Activation of aryl halides by Cu^0/1,10-phenanthroline: Cu^0 as precursor of Cu^I catalyst in cross-coupling reactions†

Mounir Mansour,[a] Roberto Giacovazzi,[a] Armelle Ouali,[b] Marc Taillefer[b] and Anny Jutand*[a]

Received (in College Station, MA, USA) 19th August 2008, Accepted 29th September 2008
First published as an Advance Article on the web 22nd October 2008
DOI: 10.1039/b814364a

The activation of aryl iodides and bromides by Cu^0/1,10-phenanthroline in acetonitrile (S) generates Cu^I(phenanthroline) S_2^+ which can be a catalyst for cross-coupling reactions.

Copper-catalyzed arylations of N- or O-nucleophiles were reported in the early 20th by Ullmann and Golberg, however at high temperatures.[1,2] In 2001, important improvements were achieved by Taillefer *et al.*[3a,b] and Buchwald *et al.*[3c] with the discovery of very efficient versatile new copper/ligand systems allowing the use of catalytic amounts of Cu^{II}, Cu^I or Cu^0 under mild conditions.[2,3] The mechanism of these cross-coupling reactions is however not fully established.[4] There is a general agreement for considering that Cu^I is the real catalyst generated from either Cu^{II} or Cu^0 precursors by an *in situ* chemical reduction or oxidation respectively.[4] In our search to get evidence of a catalytic cycle induced by the reaction of Cu^I species with aryl halides by means of electrochemical techniques, we have discovered that an electrogenerated Cu^0 complex is at the origin of the formation of Cu^I through its activation of aryl halides by electron transfer. This reaction explains why Cu^0 can be used as a precursor in Cu^I-catalyzed cross-coupling reactions.[2]

The ligands 1,10-phenanthroline or 4,7-substituted-1,10-phenanthroline associated with Cu^I (Cu_2O, CuBr, CuI, CuOTf, $Cu(CH_3CN)_4PF_6$) have been used to catalyze C–C, C–O or C–N cross-coupling reactions.[2,4g,k,5] The cyclic voltammetry of $Cu^I(CH_3CN)_4{}^+PF_6{}^-$ (2 mM) was performed in CH_3CN (containing nBu$_4$NBF$_4$, 0.3 M). It exhibited an irreversible reduction peak at $E^p_{red} = -0.681$ V *vs.* SCE (Fig. 1(a)). The reduction generated a naked "Cu^0" which deposited at the electrode surface and was characterized by an irreproducible broad adsorption oxidation wave at *ca.* −0.2 V (Fig. 1(a)). After addition of 1,10-phenanthroline (phen, 1 equiv.), the reduction peak of $CuS_4{}^+$ (S = CH_3CN) disappeared leading to a complex voltammagram, involving four successive irreversible reduction peaks: R_0 ($E^p_{R0} = -1.54$ V), R_1 ($E^p_{R1} = -1.65$ V), R_2 ($E^p_{R2} = -1.82$ V, hardly detectable), and R_3 ($E^p_{R3} = -2.03$ V) (Fig. 1(b)). Addition of a second equiv. of phenanthroline led to the disappearance of R_0, an increase of the reduction peak currents at R_1, R_2 and R_3 (Fig. 1(c)).

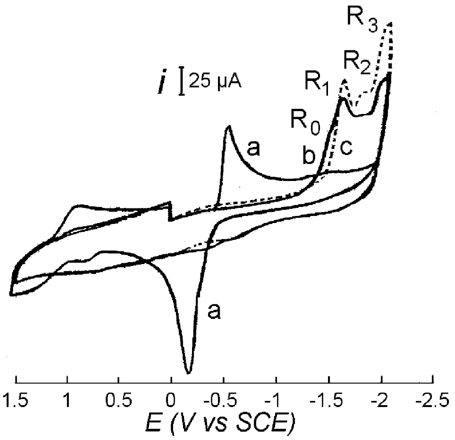


Fig. 1 Cyclic voltammetry performed in acetonitrile containing nBu$_4$NBF$_4$ (0.3 M) at a steady glassy carbon disk electrode (d = 3 mm), at the scan rate of 0.5 V s^{-1}, at 20 °C. (a) Reduction of $Cu(CH_3CN)_4{}^+PF_6{}^-$ (2 mM); (b) Reduction of $Cu(CH_3CN)_4{}^+PF_6{}^-$ (2 mM) in the presence of 1,10-phenanthroline (1 equiv.); (c) (dashed line) Reduction of $Cu(CH_3CN)_4{}^+PF_6{}^-$ (2 mM) in the presence of phenanthroline (2 equiv.).

