Precatalysts Involved in Copper-Catalyzed Arylations of Nucleophiles

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Received August 4, 2006

In spite of the importance of ligand/copper-catalyzed arylations of nucleophiles in organic chemistry, their mechanism and in particular the interactions between ligands and copper have not been well understood until now. In this work, we synthesized a precatalyst involving one of the best ligands of the literature, the tetradentate chelator **1**, and characterized it at the solid state and in solution (NMR, electrochemistry, X-ray crystallography). Thanks to the information collected, we now have a better understanding of the role of the ligand (influence on the solubility of copper and on its electrochemical properties) and the role of the solvent and can propose a description of the various reactions taking place at the early stages of copper-catalyzed arylations of nucleophiles. We thus showed that, in acetonitrile, the association of tetradentate ligand and copper(I) salts leads to the formation of an insoluble dimeric complex, behaving like a copper(I) reservoir. A very small part of the latter is soluble, but its structure is lost to the benefit of a monomeric form. This monomer, in which the copper center is at the +I oxidation level and made electron-rich by the ligand, is the only species present at the beginning of the catalytic process.

Introduction

The classical copper-mediated Ullmann and Goldberg reactions are extremely powerful tools in organic chemistry since they allow the creation of C(aryl)−N, C(aryl)−O, and C(aryl)−S bonds.[1] They are thus involved in numerous industrial applications such as the synthesis of intermediates as well as synthetic targets throughout the life science and polymer industries. However, major drawbacks of such protocols remain. These are harsh reaction conditions (high temperature in particular) and, most of the time, the use of stoichiometric amounts of copper salts. This last feature results in the production of huge amounts of wastes, making these methods now unacceptable for the environment. However, the intense attention received by these methodologies over the past 6 years resulted in some of these problems being overcome: it was indeed found that a wide range of additives, mainly neutral bidentate chelators, strongly accelerated the coupling reactions of aryl halides with various nitrogen, oxygen, or sulfur nucleophiles and enabled the performance of these reactions at mild temperatures (<120 °C). We have discovered that inexpensive chelating ligands combining nitrogen and/or oxygen chelating atoms, the tetradentate ligand **1** in particular, conferred a strong activity to copper in a wide range of copper-catalyzed reactions.[2−4] Arylation of various nucleophiles such as nitrogen nucleophiles,[2d,e] phenols,[2a,c] and malonic acid derivatives[2e] with aryl halides (Scheme 1) or vinylation reactions of azoles and phenols by vinyl bromides[4] could thus be carried out under very mild temperature conditions (20−80 °C). For all of these cross-coupling reactions, we noticed that the use of acetonitrile as the solvent is crucial to optimize the efficiency of ligand **1**.

It is worth noting that the mechanism involved in copper-mediated arylations has not been well-established: the only

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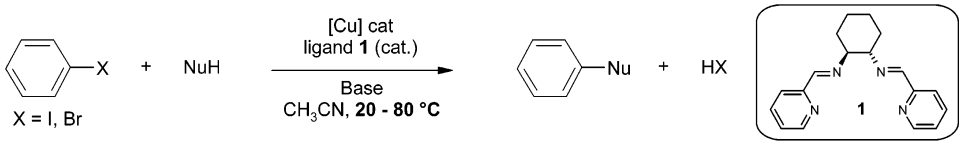
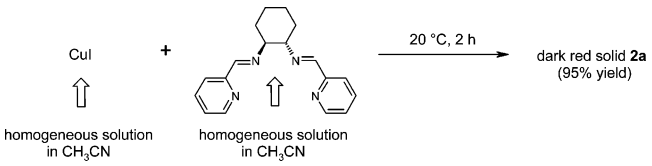
10.1021/om060706n CCC: $37.00
Publication on Web 12/01/2006

Scheme 1. Ullmann-Type Condensations under Very Mild Conditions in the Presence of the Tetradentate Ligand 1[2−4]



NuH = phenols, nitrogen heterocycles (mono-, di- and triazoles), amide derivatives, malonates

Scheme 2. Synthesis of Complex 2a



proposals[5] discussed have not been supported by experimental evidence.[1b,6] For instance, the role of the ligands, the solvents, and the oxidation states of the soluble copper species present at the beginning of the catalytic process have not been well-determined.[7]

In this paper, we have attempted to answer some of these questions through synthesizing and studying by X-ray crystallography, NMR, and cyclic voltammetry the precatalytic complexes formed in acetonitrile from the association of copper salts with our primary ligand **1**.

Results and Discussion

Synthesis of the Copper Complex Resulting from the Reaction of Copper Iodide and Tetradentate Ligand 1. A homogeneous solution of the ligand (*RR*,*SS*)-*trans*-**1** (racemic mixture) in acetonitrile, a solvent conferring a strong catalytic activity to our copper-based system,[2−4] was first added to a stoichiometric amount of copper iodide dissolved in the same solvent (Scheme 2). An air-stable and light-insensitive dark red solid (complex **2a**) immediately precipitated from the mixture (95% yield). Crystals could be obtained, and the structure of **2a** was determined by X-ray crystallography (Figure 1). It is worth noting that the remaining 5% of the materials, whose structure will be described below (see the NMR studies below), were soluble in acetonitrile.

Structure and Oxidation State of Complex 2a. Complex **2a** was found to be a dimeric dicopper complex which crystallized with two acetonitrile molecules. The two copper atoms, at the +I oxidation state, were separated by a distance of 4.6 Å, the iodide anions being out of the coordination sphere of the metal (d(Cu−I) = 5.8 Å) (Figure 1c,d). The copper(I) atoms displayed a distorted four-coordinated tetrahedral geometry, each copper atom being ligated by two imine and two pyridine nitrogen donors. In addition, both halves of compound **2a** were related by an inversion center, so that the halves of each ligand involved in the dimer were diastereotopic (Figure 1a).

The dimeric structure was also observed by electrospray ionization mass spectroscopy (ESIMS), a very soft technique that causes minimal fragmentations,[8] since the corresponding stable $Cu_2(\mathbf{1})_2^{2+}$ ion was detected in the ESI mass spectrum of complex **2a** (m/z 355). It is worth noting that a copper(I) complex involving the (*R*,*S*)-cis diastereoisomer of our tetradentate ligand **1**, studied by van Koten and co-workers,[9] was also found to be a binuclear complex; however, it displayed a C_2 axis instead of an inversion center.

Catalytic Activity of Complex 2a. The catalytic activity of complex **2a** was then tested in copper-catalyzed phenol arylations, which we previously studied extensively.[2a,c] For this purpose, arylation of 3,5-dimethylphenol with iodobenzene in the presence of tripotassium phosphate was chosen as a model (Table 1). We were pleased to find that **2a** was able to efficiently catalyze this coupling, phenyl 3,5-dimethylphenyl ether being obtained in 77% yield after 24 h at 80 °C (Table 1, entry 1). The outcome of the reaction was the same as when the complex was generated in situ (Scheme 1) from equimolar amounts of copper iodide and ligand 1 (entry 2). As described in our previous papers,[2] ligand **1** induced a significant acceleration of the coupling, since without additional ligand, the diaryl ether **3** was formed in only 30% yield after 24 h in refluxing acetonitrile (entry 3).

Hence, complex **2a** constituted an efficient catalytic precursor for Ullmann-type condensations. It was then interesting to know whether its structure, dimeric in the solid state (Figure 1), was retained or not in the solvent used in our arylation reactions: that is to say, in acetonitrile.[2−4] For that purpose, NMR studies were carried out in the latter.

Structures of Copper Complexes Involving Ligand 1 in Solution: NMR Studies. Complex **2a** $[Cu_2(\mathbf{1})_2]I_2$ being weakly soluble in acetonitrile (5%, Scheme 2), it was difficult to obtain fruitful information from its spectrum in solution (poor signal/noise ratio and resolution). Fortunately, its hexafluorophosphate analogue $[Cu_2(\mathbf{1})_2](PF_6)_2$ (**2b**), obtained from tetrakis(acetonitrile)copper(I) hexafluorophosphate, was soluble enough to be studied by NMR in deuterated acetonitrile.

