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Letter

A novel calix[6]arene-based mononuclear copper(I) complex that exhibits chirality at low temperature†

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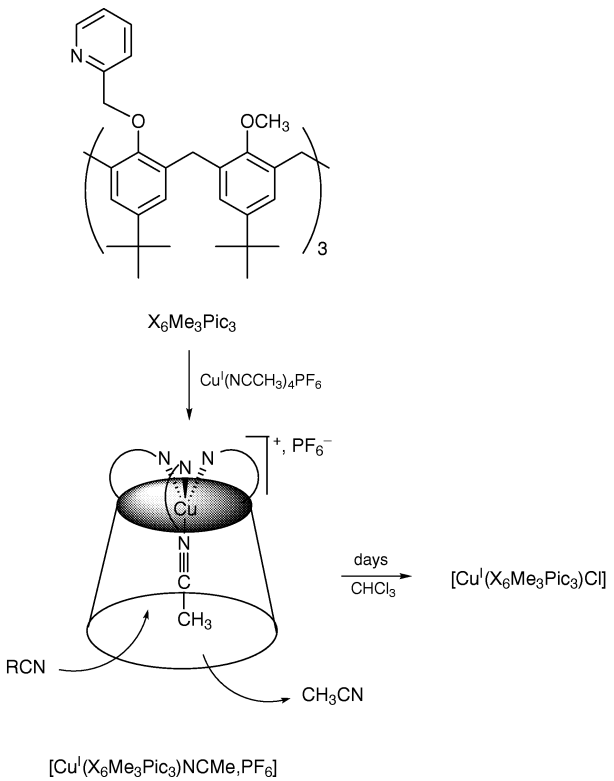
A calix[6]arene functionalized in alternate positions at the lower rim with three picolyl groups acts as a biomimetic *N*3 ligand with cuprous ion. The stable C_3 symmetrical complex derived from CuCl exists as a pair of helical enantiomers. A low temperature ^{1}H NMR study revealed that the chirality is transmitted to the calixarene skeleton, thereby providing a chiral cavity around the apical binding site of the metal center.

Although remarkable host properties have been reported for functionalized calixarenes,[1] their capacity for accommodating a transition metal has scarcely been explored.[1e] Even less is known for calix[6]arenes, compared to calix[4]arenes, partly because of their higher flexibility.[1–3a] Inhibition of the ring inversion, however, has been recently achieved through the introduction of covalent linkages between the phenolic units of the calixarene.[3] In our search for supramolecular biomimetic systems for metallo-enzymes, we are investigating the capacity of lower rim‡ functionalized calix[6]arenes to form stable mononuclear complexes with transition metals. We recently showed how covalent linkages, in alternate positions, of three picolyl (Pic) groups to the phenolic functions of a calix[6]arene provide a *N*3 donor set that mimics a polyimidazole coordination site of mononuclear copper enzymes.[4] By reacting the novel ligand $X_6Me_3Pic_3$ with $Cu(NCMe)_4PF_6$ we were able to obtain a cationic complex in which the cuprous ion is coordinated to (*i*) the three pyridyl (Py) residues of the tridentate ligand and (*ii*) an acetonitrile molecule that is located inside the calixarene conic cavity (Scheme 1). This fourth neutral ligand turned out to be labile and was easily exchanged by other nitrile molecules. In the course of studying these exchange processes, we noticed that, after standing for several days in a chloroform solution with only very little acetonitrile (less than 10 molar equivalents), the complex slowly decomposed to give a new species. We could identify the latter as $[Cu(X_6Me_3Pic_3)Cl]$, in which the neutral acetonitrile ligand has been replaced by a chloride anion. Although such a reaction with chloroform has precedents in the literature,[5] little is known about the mechanism, which we are currently investigating.

Here we wish to describe an independent and efficient synthesis of this complex—a second member of this novel calix[6]arene-based family—by reaction of CuCl with $X_6Me_3Pic_3$. A ^{1}H NMR study revealed that coordination of the cuprous ion by the three Py residues and the chloride anion constrains the calixarene skeleton in a cone conformation, which exhibits chirality at low temperature.

