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

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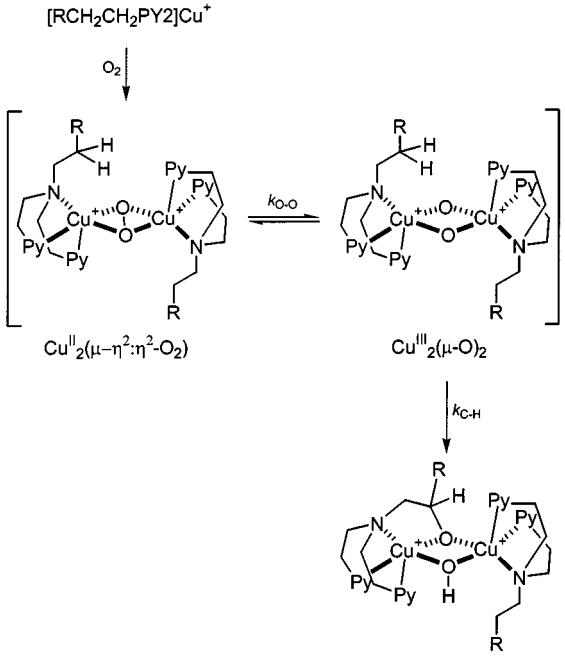
We describe the reactivity of new copper AlkylPY2 type complexes which react with dioxygen and thus hydroxylate an aliphatic C–H bond of the ligand in the same manner as copper-containing monooxygenases.

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*Pr$_2$pz)$_3$,[3] RPY2,[4,5] P(2,4-*i*Pr$_2$im)$_3$[6] and *i*Pr$_3$tacn[7] leads to $[Cu^{II}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$ 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 $[Cu^{III}_2(\mu\text{-}O)_2]^{2+}$ 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 = OSO_2CF_3) 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).

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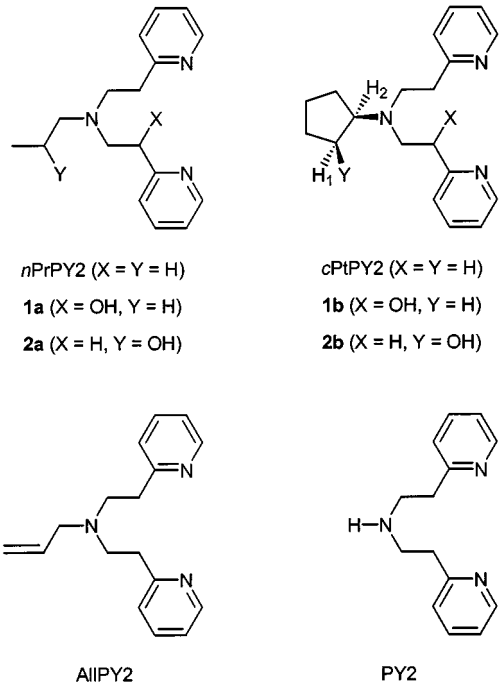
Table 1. Crystallographic data for [*n*PrPY2]Cu(OTf)$_2$·2H$_2$O

Crystal data	
Formula	$C_{19}H_{27}CuF_6N_3O_8S_2$
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) [$^{-1}$]	10.299
Data collection	
T [K]	298
Scan mode	
ϕ scans	
Scan width [°]	2
$2\theta_{max}$ [°]	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	$1/[\sigma^2F_0 + 0.03F_0^2]$
$(\text{shift/e.s.d.})_{max}$	0.0653
Goodness of fit	1.783
$\Delta\rho_{fin}$(max/min) [eÅ^{-3}]	0.55/ −0.59

The copper complex [*n*PrPY2]CuPF$_6$, was prepared in situ by interaction (under argon) of the corresponding ligand *n*PrPY2 with 1 equiv. of $(CH_3CN)_4CuPF_6$ 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*PrPY2 with no products resulting from an oxygen-atom transfer to the ligand. More interesting were the results obtained by treatment of [*n*PrPY2]Cu(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*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 ^{13}C NMR spectra which show the splitting of all pyridine signals and the appearance of two new signals at δ = 61.5 and 70.8, attributable to the N−*C*H$_2$−*C*HOH−pyr sequence, and from the ^{1}H NMR spectra which show a doublet of doublets at δ = 4.75 corresponding to N−CH$_2$−C*H*OH−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]