(5) The four main mechanisms proposed in the literature involve (1) oxidative addition/reductive elimination of ArX on copper(I), (2) π-complexation of ArX on copper(I), (3) Lewis-type complexation of ArX on copper(I), or (4) aryl radical intermediates. None of these mechanisms have been confirmed by experimental proofs.

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(7) However, it is worth noting that, recently, Buchwald's works suggested that the role of (dimethylamino)cyclohexane in copper-mediated arylation of amides was to avoid formation of copper complexes containing two amidates, which are unable to promote the coupling. Note that this study only concerned the particular case of amidation reactions: Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120.

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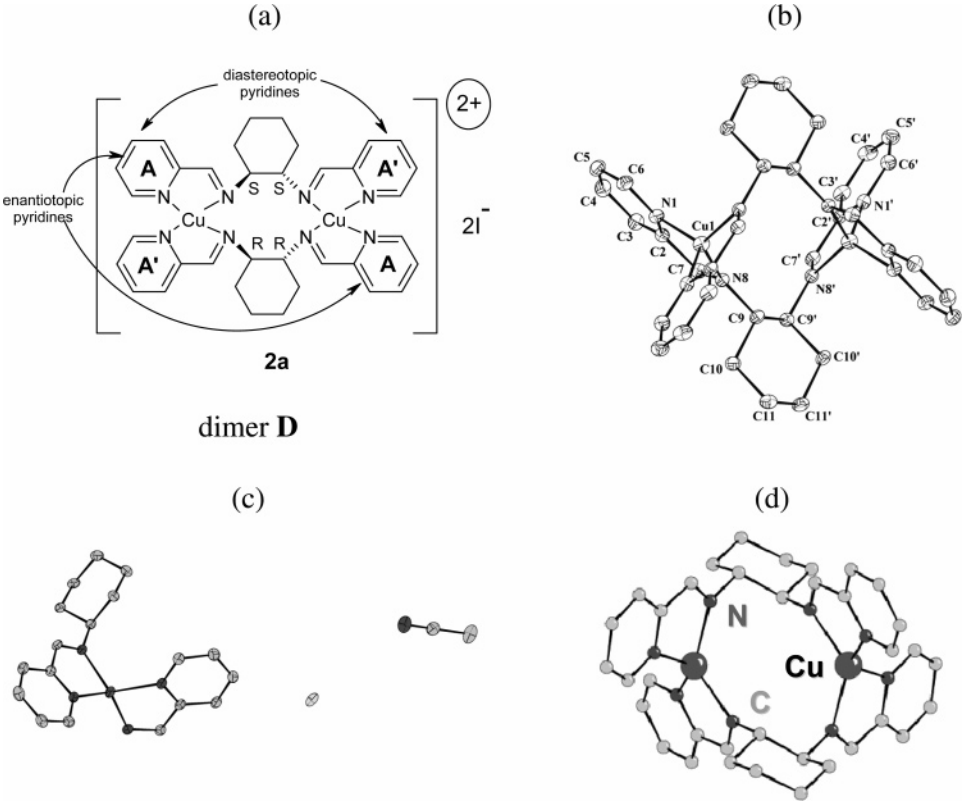
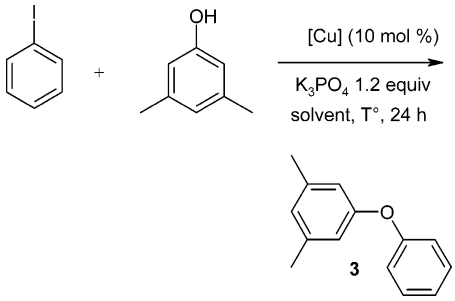


Figure 1. Structure of the dicopper complex **2a**: (a) schematic representation; (b−d) CAMERON views.

Table 1. Catalytic Activity of Complexes 2a ($[Cu_2(1)_2]I_2$) and 2b ($[Cu_2(1)_2](PF_6)_2$)[a]



entry	solvent	*T* (°C)	[Cu]	yield of **3** (%)[b]
1	CH_3CN	80	**2a**	77[d]
2	CH_3CN	80	CuI + **1**[c]	78[d]
3	CH_3CN	80	CuI without ligand	30
4	CH_3CN	80	**2b**	79[d]
5	CH_3CN	40	**2b**	26[e]
6	CH_3CN	40	CuI without ligand	0[e]

[a] Reaction conditions: iodobenzene (0.5 mmol), 3,5-dimethylphenol (0.6 mmol), K_3PO_4 (0.6 mmol), [Cu] = 0.05 mmol, CH_3CN (300 μL). [b] GC yields determined with 1,3-dimethoxybenzene as internal standard. [c] Complex generated in situ; CuI/**1** = 1:1. [d] Selectivity ∼96%; only byproduct: benzene resulting from dehydrohalogenation of PhI. [e] 70 h instead of 24 h.

We first checked that complex **2b** was able to promote the arylation of 3,5-dimethylphenol with iodobenzene under the standard conditions (Table 1, entry 4).[10] Having established that complexes **2a**,**b** displayed identical catalytic activities (entries 1 and 4), the behavior of the latter was studied in deuterated acetonitrile (Figure 2b).

The corresponding spectrum displayed the presence of a major symmetrical species (denoted **M**). The latter exhibited similar signal patterns in comparison with the free ligand (Figure 2a,b), but some at different chemical shifts: in particular, the signals for imine protons H_7 and cyclohexane protons H_9 were found to be shifted to lower field and those of pyridine protons H_3 and H_6 to upper field, whereas signals for protons H_4 and H_5 were not nearly so affected. Thus, the modifications concerned mainly protons close to potentially coordinating nitrogen atoms, which probably indicated that both types of nitrogens were coordinated to copper(I) within complex **M**.

It is worth noting that "both halves" of the ligand involved in species **M** were magnetically equivalent, as in the case of the free ligand. In this way, for instance, both imine protons H_7 gave rise to a unique singlet at 8.59 ppm.[11] Such a spectrum did not correspond to that expected for the dimeric complex described in Figure 1. Indeed, due to the inversion center previously mentioned, signals for protons of both py-2-CH═N moieties belonging to a given ligand were expected not to be magnetically equivalent and to display consequently distinct signals. Species **M** was thus believed to be a symmetric monomer (Figure 2).

The latter could result from the conversion of the dimeric complex **D** under the effect of coordinating acetonitrile. Indeed, this solvent, known to be a ligand for copper(I),[12] could favor the opening of **D**, via the partial coordination of ligand **1** as proposed in Scheme 3.

This hypothesis was reinforced by the fact that dimer **D** was also observed in the reaction mixture. Indeed, we could assign the set of minor broad signals detected in addition to **M** (Figures 2b, 3b, and 4a) to the dimeric complex **D** by performing variable temperature NMR and by changing the nature of the solvent.

(10) The catalytic activity of **2b** was also evaluated at 40 °C, since the complex has been studied up to that temperature by proton NMR in CD_3CN (see Figure 3a): at that temperature, the coupling was slower, phenyl 3,5-dimethylphenyl ether being obtained in 26% yield after 70 h (Table 1, entry 5). Better yields can be achieved by increasing the reaction time.

(11) It was, of course, the same for all of the other protons of the complexed ligand.

(12) Lahn, B.; Rehahn, M. *Macromol. Symp.* **2001**, *163*, 157.