Reacting $X_6Me_3Pic_3$ with a 1.1 molar equivalent of CuCl in a THF–MeCN mixture allowed us to isolate, in 90% yield, the new cuprous complex $[Cu(X_6Me_3Pic_3)Cl]$ (Scheme 2). The Py skeleton IR stretching frequencies§ of the complex, compared to the free ligand, suggest coordination of the cuprous ion to the pyridines. The conformational behavior of the calixarene was studied by ^{1}H NMR spectroscopy. In Fig. 1, the room and low temperature spectra of $X_6Me_3Pic_3$ in $CDCl_3$ are displayed: at 297 K, the spectrum is characteristic of a major



Scheme 1

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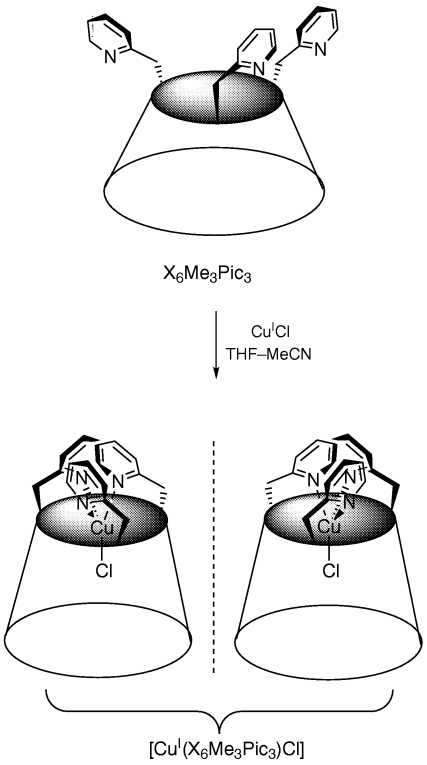
† Non-SI units employed: 1 kcal ≈ 4.18 kJ.

‡ The substructure involving the phenolic oxygens is called the lower rim.

§ IR (KBr) $X_6Me_3Pic_3$: ν_{Py} = 1595(m), 1575(w), 1480(s), 1460(sh), 1430(s) cm^{-1}; $[Cu(X_6Me_3Pic_3)Cl]$: ν_{Py} = 1605(m), 1570(w), 1480(s), 1465(sh), 1440(s) cm^{-1}.



Scheme 2

conformer possessing a flattened C_3 symmetrical cone conformation with the methoxy groups projected inside the cavity of the calixarene according to their high-field shift, thus pushing out the larger picolyl substituents.¶ However, the presence of a broad resonance at *ca.* 1 ppm between the two Bu^t peaks attests to an equilibrium with other minor conformational isomers. Indeed, this extra resonance disappeared at higher temperature, whereas the resonance of the methylene protons of the calixarene skeleton started to coalesce. At 223 K, on the other hand, new peaks characteristic of a minor conformational isomer of lower symmetry are clearly seen.

In contrast, the lines in the room temperature ^{1}H NMR spectrum of the cuprous complex [Cu($X_6Me_3Pic_3$)Cl] are surprisingly sharp (Fig. 2, top), suggesting the presence of a

¶ The conformational behavior of compounds whose structures are closely related to $X_6Me_3Pic_3$ (*i.e.*, bearing aryl substituents in place of pyridyl) has already been described in detail.[2]

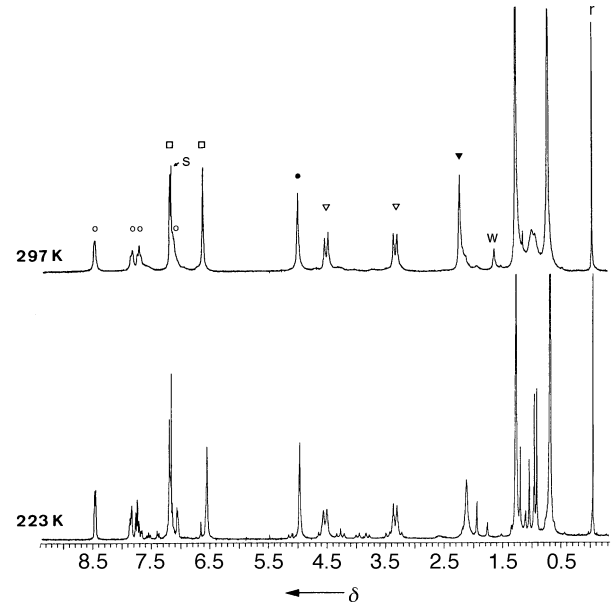


Fig. 1 Variable temperature ^{1}H NMR spectra of $X_6Me_3Pic_3$ in $CDCl_3$ at 250 MHz. (□) H_{Ar}, (○) H_{Py}, (●) CH_2Py, (▽) $ArCH_{ax}H_{eq}Ar$, (▼) OCH_3. Solvent, water and reference peaks are labeled 's', 'w' and 'r', respectively

