, *116*, 9785–9786. — ^[7b] S. Mahapatra, J. A. Halfen, E. C. Wilkinson, G. Pan, C. J. Cramer, L. Que Jr., W. B. Tolman, *J. Am. Chem. Soc.* **1995**, *117*, 8865–8866. — ^[7c] J. A. Halfen, V. G. Young Jr., W. B. Tolman, *J. Am. Chem. Soc.* **1996**, *118*, 10920–10921.
- [8] J. A. Halfen, S. Mahapatra, E. C. Wilkinson, S. Kaderli, V. C. Young Jr., L. Que Jr., A. D. Zuberbühler, W. B. Tolman, *Science* **1996**, *271*, 1397–1400; S. Mahapatra, J. A. Halfen, E. C. Wilkinson, G. Pan, X. Wang, V. G. Young Jr., C. J. Cramer, L. Que Jr., W. B. Tolman, *J. Am. Chem. Soc.* **1996**, *118*, 11555–11574; S. Mahapatra, J. A. Halfen, W. B. Tolman, *J. Am. Chem. Soc.* **1996**, *118*, 11575–11586; C. J. Cramer, B. A. Smith, W. B. Tolman, *J. Am. Chem. Soc.* **1996**, *118*, 11283–11287; J. Cahoy, P. L. Holland, W. B. Tolman, *Inorg. Chem.* **1999**, *38*, 2161–2168.
- [9] K. D. Karlin, J. C. Hayes, Y. Gultneh, R. W. Cruse, J. W. McKown, J. P. Hutchinson, J. Zubieta, *J. Am. Chem. Soc.* **1984**, *106*, 2121–2128.
- [10] ^[10a] E. Amadéi, E. H. Alilou, F. Eydoux, M. Pierrot, M. Réglier, B. Waegell, *J. Chem. Soc., Chem. Commun.* **1992**, 1782–1784. — ^[10b] M. Réglier, E. Amadéi, E. H. Alilou, F. Eydoux, M. Pierrot, B. Waegell, *Bioinorganic Chemistry of Copper* (Eds.: K. D. Karlin, Z. Tiecklar), Chapman and Hall, **1993**, pp. 348–362. — ^[10c] I. Blain, P. Bruno, M. Giorgi, E. Lojou, D. Lexa, M. Réglier, *Eur. J. Inorg. Chem.* **1998**, 1297–1304.
- [11] *N*-Dealkylation is a process already observed in the reaction of [BnPY2]CuPF₆ with dioxygen: I. Sanyal, M. Mahroof-Tahir, M. S. Nasir, P. Ghosh, Y. Gultneh, R. W. Cruse, A. Farooq, K. D. Karlin, S. Liu, J. Zubieta, *Inorg. Chem.* **1992**, *31*, 4322–4332.
- [12] An authentic sample of compound **2a** was obtained by addition of 2-hydroxypropylamine to vinylpyridine in a methanol/acetic acid mixture.
- [13] A sample of *trans*-**2b** was obtained by addition of PY2 to cyclopentene oxide and compared to the product obtained by β -hydroxylation.
- [14] A. P. Cole, D. E. Root, P. Mukherjee, E. I. Solomon, T. D. P. Stack, *Science* **1996**, *273*, 1848–1850.
- [15] Another possibility is to consider the occurrence of a mononuclear Cu^{II}–O• ($\rightleftharpoons$ Cu^{III}–O[–]) species **D** that could result from a dissociation of **C**.
- [16] The copper(II) complex of **2a** placed under O₂/Benzoin/NEt₃ does not produce any AlIPY2 compound.
- [17] ^[17a] K. Wang, J. M. Mayer, *J. Am. Chem. Soc.* **1997**, *119*, 1470–1471. — ^[17b] J. M. Mayer, *Acc. Chem. Res.* **1998**, *31*, 441–450.

Received June 4, 1999
[199203]