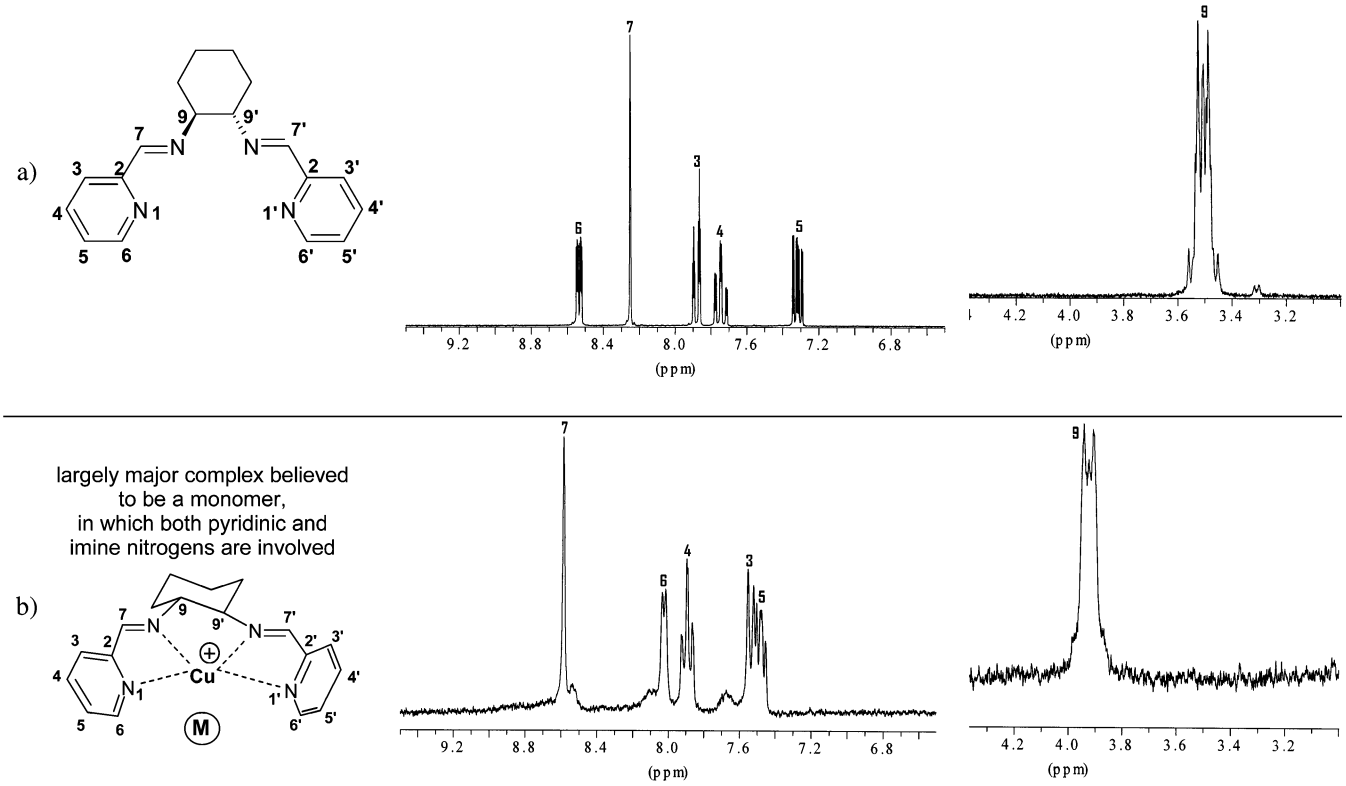
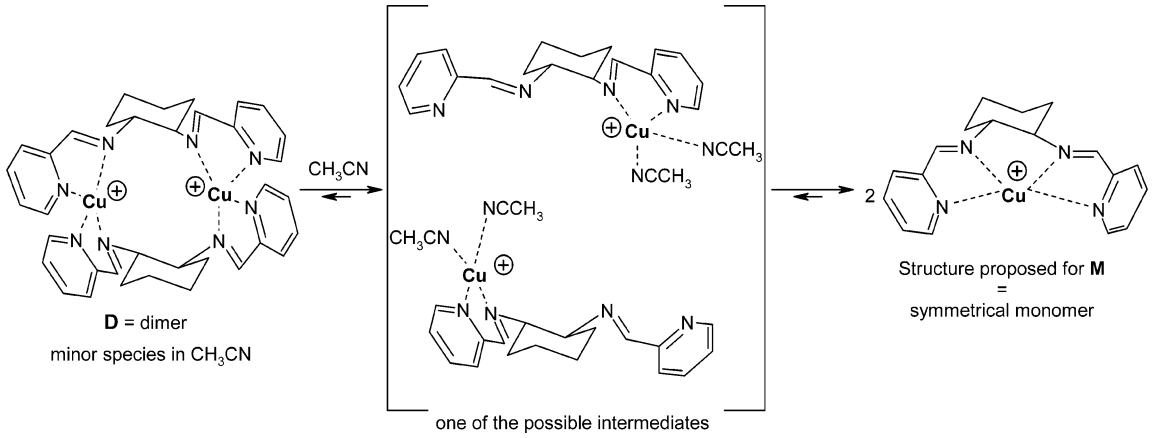


Figure 2. ^{1}H NMR in CD_3CN (250 MHz; 20 °C): (a) free ligand **1**; (b) **2b** (homogeneous solutions).

Scheme 3. Equilibrium in Solution between the Dimer and the Symmetrical Monomer: Possible Pathway[a]



[a] Counteranions have been omitted for clarity.

Thus, recording the spectrum at 0 and −30 °C led to a refinement of these minor signals and to the emergence of two singlets at 8.91 and 8.67 ppm, respectively (Figure 3c,d). The latter corresponded to the signals of the two nonmagnetically equivalent imine protons H_{7D} and $H_{7'D}$ involved in the dicopper complex **D** (Figure 3d). Two other patterns emerged at 4.47 and 3.73 ppm, which could be assigned to cyclohexane protons H_{9D} and $H_{9'D}$. At this stage of the study, however, it was difficult to completely describe **D**, since the dimer was a minor species regardless of temperature (Figure 3).

However, we were pleased to find that, after addition of noncoordinating deuterated dichloromethane to the previous sample, the proportion of **D** increased at the expense of **M** (Figure 4). In pure CD_2Cl_2 (Figure 4d and Figure 5a), species **D** was even found to be the major complex in solution, coexisting with **M** (**M**/**D** = 1:2.7 at 20 °C). Both sets of signals were then assigned from a 2D NMR spectrum (COSY: Figure 5b). As expected, **D** displayed two distinct resonance patterns for the pyridine ring (H_2 to H_6), for the imine protons (H_7), and for the cyclohexane protons H_9.