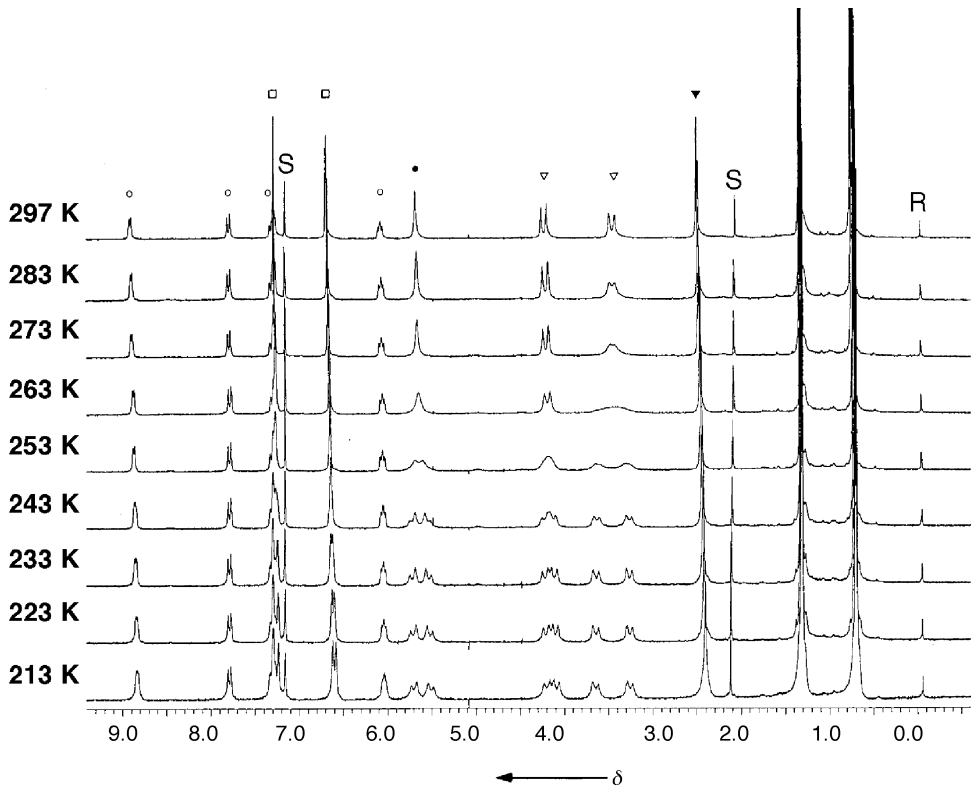


Fig. 2 Variable temperature ^{1}H NMR spectra of [Cu($X_6Me_3Pic_3$)Cl] in $CDCl_3$ at 250 MHz. From all the coalescence processes, an enantiomerization barrier of 12.8(2) kcal mol^{-1} was determined from the relationship[6] $k_c = 2.22\sqrt{(\delta\nu^2 + 6J_{AB}^2)}$. (□) H_{Ar}, (○) H_{Py}, (●) CH_2Py, (▽) $ArCH_{ax}H_{eq}Ar$, (▼) OCH_3. Solvent and reference peaks are labeled 's' and 'R', respectively