In the presence of more phenanthroline (up to 5 equiv.), the reduction peak current at R_1 slightly increased as well as that of R_2 to reach a limit. The reduction peak current of R_3 also increased. R_3 characterizes the first reduction step of phenanthroline (comparison to an authentic sample).

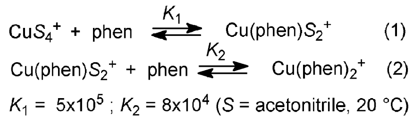
According to literature, two successive equilibrium are involved in acetonitrile (Scheme 1).[6]

From the value of K_1 (Scheme 1), it emerges that 97% of $CuS_4{}^+$ was converted to $Cu^I(phen)S_2{}^+$ when phen (2 mM) was added to $CuS_4{}^+$ (2 mM). Consequently the reduction peak R_0 observed as a shoulder characterizes $CuS_4{}^+$ (less easily reduced than in the absence of ligand (phenanthroline) because of equilibrium (1)[7]) while the reduction peak R_1 characterizes $Cu(phen)S_2{}^+$. R_3 characterizes the reduction of the phenanthroline in the equilibrium (1) in Scheme 1. The relative reduction peak currents at R_0, R_1 and R_3 did not necessarily reflect the thermodynamic concentration of the three species in equilibrium (1) because the equilibrium might be shifted due to the consumption of the species by the reduction process in the diffusion layer at low scan rate (CE mechanism).[7] Indeed, R_0 was no longer observed at higher scan rates (Fig. 2(b)). The reduction of $Cu(phen)S_2{}^+$ at R_1 was irreversible at low scan rates and a badly defined oxidation peak was observed on the reverse scan at O_x (Fig. 2(a)). The reduction peak R_1 became partly reversible at higher scan rates while the oxidation peak

---

[a] *Ecole Normale Supérieure (ENS), Département de Chimie, UMR CNRS, 8640, 24 Rue Lhomond, F-75231 Paris Cedex 05, France. E-mail: Anny.Jutand@ens.fr; Fax: 33144322402; Tel: 33144323872*
[b] *Institut Charles Gerhardt Montpellier, AM$_2$N, ENSCM, 8 rue de l'Ecole Normale, F-34296 Montpellier Cedex 5, France*

† Electronic supplementary information (ESI) available: Experimental procedure and discussion. See DOI: 10.1039/b814364a



Scheme 1

current of O_x decreased (Fig. 2(b)). The unsaturated complex Cu^0(phen) generated in the reduction of $Cu^I(phen)S_2^+$ was not stable and decomposed to a badly defined $\{Cu^0\}$ species oxidized at O_x. Cu^0(phen) was however intercepted at shorter times (higher scan rates) and was oxidized back to $Cu^I(phen)S_2^+$ at O_1 (Fig. 2(b), Scheme 2 left).