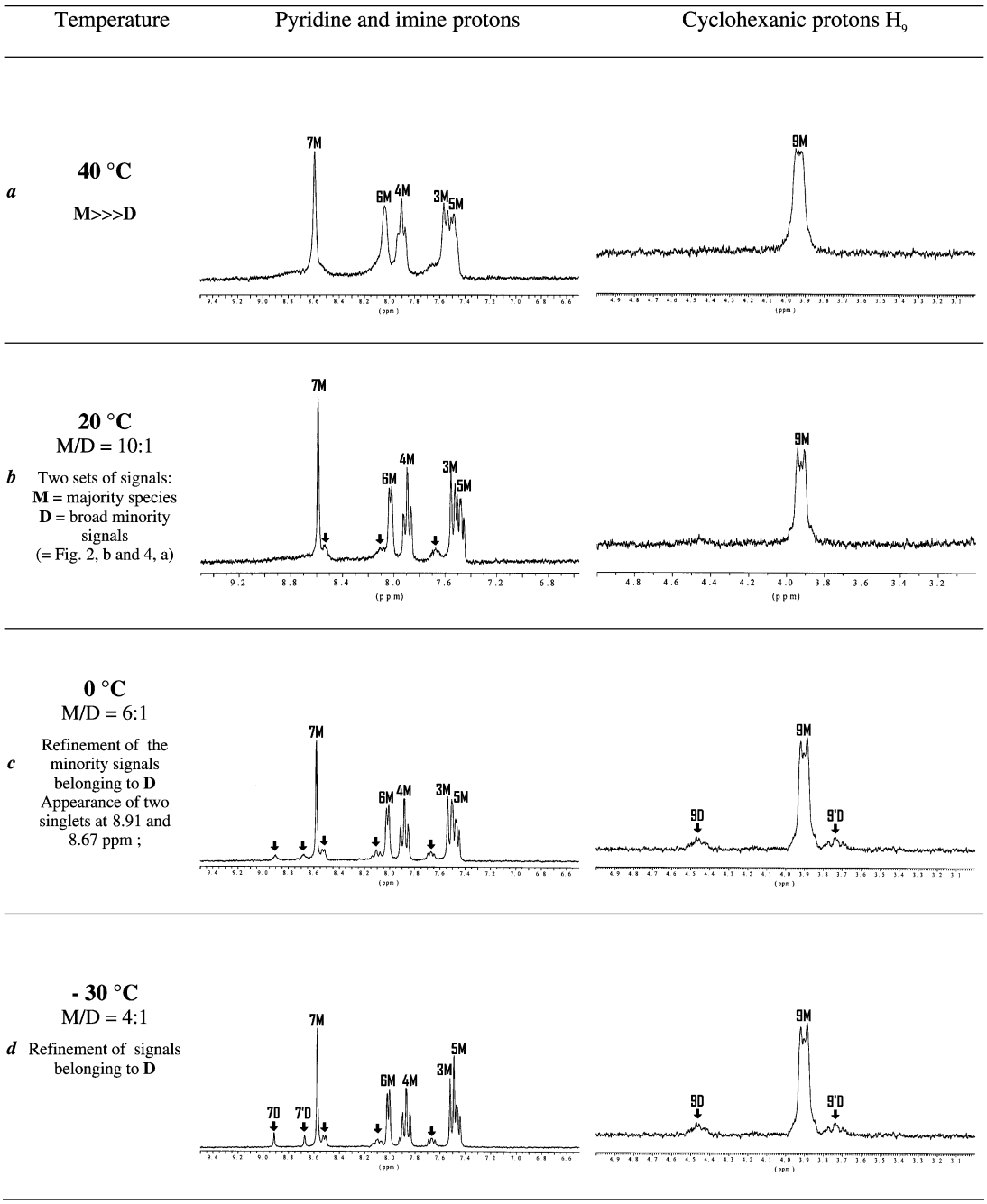


Figure 3. ^{1}H NMR spectra of complex **2b** in CD_3CN recorded at different temperatures (250 MHz).

Interestingly, Brooker and al. also observed that the acetonitrile-promoted displacement of equilibrium between dimeric and monomeric copper(I) complexes, proposed above, took place in the case of very similar ligands, possessing imine and pyridazine nitrogen donors (Chart 1).[13]

In conclusion, NMR studies thus demonstrated that, on dissolution in acetonitrile at 20 °C, the dimeric structure of our copper(I) complex (Figure 1) was almost totally lost to the benefit of a symmetrical monomer. As shown below, we also observed this phenomenon by means of electrochemical studies. Finally, it is worth noting that, from a temperature of 30 °C (see for example the spectra of the medium at 40 °C, Figure 3a), only the monomeric form is present in the solution.

Cyclic Voltammetry of Complex 2b in Acetonitrile. The cyclic voltammetry of complex **2b** was indeed performed at 20 °C in acetonitrile (Figure 6a, solid line). The corresponding voltammogram displayed a quasi-reversible Cu(I/II) oxidation process at +0.49 V and a chemically irreversible Cu(I/0) reduction process at −1.52 V. Interestingly, both oxidation and reduction processes exhibited two very close peaks (see Figure 6b,c, giving enlargements of Figure 6a), which indicated the presence of two complexes in solution, one of them being very predominant. Moreover, the ratio of these complexes, as expressed by their relative oxidation peak currents, varied with the initial concentration of complex **2b** in CH_3CN ($[Cu]_0 = 2$,

(13) Brooker, S.; Davidson, T. C.; Hay, S. J.; Kelly, R. J.; Kennepohl, D. K.; Plieger, P. G.; Moubakari, B.; Murray, K. S.; Bill, E.; Bothe, E. *Coord. Chem. Rev.* **2001**, *216-217*, 3. This study deals with a tetracopper(I) complex involving the octadentate ligand L. L, comprising four imine nitrogen donors and four pyridazine nitrogen donors, could thus be regarded as a "dimer" of our tetradentate ligand **1**. According to proton NMR spectra, the structure of the tetracopper(I) complex was maintained in noncoordinating solvents such as nitromethane and acetone, whereas in acetonitrile, the latter existed in equilibrium with a dicopper(I) complex, resulting from the opening of the tetramer under the effect of the solvent.

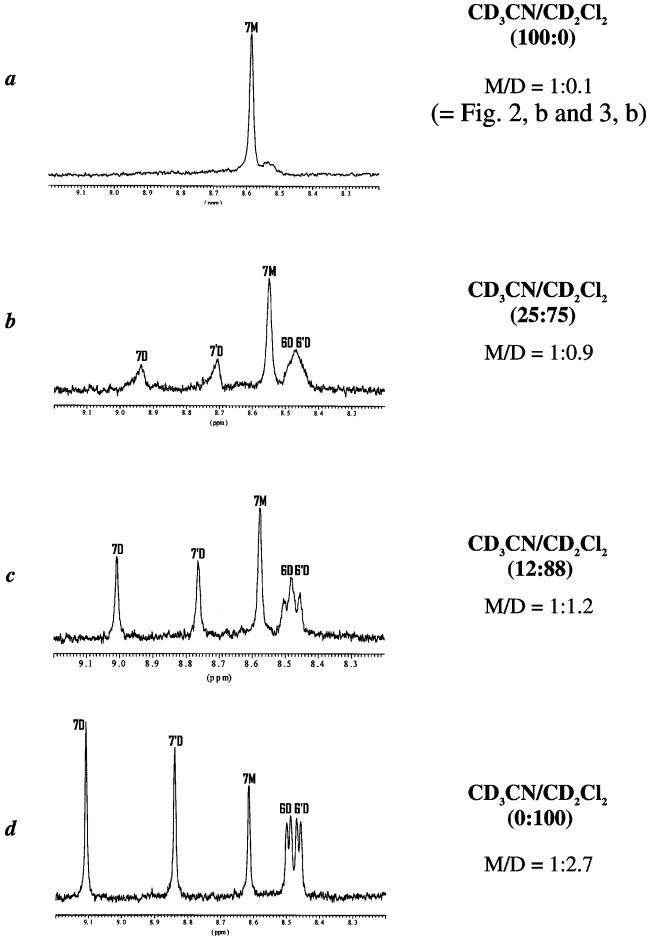


Figure 4. Spectra of **2b**: effect of the solvent on the proportions of **M** and **D** (20 °C, 250 MHz). For clarity, only the area 8.2−9.2 ppm has been depicted, but the corresponding evolution is obvious for the whole spectrum.

1 mM, Figure 6c). This suggests a reversible dissociation of dimer **2b** into its monomeric form (Scheme 3), whose concentration was expected to increase when the initial concentration of **2b** was decreased. For $C_0 = 1$ mM (Figure 6c, right), the major complex would thus correspond to the monomeric complex, which underwent the first oxidation at +0.44 V and the first reduction process at −1.35 V. Hence the second and very weak peak could be assigned to the dimeric form, whose oxidation and reduction would occur at +0.55 and −1.53 V, respectively.

Consequently, these electrochemical studies, consistent with the coexistence of a major monomeric and a very minor dimeric form in acetonitrile, at least at 20 °C, corroborated the NMR studies (Figure 2b).

Other interesting information could be obtained from this study. First of all, the results of the electrochemistry demonstrated that, in solution, the copper complexes were at the +I oxidation level, as in the solid state (Figure 1).

In addition, the influence of ligand **1** on the oxidation and reduction potentials of copper(I) was also evaluated. For that purpose, the cyclic voltammetry of complex **2b** was compared to that of the tetrakis(acetonitrile)copper(I) complex $Cu(CH_3CN)_4PF_6$ (Figure 6a, dashed line). We chose the latter, formed when dissolving a copper(I) salt in acetonitrile in the absence of additional ligand,[14,15] because it was not able to efficiently catalyze the arylation reaction (Table 1, entries 3 and 6). The voltammogram of $[Cu(CH_3CN)_4]^+$ exhibited a quasi-reversible Cu(I/II) oxidation process at +1.10 V and a quasi-reversible reduction process at −0.80 V. Ligand **1** thus made the copper(I) center more electron-rich, its oxidation potential being significantly lower within the soluble monomer (decrease of about 0.8 V: Figure 6a).