unique conformer. The simplicity of the overall profile together with the large shifts for the Py protons (compared to the free ligand) are in accordance with the formation of a mononuclear complex possessing a cone structure of C_3 symmetry. A 2D EXSY (exchange spectroscopy) study, recorded at 297 K and with $\tau_m = 300$ ms, showed no exchange peaks for the axial and equatorial methylene protons of the cyclic skeleton under the same conditions where these were observed for the free ligand. This demonstrates that the cone-cone inversion of the calixarene was inhibited, at least on the timescale of the NMR experiment:[3e,f] coordination of Cu^+ to the three Py groups draws them toward the annulus of the calixarene, thereby ejecting the methoxy groups‖ and rigidifying the whole edifice. Molecular conductivity studies have been carried out at 296 K in order to compare $[Cu(X_6Me_3Pic_3)NCMe]^+PF_6^-$ with $[Cu(X_6Me_3Pic_3)Cl]$ (*ca.* 1×10^{-3} M): in THF the molar conductivity Λ_M of the cationic complex was 12.6(1) Ω^{-1} cm^2 mol^{-1}, whereas no electrical conductivity was detectable for $[Cu(X_6Me_3Pic_3)Cl]$; in DMF, Λ_M was 59(1) Ω^{-1} cm^2 mol^{-1} for the former complex** and only 12(1) Ω^{-1} cm^2 mol^{-1} for the latter. These values suggest that $[Cu(X_6Me_3Pic_3)Cl]$ is essentially electroneutral, the chloride anion being only partly dissociated from the metal center in a highly polar solvent such as DMF. Furthermore, on the time course of the reaction of $[Cu(X_6Me_3Pic_3)NCMe]^+$ with chloroform leading to $[Cu(X_6Me_3Pic_3)Cl]$, the ^{1}H NMR signal corresponding to the coordinated acetonitrile molecule gradually vanished with a concomitant increase of the signal of uncoordinated MeCN. This shows that the acetonitrile ligand, which occupied the fourth coordination site situated inside the cavity of the calixarene, has been replaced by the anionic chloride ion. Finally, this new compound appeared insensitive to oxidation since bubbling dioxygen through a millimolar solution of the cuprous complex gave rise neither to a color change (which would indicate the formation of cupric species) nor to a modification of its ^{1}H NMR pattern. This surprising inertness may be ascribed to the high steric hindrance around the metal center, which prevents either coordination of O_2 or formation of binuclear cupric complexes that are usually quickly formed upon the reaction of dioxygen with Cu^+ in solution.[8,9]

An energy-minimized structure obtained through computer modeling†† is shown in Fig. 3: the cuprous ion is in a regular tetrahedral geometry with C_{3v} symmetry and the Cl^- ion along the z axis. The three Py ligands wrapping the metal form a helix that caps the lower rim of the calixarene.

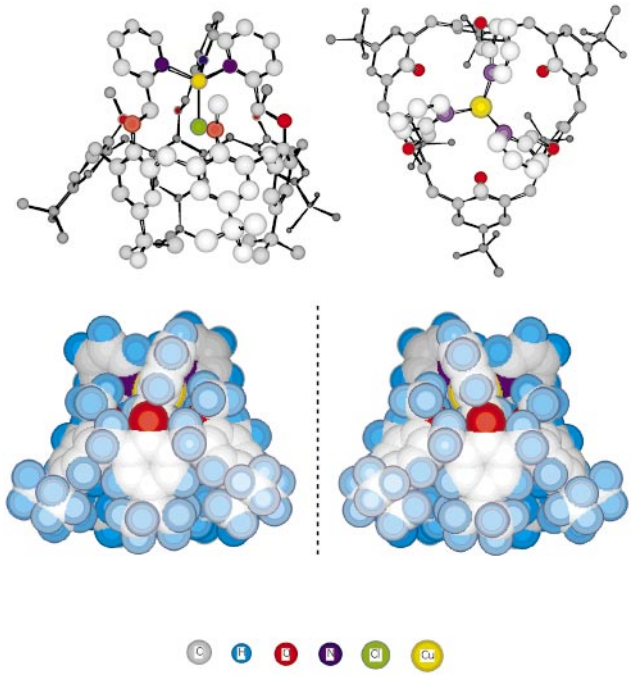


Fig. 3 Energy minimized†† structure of $[Cu(X_6Me_3Pic_3)Cl]$. (*Top*) Ball-and-stick representations of the top view (left) and profile view (right); hydrogen atoms are omitted for clarity. (*Bottom*) Space-filling representation of the profile view as a pair of enantiomers

Noticing the potential chirality of such a helical structure,‡‡ we sought to check whether the two enantiomeric forms could be characterized.