Addition of a second equiv. of phenanthroline achieved to convert all CuS_4^+ into Cu^I/phen complexes (R_0 no longer detected in Fig. 1(c)). The reduction peak current at R_1 did not decrease upon addition of more than two equiv. of phenanthroline. Consequently, R_1 characterizes the reduction of the two complexes $Cu^I(phen)S_2^+$ and $Cu^I(phen)_2^+$ involved in a fast equilibrium (right part of Scheme 2). From the value of K_2,[6] it emerges that $Cu(phen)_2^+$ was the main complex when phen (4 mM) was added to CuS_4^+ (2 mM) ($[Cu(phen)_2^+]/[Cu(phen)S_2^+]$ = 89/11 at 20 °C). The mixture CuS_4^+ (2 mM) and phenanthroline (10 mM) was investigated at various scan rates (from 0.5 to 1000 V s^{-1}). The ratio i^p_{R2}/i^p_{R1} decreased when the scan rate increased, while R_1 became partly reversible. This indicates that the species reduced at R_2 was not directly generated by the reduction of $Cu^I(phen)_2^+$ to $Cu^0(phen)_2$ at R_1 but characterized a badly defined $\{Cu^0\{$ species formed in the chemical evolution of $Cu^0(phen)_2$ (Scheme 2). Such complex is not a dimer since the ratio i^p_{R2}/i^p_{R1} was not affected by the initial Cu^I concentration.

The addition of phenanthroline to CuI used as precursor in catalytic reactions,[4] led to similar voltammograms since CuI was fully dissociated to ionic $Cu(CH_3CN)_4^+$ and I^- (conductivity: 110 μS cm^{-1} for CuI (2 mM)).[8] Consequently, CuI behaved as the cationic $Cu(CH_3CN)_4^+$ in acetonitrile.

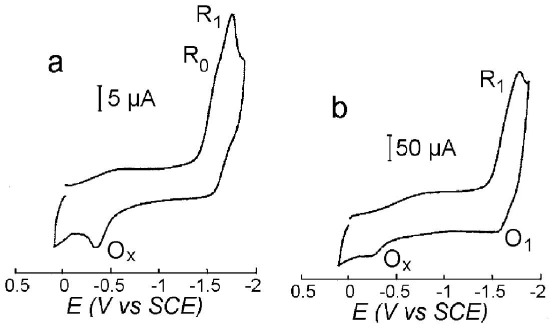
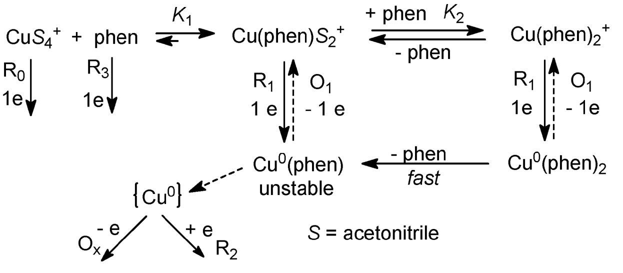


Fig. 2 Cyclic voltammetry of $Cu(CH_3CN)_4^+PF_6^-$ (2 mM) in the presence of 1,10-phenanthroline (2 mM), in acetonitrile containing nBu_4NBF_4 (0.3 M) at a steady glassy carbon disk electrode (d = 1 mm) at the scan rate of: (a) 5 V s^{-1}; (b) 100 V s^{-1} at 20 °C.



Scheme 2

The reactivity of complex $Cu^I(phen)S_2^+$ formed by addition of phen (2 mM) to $Cu(CH_3CN)_4^+PF_6^-$ (2 mM) with aryl halides was investigated in acetonitrile. If a fast reaction occurred, the reduction peak current at R_1 should decrease since currents are proportional to the concentrations of electroactive species.[7] Surprisingly, the reverse situation was observed: the reduction peak current at R_1 increased as the concentration of PhI was increased whereas the oxidation peak O_x on the reverse scan assigned to the oxidation of an electrogenerated $\{Cu^0\}$ moiety disappeared (Fig. 3).