Hence, one of the roles of ligand **1** would be to make the copper(I) center more electron-rich at the early stages of the catalytic process. These results could be in agreement with a mechanism involving an oxidative addition of the aryl halide with a copper(I) complex as the first step of the catalytic cycle.

Summary of the Results: Precatalysts Formed in Copper-Catalyzed Arylations Involving Ligand 1. Thanks to the information collected in the preceding studies, we can propose a description of the various stages taking place at the early beginning of copper-catalyzed arylations of nucleophiles (Scheme 4).

(a) Generation of a Copper(I)-Insoluble Reservoir: Precatalyst D. First, the addition of equimolar amounts of ligand **1** to a homogeneous solution of copper(I) salts in acetonitrile led to the almost quantitative precipitation of a dimeric dicopper(I) complex, obtained in 95% yield by straightforward filtration (Scheme 2) and characterized by X-ray methods. The latter, displaying high catalytic activity in phenol arylations, was then poorly soluble in acetonitrile,[16] the solvent of choice to carry out coupling reactions. In addition, the remaining 5% of the complex was soluble in acetonitrile (see the solubility equilibrium in Scheme 4) but its dimeric structure was mainly lost to the benefit of a monomeric intermediate involved in the catalytic process.

An examination of the literature shows that few studies have been carried out to give a plausible explanation for the ligand effect and to understand why ligands can confer to copper a higher activity.[7] However, some authors have proposed the contribution of the ligand as a solubilizing agent for the copper source,[6g,n,q,17] although such a hypothesis was not supported by experimental evidence.

We are sure that our tetradentate ligand **1** did not act as a solubilizer. One of the roles of ligand **1** might rather be to "store" the main part of copper in the insoluble dimeric form, preventing any degradation process in solution (dismutation of Cu(I), for example). The precatalyst could thus be "kept alive", partially solubilized in a monomeric form involved in the catalytic cycle and displayed at very low concentration in the reaction mixture. This latter assumption was supported by the fact that it was possible to decrease the catalyst loading from 10 mol % to 2 mol %, without affecting the outcome of the coupling of 3,5-dimethylphenol with iodobenzene (Figure 7).

(b) Generation of a Copper(I)-Soluble Precatalyst: Monomer M. As previously indicated, NMR and electrochemical studies revealed that in acetonitrile the weak amount of solubilized dimeric structure was mainly lost to the benefit of a symmetrical monomeric complex, in which the copper center is at the +I oxidation level and made highly electron-rich by the ligand (Scheme 4).

In addition, when the temperature of the medium increased, only the monomer was present starting from a temperature of 30 °C (see, for example, the spectrum of the medium at 40 °C:

(14) Hathaway, B. J. In *Comprehensive Coordination Chemistry*, 1st ed.; Wilkinson, G., Gaillard, R. D., McCleverty J. A., Eds.; Pergamon Press: Oxford, U.K., 1987; Vol. 5, pp 536−537.

(15) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; Wiley: New York, 1988; pp 755−775.

(16) The solubility of this complex is also very weak, even on reflux in acetonitrile.

(17) Marcoux, J. F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539.

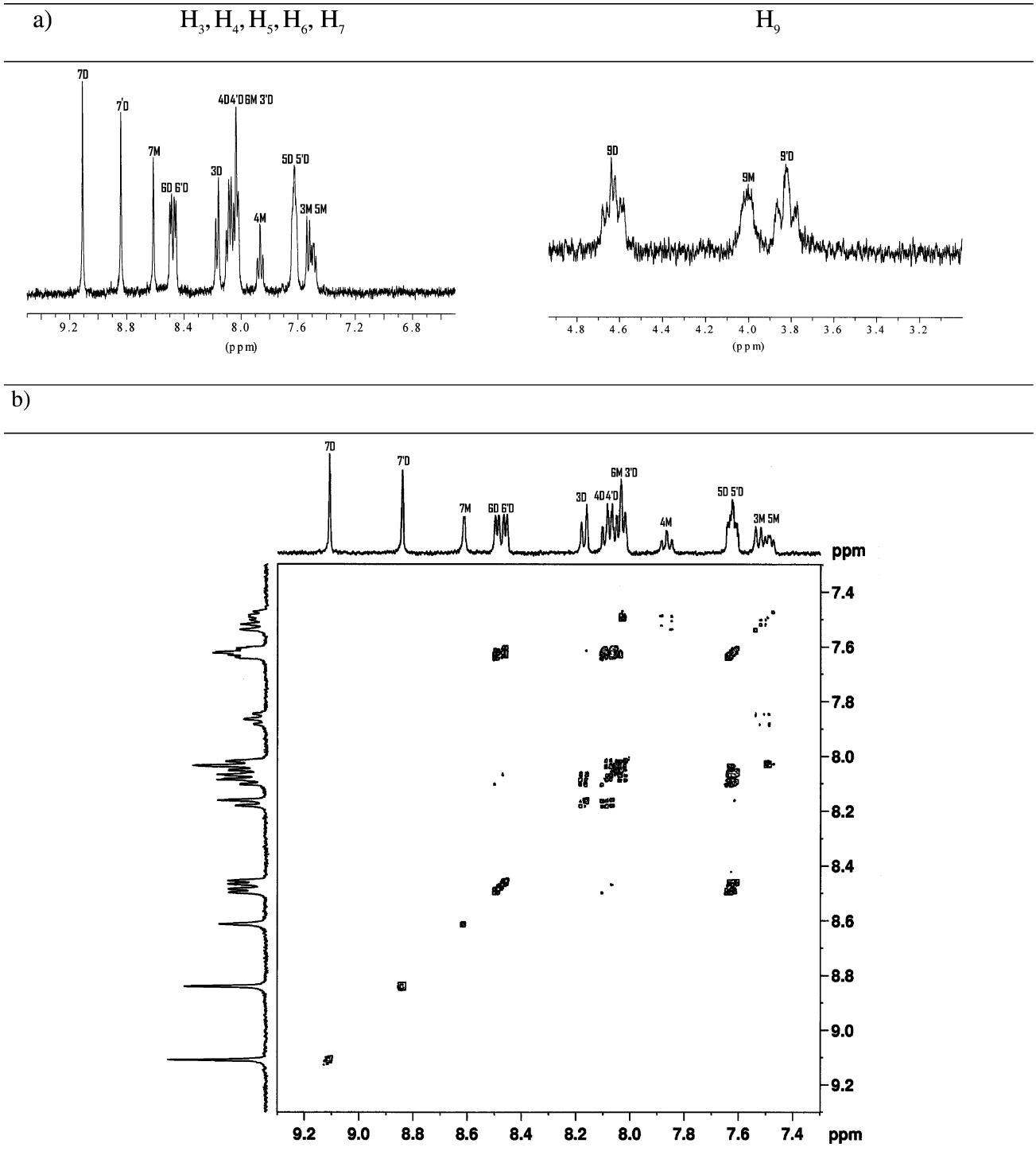


Figure 5. NMR studies of **2b** dissolved in CD_2Cl_2: (a) ^1H spectrum recorded at 20 °C (identical at 40 °C); (b) COSY ^1H (400 MHz).

Chart 1. Analogy with Brooker's Octadentate Ligand 4, "Dimer of Our Ligand 1"[13]

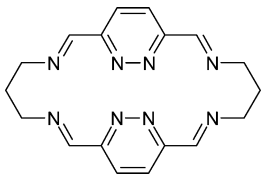


Figure 3a). This important information means that, under our classical arylation conditions, the monomer **M** is the single species present at the beginning of the reaction.[18] It was thus reasonable to think that **M** was involved in the catalytic process (Scheme 4).