Indeed, a series of ^{1}H NMR spectra recorded at low temperature (Fig. 2, bottom), revealed a diastereo-differentiation of the methylene protons linked to the Py ligands: the singlet observed at 297 K was split into two doublets of equal intensity at temperatures below 253 K. Likewise, each set of resonances, corresponding to the two methylene and aromatic protons of the calixarene skeleton, were split into pairs. The Bu^t, Me and Py protons, on the other hand, were unaffected. In order to confirm that $[Cu(X_6Me_3Pic_3)Cl]$ consists of a pair of enantiomers connected by a conformational equilibrium, we recorded its ^{1}H NMR spectrum in the presence of Pirkle's chiral shift reagent§§ (Fig. 4). We found the reagent effective, provided that the temperature was low enough, that is below the coalescence temperature. At 223 K, the splitting into pairs was observed for the methylene and methyl groups linked to the phenolic functions of the calixarene skeleton, allowing us to measure a 2 : 3 integral intensity ratio for the diastereomers [d.e. = 40 ± 4%]. Finally, the temperature T_c, below which the enantiomers could be differentiated by ^{1}H NMR spectroscopy, was increased by 10 K when CuBr replaced CuCl for the synthesis of the cuprous complex. This can be related to the larger size of the fourth ligand (Br *vs.* Cl), which induces an increase of the steric bulk around the metal ion and hence a rigidification of the whole edifice.

Although many helical structures have been described using Cu^+ ions as an anchor,[10] they generally involve ligands with multiple diimine binding sites. The resulting strong complexation provided by a pair of bidendate ligands constrains the cuprous ion in a C_{2v} symmetric tetrahedral geometry with $N4$

‖ Although the high-field shift ($\delta_H = 2.3$) for the methoxy groups of the free ligand is in agreement with their location in the annulus of the calixarene,¶ one could wonder about the relatively low down-field shift ($\delta_H = 2.6$) observed upon complexation. However, in the case of the closely related complex $[Cu(X_6Me_3Pic_3)NCMe,PF_6]$, a relatively high-field value ($\delta_H = 3.0$) was observed as well.[4] Since a normal signal between 3.5 and 4.0 ppm is expected for a conformation in which the methoxy groups are standing outside of the cavity, a possible explanation may lie in the particular geometry of the system, which constrains the methyl substituents in the anisotropic cone of the aromatic π shell of the coordinating pyridines (see Fig. 3).

** This value is in agreement with a 1 : 1 electrolyte.[7]

†† The molecule was sketched and optimized by using the esff force field of the Biosym package Insight/Discover (Release 95.0, Biosym/MSI, San Diego, CA, 1995), on an IBM RISC 6K workstation. The standard Discover 3 algorithms were selected with their default inputs (0.001 for BFGS Newton energy convergence). Due to the medium size of calixarenes, no cutoff was used to compute the non-bond contribution. The geometry around the metal center and the conformation of the calix[6]arene obtained after energy minimization are very similar to those depicted in the X-ray structure[4] of $[Cu(X_6Me_3Pic_3)NCEt]^+$. Modeling of the complex with the chloride ligand standing outside of the calixarene cavity gave rise to a flattened tetrahedral geometry around the metal center and a calculated steric energy increased by 25 kcal mol^{-1}.

‡‡ Although the crystallographic unit cell of the closely related complex $[Cu(X_6Me_3Pic_3)NCEt,PF_6]$ contained two enantiomeric molecules, rapid exchange occurred in solution, hence preventing differentiation of the diastereotopic protons by ^{1}H NMR under similar experimental conditions.[4]

§§ For a previous example of the use of Pirkle's reagent with a chiral calix[6]arene, see ref. 3*g*.

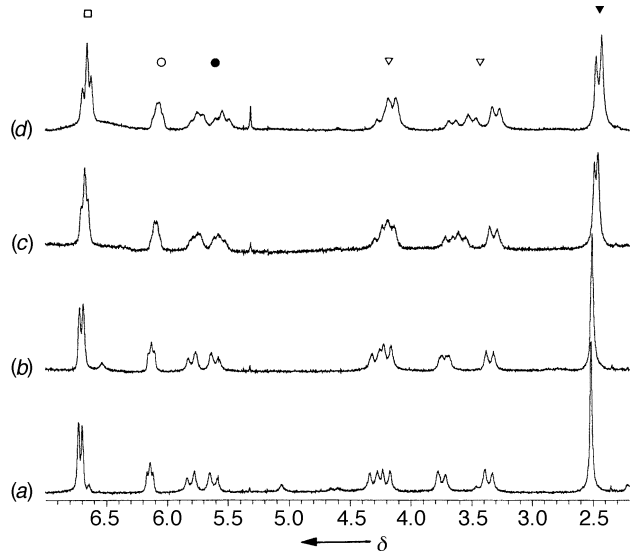


Fig. 4 Partial ^{1}H NMR spectra ($CDCl_3$, 250 MHz) at 223 K of $[Cu(X_6Me_3Pic_3)Cl]$ (10 mM) with gradual addition of Pirkle's reagent [(*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol: R*OH]§§. (*a*) Without R*OH and with (*b*) 1.2 equiv., (*c*) 8 equiv. and (*d*) 13 equiv. R*OH. (□) H_{Ar}, (○) H_{Py}, (●) CH_2Py, (▽) $ArCH_{ax}H_{eq}Ar$, (▼) OCH_3