Scheme 2

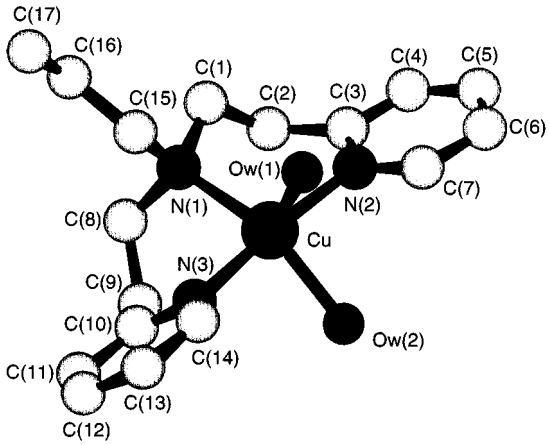


Figure 1. Perspective view of the copper(II) complex [*n*PrPY2]-Cu(OTf)$_2$ emphasizing the central coordination sphere; selected bond distances (Å): Cu−Ow(1), 2.224 (3), Cu−Ow(2), 2.045 (3), Cu−N(1), 2.088 (3), Cu−N(2), 1.994 (3), Cu−N(3), 1.990 (4); bond angles (°): Ow(1)−Cu−Ow(2), 102.8 (1), Ow(1)−Cu−N(2), 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).

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*PtPY2-derived copper complexes. As already mentioned for [*n*PrPY2]CuPF$_6$, we did not observe any hydroxylation products by reaction of [*c*PtPY2]CuPF$_6$, prepared in situ, with dioxygen. However two equiv. of

Table 2. Reactions of [RPY2]Cu(OTf)$_2$ complexes with O_2/Benzoin/NEt_3 in CH_2Cl_2

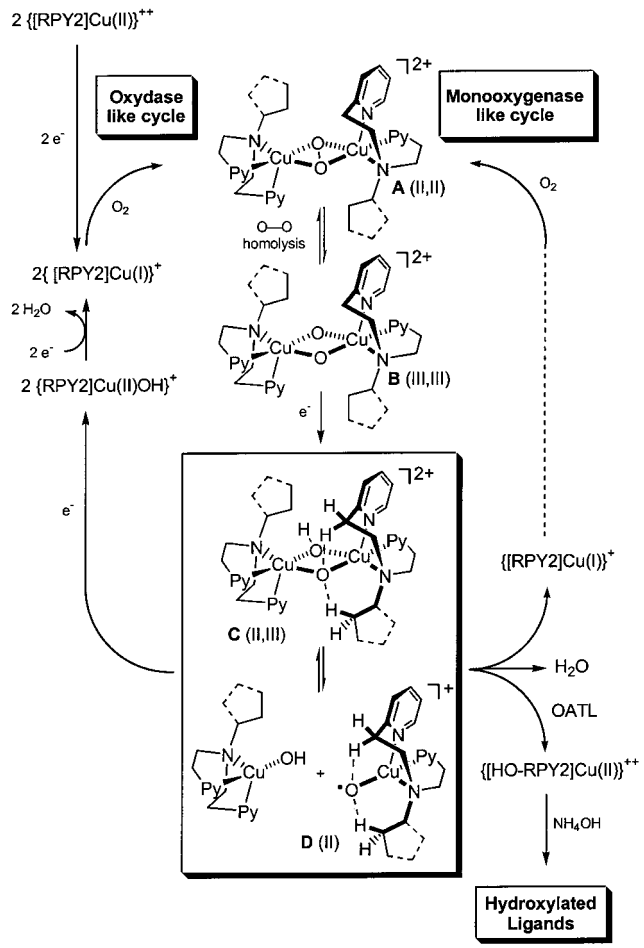
Entries	Ligands	Ratios Cu/Benzoin/NEt_3	Product Distributions[a]
1	*n*PrPY2	1/0/2	*n*PrPY2 (98%) + PY2 (2%)
2	*n*PrPY2	1/2/2	*n*PrPY2 (44%) + **1a** (37%) + **2a** (8%) + AllPY2 (2%) + PY2 (9%)
3	*n*PrPY2	1/2/4	*n*PrPY2 (37%) + **1a** (36%) + **2a** (6%) + AllPY2 (3%) + PY2 (18%)
4	*n*PrPY2	1/4/4	**1a** (64%) + **2a** (10%) + AllPY2 (6%) + PY2 (12%)
5	*c*PtPY2	1/2/2	*c*PtPY2 (35%) + **1b** (42%) + **2b** (13%) + PY2 (5%)

[a] Determined by HPLC (Ultrasphere C18 column, Beckmann) using H_2O/CH_3CN 90/10 containing 1% TFA as mobile phase, detection at 270 nm using diode array detector.