This transformation of **D** into the key intermediate **M** being enabled thanks to the intervention of acetonitrile, a labile ligand favoring exchanges around the copper(I) center, we thus have a possible explanation for the efficiency of this solvent in our

(18) Not only at 80 °C but also at 40 °C (monomer exclusively present, Figure 3a), the **2b**-catalyzed copper arylation of 3,5-dimethylphenol with iodobenzene takes place (no reaction without ligand at 40 °C) (Table 1). The yield after 24 h is, however, relatively average (26%, Table 1, entry 5), thus accounting for the low reaction temperature.

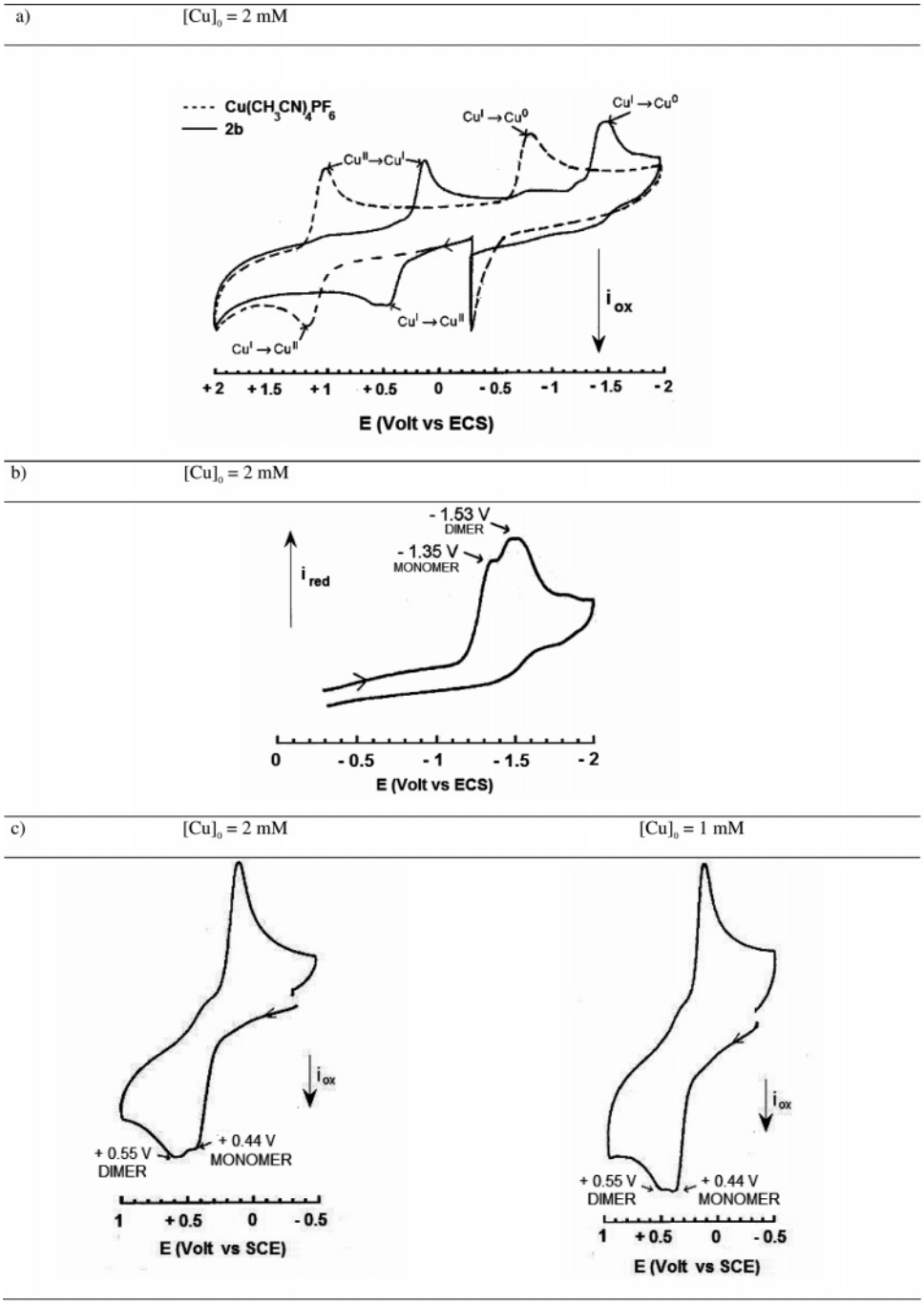


Figure 6. (a) Cyclic voltammetry of complex **2b** (solid line) and $Cu(CH_3CN)_4PF_6$ (dashed line) solubilized in CH_3CN at 20 °C ($[Cu]_0$ = 2 mM, $n$$NBu_4BF_4$, 0.3 M) at a stationary carbon disk electrode (diameter 2 mm) with a scan rate of 0.5 V s^1. (b) Enlargement of the reduction waves of **2b** ($[Cu]_0$ = 2 mM); (c) Enlargement of the oxidation waves of **2b** ($[Cu]_0$ = 2, 1 mM).

cross-coupling reactions. In any event, it is worth noting that the influence of the solvent on the outcome of Ullmann-type reactions has often been underlined, without, however, being understood or supported by experimental evidence.[1,6i,19,20]

At this stage of the study, we would need more information to propose a catalytic cycle. For example, the 18-electron monomer **M** as represented is not able to coordinate a further reagent (aryl halide, for instance) without making coordination sites free. The ability of acetonitrile to promote ligand displacement highlighted above could, however, favor the partial dissociation of one or two nitrogens of the ligand and the further coordination of the aryl halide with a copper(I) on the way to a postulated oxidative addition.

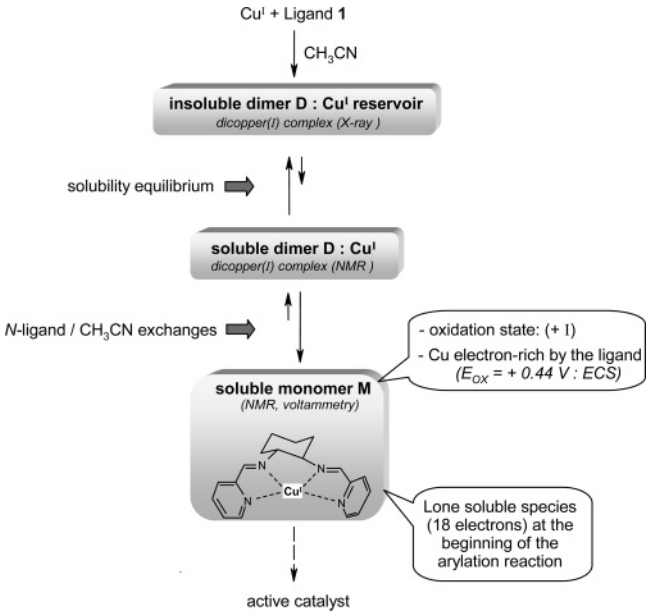
Conclusion

The copper/ligand-promoted arylations of nucleophiles constitute extremely powerful tools in organic chemistry and are thus involved in numerous industrial applications throughout the life science and polymer industries. However, in spite of the importance of these reactions, the involved mechanism has not been well established until now and, in particular, the interactions between ligands and copper at the early stages of the catalytic process are unknown.

In this paper, we report information concerning this last aspect in the case of our best catalytic system involving copper, ligand

(19) Bacon, R. G. R.; Hill, H. A. O. *J. Chem. Soc.* **1964**, 1097.
(20) Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Rev.* **1974**, *43*, 679.

Scheme 4. Summary of the Results: Precatalysts Formed in Copper-Catalyzed Arylations Involving Ligand 1



1, and acetonitrile. Indeed, we synthesized a precatalyst and characterized it in the solid state and in solution (NMR, electrochemistry, X-ray crystallography). Thanks to the information collected, we have a better understanding of the role of the ligand (influence on the solubility of copper and on its electrochemical properties) and the role of the solvent (coordinating acetonitrile facilitates ligand exchanges at the copper center) and can now propose a global description of the various reactions taking place at the early stages of copper-catalyzed arylations of nucleophiles.