Consequently, the reduction of $Cu^I(phen)S_2^+$ at R_1 generated Cu^0(phen) which reacted with PhI to regenerate the initial $Cu^I(phen)S_2^+$ and a catalytic reduction current was observed at R_1 which increased as the PhI concentration was increased (Fig. 3(b)). It is worthwhile to note that the direct reduction of PhI occurred at a more negative potential (Table 1).[9] For a given PhI concentration, the catalytic effect at R_1, expressed by the ratio $i^p_{R1(PhI)}/i^p_{R1(0)}$ ($i^p_{R1(PhI)}$: reduction peak current at R_1 in the presence of PhI; $i^p_{R1(0)}$: reduction peak current at R_1 in the absence of PhI), was less important when the scan rate or phenanthroline concentration was increased. At high scan rates (shorter times), the concentration of Cu^0(phen) remained high because it had less time to decompose to $\{Cu^0\}$ but on the other hand, it had less time to react with PhI. This competition seems to be in favor of the latter effect. A catalytic current at R_1 was observed for 4-Z–C_6H_4–X (Z = CN, H, MeO, X = I, Br) but not for 4-NC–C_6H_4–Cl. All ArX were reduced at potentials more negative than that of R_1 (Table 1). Therefore, the Cu^0(phen) complex generated in the reduction of $Cu^I(phen)S_2^+$ could activate aryl iodides and bromides (even deactivated by EDG groups) but could not activate aryl chlorides (even activated by an EWG group as CN) during the potential scan. Exhaustive electrolyses of solutions containing ArI or ArBr (0.5 mmol), $Cu(CH_3CN)_4PF_6$ (10 mol%) and phenanthroline (10 mol%) in 12 mL of acetonitrile, performed at the reduction potential of R_1

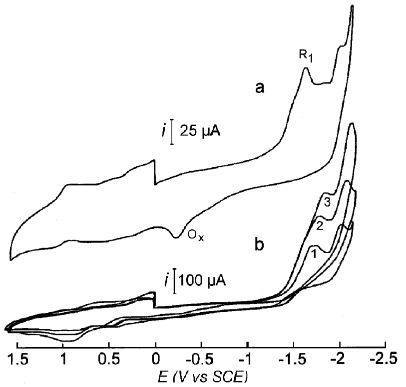


Fig. 3 (a) Cyclic voltammetry of $Cu(CH_3CN)_4^+PF_6^-$ (2 mM) in the presence of 1,10-phenanthroline (2 mM), in acetonitrile containing nBu_4NBF_4 (0.3 M) at a steady glassy carbon disk electrode (d = 3 mm) at the scan rate of 0.5 V s^{-1}, at 20 °C. (b) After successive additions of PhI (the numbers indicate the cumulative number of equivalents of added PhI). The current scale has been divided by 4 when going from (a) to (b).

Table 1 Reduction peak potential $E^{\mathrm{p}}_{\mathrm{red}}$ of ArX (X = I, Br, Cl) in acetonitrile. Results of the electrolyses performed in the presence of catalytic Cu(CH$_3$CN)$_4$PF$_6$ and 1,10-phenanthroline.

$$\mathrm{ArX\ (X = I, Br)} + 2\,\mathrm{e} \xrightarrow[\text{acetonitrile, 20 °C}]{\mathrm{Cu(CH_3CN)_4PF_6}\ \text{(10 mol \%)}\ \text{phenanthroline (10 mol \%)}} \mathrm{Ar^-} + \mathrm{X^-}$$

ArX[a]	$E^{\mathrm{p}}_{\mathrm{red}}$ [b] (E^{0}_{red})[c]	$E^{\mathrm{elect}}_{\mathrm{red}}$ [d]	C[e]	F/mol[f]	ArH (%)[g]	ArX (%)[h]
4-CNC$_6$H$_4$I	−2.00 (−1.81)	−1.5	106	2.0	78	0
C$_6$H$_5$I	−2.51 (−1.91)	−1.5	112	2.11	—[i]	0
4-CH$_3$C$_6$H$_4$I	−2.43	−1.5	115	2.17	12[i]	0
4-CH$_3$OC$_6$H$_4$I	−2.26	−1.5	106	2.0	76	2
4-NCC$_6$H$_4$Br	−2.11 (−1.94)	−1.5	123	2.3	80	0
4-CH$_3$OC$_6$H$_4$Br	< −2.8	−1.5	119	2.24	54	0
4-NCC$_6$H$_4$Cl	−2.16 (−2.03)	−1.5	26	0.49	0	100

[a] ArX = 0.5 mmol in 12 mL of acetonitrile containing nBu$_4$NBF$_4$ (0.3 M). [b] Peak potentials *vs.* SCE at a steady glassy carbon disk electrode (d = 1 mm) at the scan rate of 0.5 V s^{-1}, 20 °C. [c] Standard reduction potentials of ArX *vs.* SCE in DMF at 20 °C.[9b] [d] Cathodic electrolysis potential. [e] C: charge passed through the cell expressed in Coulomb (theoretical charge: 106 C). [f] Faraday per mol. [g] Isolated yield. [h] Recovered. [i] ArH was isolated in low yield due to low boiling point.