coordination set. The complex $[Cu(X_6Me_3Pic_3)Cl]$ thus represents an interesting case where, out of the four coordination sites, only three really do participate in the formation of the helix. The resulting chirality is transmitted to the calixarene skeleton, thereby providing a chiral cavity around the apical binding site occupied by the halide. While calix[6]arenes that are capped with a triple covalent linkage[3c–f] have previously been shown to be partially immobilized in a unique cone conformation with potential chirality, our complex represents the first case where the two C_3 symmetrical enantiomers could be distinguished in solution.

This work demonstrates that although very flexible, a properly functionalized calix[6]arene can participate both in the formation of a stable mononuclear transition metal complex and in the construction of a chiral edifice in the coordination sphere of the metal. The environment provided by the *N*3 donor set of the new ligand $X_6Me_3Pic_3$ is reminiscent of the polyimidazole anchor for cuprous ion at mononuclear sites of cupro-proteins. Hence, the chiral hydrophobic cavity of the calixarene twisted around the remaining fourth binding site of Cu^+ makes it highly relevant to biological systems.[8,11] The synthesis of related complexes that could be chiral at room temperature, as well as the study of their reactivity, is under investigation.

Experimental

Unless otherwise noted, chemicals were obtained from commercial suppliers and were used without further purification. THF was freshly distilled from sodium–benzophenone. MeCN was distilled over P_2O_5 and was kept under argon on molecular sieves. ^{1}H NMR spectra were recorded at 250 MHz (Bruker ARX 250 spectrometer) in $CDCl_3$. The standard Bruker NOESYTP program was used for 2D EXSY measurements using a $^1H/^{13}C$ inverse probe. A high resolution MS/MS mass spectrometer (ZabSpec TOF Micromass) was used for recording mass spectra with electrospray ionization (in CH_2Cl_2) and positive detection mode.

$[Cu(X_6Me_3Pic_3)Cl]$

In a Schlenk flask containing $X_6Me_3Pic_3$ (200 mg, 0.155 mmol) and CuCl (17 mg, 0.170 mmol, 1.1 equiv.) under an argon stream, were successively introduced dry, dioxygen-free THF (4 ml) and MeCN (1 ml). The mixture was stirred for 4 h, then filtered over Celite and concentrated by bubbling argon through the pale yellow solution. The white precipitate thus obtained was collected by filtration, washed with MeCN, recrystallized from $CHCl_3$–MeOH and finally dried under vacuum for two days at 30 °C. Yield: 214 mg (0.139 mmol, 90%). Mp > 270 °C (dec.). Anal. calcd for $C_{87}H_{105}N_3O_6CuCl \cdot 2H_2O \cdot CHCl_3$: C 68.49, H 7.18, N 2.72; found: C 68.48, H 7.26, N 2.79. ESI-HRMS, *m*/*z* calcd for $C_{87}H_{105}N_3O_6{}^{63}Cu^+$ ($[M - Cl]^+$): 1350.7299; found: 1350.7295 (100%); a small peak at *m*/*z* = 1386.7 ($[M - H]^+$, 1%) was detected: its isotopic pattern confirmed the presence of one chlorine and one atom of copper. ^{1}H NMR (297 K, $CDCl_3$): δ = 0.86 (s, 27H, Bu^t), 1.45 (s, 27H, Bu^t), 2.6 (s, 9H, OCH_3), 3.56 (d, *J* = 16 Hz, 6H, $Ar{-}\alpha CH_{eq}$), 4.34 (d, *J* = 16 Hz, 6H, $Ar{-}\alpha CH_{ax}$), 5.78 (s, 6H, $Py{-}\alpha CH_2$), 6.18 (t, *J* = 5 Hz, 3H, Py*H*), 6.79 (s, 6H, Ar*H*), 7.38 (s, 6H, Ar*H*), 7.38 (t, *J* = 3 Hz, 3H, Py*H*), 7.89 (d, *J* = 8 Hz, 3H, Py*H*), 8.99 (d, *J* = 5 Hz, 3H, Py*H*).

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