First, the association of copper(I) salts and tetradentate ligand in acetonitrile led to the formation of a highly insoluble dimeric complex, behaving as a copper(I) reservoir. A very minor part of the latter is soluble, but its dimeric structure is lost to the benefit of a monomeric form put forward to be involved in the catalytic process. Within this monomer, the copper center is at the +I oxidation level and is made more electron rich by the ligand. This last feature and the fact that the monomeric complex is the only species present in solution could be compatible with an oxidative addition of the aryl halide with a Cu^{I} complex as the first step of the catalytic cycle (this step would be possible after partial dissociation of the ligand).

Further investigations to clarify the mechanism of copper-catalyzed arylation reactions and, in particular, to better define the interactions between the active complex and the arylating agent are presently underway, and the final results will be reported soon.

Experimental Section

General Considerations. Products were characterized by their NMR, GC/MS, and IR spectra. NMR spectra were recorded at 20 °C on DRX-250 and DRX-400 spectrometers working respectively at 250.13 and 400.13 MHz for ^{1}H and at 62.90 and 100.61 MHz for ^{13}C. Coupling constants are reported in Hz and chemical shifts in ppm/TMS for ^{1}H and ^{13}C{^{1}H} (δ 77.00 for the *C*DCl_3 signal). The first-order peak patterns are indicated as s (singlet), d (doublet), t (triplet), and q (quadruplet). Complex non-first-order signals are indicated as m (multiplet) and broad signals as br. ^{13}C NMR signals were assigned using HMQC and HMBC sequences. Gas chromatography−mass spectra (GC/MS) were recorded on an Agilent Technologies 6890 N instrument with an Agilent 5973 N mass detector (EI) and an HP5-MS 30 m × 0.25 mm capillary apolar column (stationary phase: 5% diphenyldimethylpolysiloxane film, 0.25 μm). GC/MS method: initial temperature, 45 °C; initial time, 2 min; ramp, 10 °C/min; final temperature, 250 °C; final time, 10 min. IR spectra were recorded on a Nicolet 210 FT-IR instrument (neat, thin film for liquid products and KBr pellet or carbon tetrachloride solution for solid products). FAB+ mass spectra and HRMS were recorded on a JEOL JMS-DX300 spectrometer (3 keV, xenon) in a *m*-nitrobenzyl alcohol matrix, and ESI was performed on a Micro-Mass apparatus (Q-TOF, ES+). Melting points were determined using a Büchi B-540 apparatus and are uncorrected.

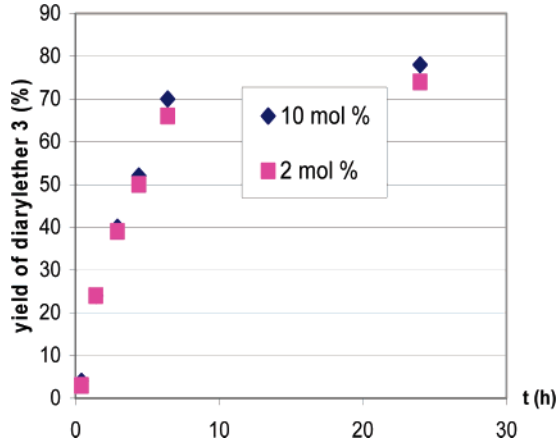


Figure 7. Yield of diaryl ether **3** as a function of time in the presence of 2 or 10 mol % of catalyst. Reaction conditions: iodobenzene (2.0 mmol), 3,5-dimethylphenol (2.4 mmol), K_3PO_4 (2.4 mmol), CuI/**1** (0.04 or 0.20 mmol of each) or complex **2a** (0.04 or 0.20 mmol), CH_3CN (1200 μL), 80 °C. GC yields were determined with 1,3-dimethoxybenzene as internal standard.

Materials. All reactions were carried out in 35 mL Schlenk tubes or in Carousel "reaction stations RR98030" Radley tubes, under a pure and dry nitrogen atmosphere. Dichloromethane and acetonitrile were distilled from P_4O_{10}, and the latter was stored protected from light on 4 Å activated molecular sieves under a nitrogen atmosphere. All of the solid materials were stored in the presence of P_4O_{10} in a benchtop desiccator under vacuum at room temperature and weighed in the air. Copper(I) iodide was purified according to literature procedures[21] and stored protected from light. The synthesis of ligand **1** was reported in our previous papers.[2,3] Aryl halides and phenols were purchased from commercial sources (Aldrich, Acros, Avocado, Fluka, Lancaster). Solids were recrystallized in an appropriate solvent.[22] Liquids were distilled under vacuum and stored under an atmosphere of nitrogen. Cyclic voltammetry and amperometry were performed with a homemade potentiostat and a GSTP4 wave form generator (Radiometer Analytical). The current was recorded on a Nicolet 301 oscilloscope.

General Procedure for the Arylation of 3,5-Dimethylphenol with Iodobenzene. After standard cycles of evacuation and back-filling with dry and pure nitrogen, an oven-dried Radley tube (Carousel "reaction stations RR98030") equipped with a magnetic stirring bar (12 × 4.5 mm) was charged with CuI (9.5 mg, 0.05 mmol) and ligand **1** (14.6 mg, 0.05 mmol) or with complex **2a** (0.05 mmol) or complex **2b** (0.05 mmol), phenol (73.3, 0.6 mmol), and K_3PO_4 (127.2 mg, 0.6 mmol). The tube was evacuated and back-filled with nitrogen. Iodobenzene (56 μL, 0.5 mmol) was added under a stream of nitrogen by syringe at room temperature, followed by anhydrous and degassed solvent (acetonitrile or dichloromethane, 300 μL). The tube was sealed under a positive

(21) Dieter, R. K.; Silks, L. A., III; Fishpaugh, J. R.; Kastner, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 4679.

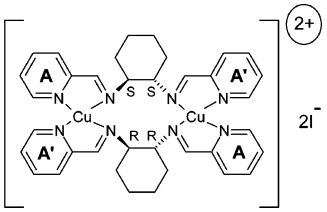
(22) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: New York, 1985.

pressure of nitrogen, stirred, and heated to 40 or 80 °C for the period mentioned in Table 1. The reaction mixture was cooled to room temperature and diluted with dichloromethane (5 mL). A 65 μL portion of 1,3-dimethoxybenzene (internal standard) was added. A small sample of the reaction mixture was taken and filtered through a plug of Celite, the filter cake being further washed with dichloromethane. The filtrate was washed three times with water and analyzed by gas chromatography. The GC yields were determined by obtaining the correction factors using authentic samples of the expected products.

General Procedure To Record the Voltammograms of Cu(CH$_3$CN)$_4$PF$_6$ and Complex 2b. Experiments were carried out in a three-electrode thermostated cell (25 °C) connected to a Schlenk line. The reference was a saturated calomel electrode (Radiometer) separated from the solution by a bridge filled with 3 mL of acetonitrile containing *n*Bu$_4$NBF$_4$ (0.3 M). The counter electrode was a platinum wire of ca. 1 cm^2 apparent surface area. The working electrode was a carbon disk (diameter 2 mm) inserted into Teflon (EDI 65109, Radiometer Analytical). A 15 mL portion of acetonitrile containing *n*Bu$_4$NBF$_4$ (0.3 M) was poured into the cell, followed by 15.0 mg (15 μmol, 1 mM) of dimer **2b** (or 11.2 mg (30 μmol) of Cu(CH$_3$CN)$_4$PF$_6$). The cyclic voltammetry was performed at the steady carbon disk electrode at a scan rate of 0.5 V s^{-1}.

Complex 2a. To a homogeneous solution of ligand **1** (292.0 mg, 1 mmol) in acetonitrile (15 mL) was added a homogeneous solution of copper iodide (190.4 mg, 1 mmol) in the same solvent (20 mL), provoking the immediate precipitation of a dark red solid. After 2 h at 20 °C, complex **2a** was filtered, dried in the presence of P_4O_{10}, and obtained as a dark red solid (460 mg, 95%). Dark red crystals could be obtained by slow evaporation of a homogeneous solution of **2a** in acetonitrile.