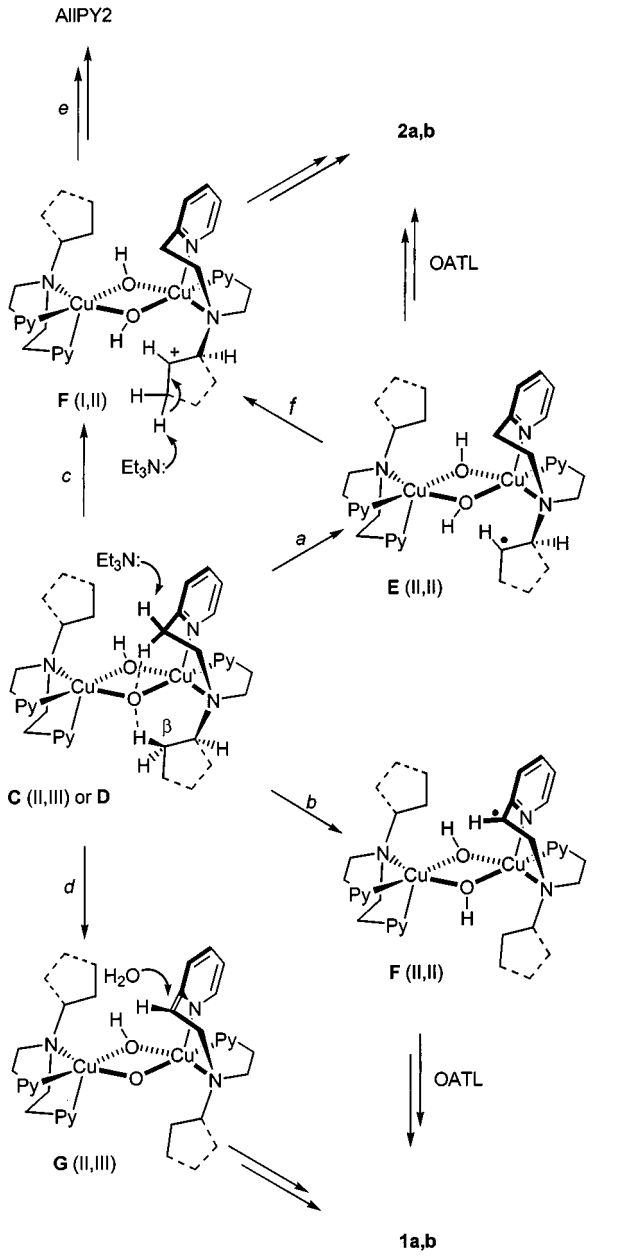
benzoin/NEt_3 in dichloromethane at 25°C transformed [*c*PtPY2]Cu(OTf)$_2$ into the hydroxylated compounds **1b** and **2b** (Table 2, entry 5). Compound **1b**, which showed the same spectroscopic features as **1a** (^{13}C NMR: splitting of all pyridine signals and appearance of two new signals at $\delta = 71$ and 59; ^1H NMR: dd at $\delta = 4.76$), 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]$CuPF_6$/O_2 relative to that of [IndPY2]Cu(OTf)$_2$/benzoin/NEt_3/O_2 (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]$CuPF_6$ 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]$CuPF_6$ and [MePY2]$CuPF_6$ complexes, respectively, have shown that such complexes lead to $\{[RPY2]Cu^{II}_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)\}^{2+}$ 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 $\{[RPY2]Cu^{III}_2(\mu\text{-}O_2)\}^{2+}$ 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 $Cu^{III}_2(\mu\text{-}O_2)^{2+}$ species is not reactive enough to abstract a hydrogen atom from methane.[1d] Nevertheless, these authors suggested that transfer of an additional electron, probably from another copper atom, and the occurrence of the mixed valence $Cu^{II}Cu^{III}(\mu\text{-}O_2)^{2+}$ 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 [nPrPY2]Cu(OTf)$_2$/Benzoin/O_2 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



Scheme 4. Mechanism proposed for β-hydroxylations

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, Et_2O from sodium benzophenone ketyl and CH_2Cl_2 from P_2O_5. 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 CH_2Cl_2, washed with a saturated solution of $NaHCO_3$ and dried over Na_2SO_4. Evaporation of CH_2Cl_2 under reduced pressure (18 Torr) and flash chro-

matography (Silica gel, CH_2Cl_2/MeOH 85/15) afforded ligands RPY2.

***n*PrPY2:** Yield: 610 mg (2.3 mmol, 38%) [from *n*-propylamine (354 mg, 6 mmol), 2-vinylpyridine (3.88 mL, 36 mmol), CH_3COOH (420 mL, 7.5 mmol), MeOH (8 mL), 2 day reflux]. − ^{1}H NMR (200 MHz, $CDCl_3$): 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). − ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 11.47 (CH_3), 19.64 (CH_2), 34.99 (CH_2), 53.48 (CH_2), 55.46 (CH_2), 120.96 (CH), 123.18 (CH), 136.10 (CH), 148.82 (CH), and 159.86 (C).