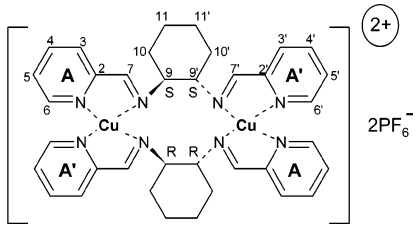
2a:



F: 256−257 °C (CH$_3$CN). IR (KBr): ν (cm^{-1}) 2935, 2858, 2192, 1593, 1471, 1439, 1384, 1291, 1223, 1156, 771, 746. ESI+ (CH$_2$Cl$_2$): *m*/*z* 355 (100%, 2 ligands + 2 ^{63}Cu$^+$), 356 (98%, 2 ligands + ^{63}Cu$^+$ + ^{65}Cu$^+$), 357 (50%, 2 ligands + 2 ^{65}Cu$^+$), 647 (51%, 2 ligands + ^{63}Cu$^+$), 649 (35%, 2 ligands + ^{65}Cu$^+$), 837 (20%, 2 ligands + 2 ^{63}Cu$^+$ + I$^-$), 839 (20%, 2 ligands + ^{63}Cu$^+$ + ^{65}Cu$^+$ + I$^-$), 841 (6%, 2 ligands + 2 ^{65}Cu$^+$ + I$^-$). Anal. Calcd for $C_{36}H_{40}N_8Cu_2I_2$: C, 44.78; N, 11.60; H, 4.18. Found: C, 44.40; N, 11.56; H, 4.03. HRMS: calcd for $C_{36}H_{40}N_8{}^{63}Cu_2{}^{2+}$, 355.0984; found, 355.0977.

Complex 2b. The procedure was analogous to that described by van Koten.[9] To a suspension of Cu(CH$_3$CN)$_4$PF$_6$ (372.7 mg, 1 mmol) in benzene (2 mL) was added a homogeneous solution of ligand **1** (292.0 mg, 1 mmol) in the same solvent (10 mL), provoking the immediate precipitation of a dark red solid. After 24 h at 25 °C, complex **2b** was filtered, dried in the presence of P_4O_{10}, and obtained as a dark red solid (473 mg, 95%).

2b:



F: 255−258 °C (C$_6$H$_6$). ^{1}H NMR (CD$_3$CN): symmetrical monomer, δ 8.59 (s, H$_7$), 8.02 (d, ^3J(H$_5$,H$_6$) = 5,3 Hz, H$_6$), 7.89 (ddd, ^3J(H$_3$,H$_4$) = 7.8 Hz, ^3J(H$_4$,H$_5$) = 7.7 Hz, ^4J(H$_4$,H$_6$) = 1.4 Hz, H$_4$), 7.54 (d, ^3J(H$_3$,H$_4$) = 7.8 Hz, H$_3$), 7.48 (dd, ^3J(H$_4$,H$_5$) = 7.7 Hz, ^3J(H$_5$,H$_6$) = 5.3 Hz, H$_5$), 3.92 (m, H$_9$), 2.10 (m, H$_{10,ax}$), 1.82 (m, H$_{11,eq}$), 1.64 (m, H$_{10,eq}$), 1.36 (m, H$_{11,ax}$). ^{1}H NMR (CD$_2$Cl$_2$): symmetrical monomer **M**, δ 8.61 (s, H$_7$), 8.03 (d, ^3J(H$_5$,H$_6$) = 4.9 Hz, H$_6$), 7.87 (ddd, ^3J(H$_3$,H$_4$) = 7.7 Hz, ^3J(H$_4$,H$_5$) = 7.7 Hz, ^4J(H$_4$,H$_6$) = 1.6 Hz, H$_4$), 7.53 (d, ^3J(H$_3$,H$_4$) = 7.7 Hz, H$_3$), 7.49 (ddd, ^3J(H$_4$,H$_5$) = 7.7 Hz, ^3J(H$_5$,H$_6$) = 4.9 Hz, ^4J(H$_3$,H$_5$) = 1.2 Hz, H$_5$), 4.00 (m, H$_9$), 0.9−2.0 (m, H$_{10}$, H$_{11}$, H$_{10'}$, H$_{11'}$);[23] dimer **D**, δ 9.11 (s, H$_7$), 8.84 (s, H$_{7'}$), 8.49 (d, ^3J(H$_5$,H$_6$) = 4.8 Hz, H$_6$), 8.46 (d, ^3J(H$_{5'}$,H$_{6'}$) = 5.0 Hz, H$_{6'}$), 8.17 (d, ^3J(H$_3$,H$_4$) = 8.0 Hz, H$_3$), 8.09 (ddd, ^3J(H$_3$,H$_4$) = 8.0 Hz, ^3J(H$_4$,H$_5$) = 7.4 Hz, ^4J(H$_4$,H$_6$) = 1.5 Hz, H$_4$), 8.04 (ddd, ^3J(H$_{3'}$,H$_{4'}$) = 8.0 Hz, ^3J(H$_{4'}$,H$_{5'}$) = 7.6 Hz, ^4J(H$_{4'}$,H$_{6'}$) = 1.4 Hz, H$_{4'}$), 8.03 (d, ^3J(H$_{3'}$,H$_{4'}$) = 8.0 Hz, H$_{3'}$), 7.63 (dd, ^3J(H$_4$,H$_5$) = 7.4 Hz, ^3J(H$_5$,H$_6$) = 4.8 Hz, H$_5$), 7.62 (dd, ^3J(H$_{4'}$,H$_{5'}$) = 7.6 Hz, ^3J(H$_{5'}$,H$_{6'}$) = 5.0 Hz, H$_5$), 4.60 (m, H$_9$), 3.79 (m, H$_{9'}$), 0.9−2.0 (m, H$_{10}$, H$_{11}$, H$_{10'}$, H$_{11'}$).[23] ^{13}C NMR (CD$_3$CN): δ 161.9 (C$_7$), 148.5 (C$_6$), 138.8 (C$_4$), 128.5 (C$_5$), 127.2 (C$_3$), 70.5 (C$_9$), 33.0 (C$_{10}$), 24.5 (C$_{11}$). IR (KBr): ν (cm^{-1}) 2950, 2925, 2899, 2862, 1618, 1588, 1477, 1442, 1381, 1349, 937, 876, 839, 778, 741. Anal. Calcd for $C_{36}H_{40}N_8Cu_2P_2F_{12}$: C, 43.16; N, 11.19; H, 4.02. Found: C, 43.04; N, 11.27; H, 3.93. HRMS: calcd for $C_{36}H_{40}N_8{}^{63}Cu_2{}^{2+}$, 355.0984; found, 355.1006. ESI+ (CH$_2$Cl$_2$; the ESI spectrum of **2b** (independent of the associated anion, either hexafluorophosphate or iodide) is the same as for **2a**): *m*/*z* 355 (100%, 2 ligands + 2 ^{63}Cu$^+$), 356 (98%, 2 ligands + ^{63}Cu$^+$ + ^{65}Cu$^+$), 357 (50%, 2 ligands + 2 ^{65}Cu$^+$), 855 (15%, 2 ligands + 2 ^{63}Cu$^+$ + PF$_6^-$), 857 (15%, 2 ligands + ^{63}Cu$^+$ + ^{65}Cu$^+$ + PF$_6^-$), 859 (5%, 2 ligands + 2 ^{65}Cu$^+$ + PF$_6^-$).

CCDC-611692 contains the supplementary crystallographic data for this paper (complex **2a**). These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgment. We thank Rhodia Organique Fine and the CNRS for a Ph.D. grant and financial support. Prof. A. Fruchier (NMR) and J. C. Daran (X-ray) are also gratefully acknowledged for their help.

Supporting Information Available: Crystallographic data (CIF, PDF) for complex **2a**. This material is available free of charge via the Internet at http:/pubs.acs.org.

OM060706N

(23) The coexistence of monomer and dimer in the solution led to a high complexity of the signals for cyclohexane protons, thus preventing us from assigning precisely this part of the spectrum.