***c*PtPY2:** Yield: 1.18 g (4 mmol, 40%) [*c*-pentylamine (850 mg, 10 mmol), 2-vinylpyridine (10 mL, 0.1 mol), CH_3COOH (2.3 mL, 40 mmol), MeOH (10 mL), 5 day reflux]. − ^{1}H NMR (200 MHz, $CDCl_3$): 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). − ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 23.93 (CH_2), 30.10 (CH_2), 35.71 (CH_2), 51.80 (CH_2), 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 CH_2Cl_2 (5 mL) was added dropwise a solution of ligand RPY2 (1.9 mmol) in CH_2Cl_2 (5 mL). The mixture was allowed to stir for 2 h, and Et_2O was added until precipitation. The precipitate obtained was centrifuged, washed with Et_2O and dried in vacuo to give [RPY2]Cu(OTf)$_2$.

[*n*PrPY2]Cu(OTf)$_2$: blue solid. − Yield: 1.10 g (1.66 mmol, 87%) − $C_{19}H_{23}CuF_6N_3O_6S_2$ (631.06): calcd. C 36.16, H 3.67, N 6.66; found C 35.16, H 3.88, N 6.47.

[*c*PtPY2]Cu(OTf)$_2$: blue solid. − Yield 1.23 g (1.78 mmol, 94%) − $C_{21}H_{25}CuF_6N_3O_6S_2$ (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]CuPF$_6$ With O$_2$: To a solution of $[CH_3CN]_4CuPF_6$ (0.1 mmol) in degassed CH_2Cl_2 (50 mL), was added dropwise a solution of RPY2 (0.1 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred under argon for 1 h, and then exposed to an O_2 atmosphere for 24 h. The CH_2Cl_2 was subsequently evaporated in vacuo, Et_2O (50 mL) was added, and the precipitate thus obtained was filtered off, washed with Et_2O, and dried in vacuo to give a mixture of copper(II) complexes. This mixture was dissolved in CH_2Cl_2 (20 mL), washed with 35% NH_4OH (5 mL) and brine (3 × 5 mL), and dried over Na_2SO_4. Evaporation of the CH_2Cl_2 under reduced pressure (18 Torr) gave the crude product. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 90:10) afforded the recovered ligands RPY2.

Oxidation of [RPY2]Cu(OTf)$_2$ With O$_2$ in the Presence of Benzoin: To a solution of [RPY2]Cu(OTf)$_2$ in degassed CH_2Cl_2 were added benzoin (1 equiv.) and NEt_3 (1 equiv.). This mixture was stirred under argon for 2 h and then exposed to an O_2 atmosphere for 24 h. The CH_2Cl_2 was subsequently evaporated in vacuo and Et_2O was added. The precipitate thus obtained was filtered off, washed with Et_2O, dissolved in CH_2Cl_2, washed with 35% NH_4OH and brine, and dried over Na_2SO_4. Evaporation of the CH_2Cl_2 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 (SiO_2, CH_2Cl_2/MeOH, 90:10).

1a: ^{1}H NMR (200 MHz, $CDCl_3$): 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). − ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 11.6 (CH_3), 20.0 (CH_2), 35.6 (CH_2), 54.1 (CH_2), 56.2 (CH_2), 61.5 (CH_2), 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: ^{1}H NMR (200 MHz, $CDCl_3$): 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). − ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 29.8 (CH_2), 27.6 (CH_2), 24.0 (CH_2), 23.9 (CH_2), 36.2 (CH_2), 52.3 (CH_2), 59.0 (CH_2), 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: ^{1}H NMR (200 MHz, $CDCl_3$): 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 (dqd, *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). − ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 19.5 (CH_3), 35.6 (CH_2), 53.9 (CH_2), 62.1 (CH_2), 63.5 (CH), 120.8 (CH), 123.9 (CH), 135.9 (CH), 148.7 (CH), 160.0 (C).

2b: ^{1}H NMR (200 MHz, $CDCl_3$): 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). − ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 20.7 (CH_2), 26.6 (CH_2), 31.8 (CH_2), 32.5 (CH_2), 68.3 (CH), 51.0 (CH_2), 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 ^{1}H/^{13}C probehead was used to acquire the 2D phase-sensitive NOESY data.

AllPY2: ^{1}H NMR (200 MHz, $CDCl_3$): 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). − ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 35.7 (CH_2), 53.3 (CH_2), 58.8 (CH_2), 116.9 (CH_2), 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 [*n*PrPY2]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].

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