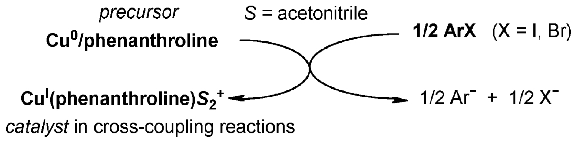
(−1.5 V) delivered after consumption of 2 electrons per mole of ArX the corresponding ArH after fast protonation of Ar$^-$ by the solvent (Table 1). When an electrolysis was performed from 4-CN–C$_6$H$_4$–Cl at −1.5 V, the reduction current dropped to zero just after the reduction of the complex Cu$^{\mathrm{I}}$(phen)$S_2{}^+$ and no PhCN was produced in agreement with the absence of catalytic current observed on the cyclic voltammogram.

Therefore, the electrogenerated Cu^0(phen) complex catalyses the reduction of ArX (X = I, Br) to Ar$^-$ at a potential which is less negative than the reduction potentials of ArX (Table 1). Such reactions generate a Cu$^{\mathrm{I}}$ complex after activation of the aryl halide by electron transfer in an inner sphere mechanism (see ESI†).

This electrochemical reduction of ArX to ArH catalysed by a Cu^0 moiety is unprecedented. The reaction is selective since no biaryl ArAr is formed. This contrasts with the reported electrochemical reduction of ArX in the presence of Pd or Ni catalysts which do not provide any arene ArH (except as by-product) but the homocoupling product ArAr.[10] This is a consequence of the formation of Ar–Pd$^{\mathrm{II}}$–X or Ar–Ni$^{\mathrm{II}}$–X complexes by oxidative addition of ArX to electrogenerated Pd^0 or Ni^0 complexes, respectively.[10]

All our attempts to characterize Ar–Cu$^{\mathrm{III}}$ complexes formed by oxidative addition of ArX to the cationic Cu$^{\mathrm{I}}$(phen)$S_2{}^+$ failed. The reaction of 4-NC–C$_6$H$_4$–I with the neutral yellow complex CuBr(PPh$_3$)(phen) in reflux toluene provided an elusive pale green complex whose ESI MS revealed the formation of 4-NC–C$_6$H$_4$–Cu$^{\mathrm{III}}$–Br(phen)$^+$ by an oxidative addition. But the reaction has never been reproduced. Cationic Cu$^{\mathrm{I}}$ complexes must be *a priori* poor candidates for the activation of Ar–X bond (X = I, Br, Cl) by oxidative addition owning to their cationic character.[11] However, DFT calculations by Liu, Guo *et al.*[4f] suggest that the oxidative addition could take place from a cationic Cu$^{\mathrm{I}}$. In the presence of a nucleophile (Nu$^-$ or NuH + base), neutral complexes Nu–Cu$^{\mathrm{I}}$L$_n$ must be formed and be good candidates for the oxidative addition of ArX, as proposed by Buchwald *et al.*,[4g,j] supported by DFT calculations by Liu, Guo *et al.*,[4f] and very recently established by Hartwig *et al.*,[4k] for *N*-nucleophiles.

In conclusion, cross-coupling reactions of ArX (X = I, Br) and nucleophiles can be performed by using a Cu^0 precursor which will be transformed *in situ* into a Cu$^{\mathrm{I}}$ species by its reaction with ArX at the very beginning of the catalytic reactions.



Moreover, such reaction can be used for preparative purpose since the electrogenerated Cu^0(phenanthroline) catalyses the selective electrochemical reduction of ArX (X = I, Br) to ArH.

We thank ANR (ANR-07-CP2D-08-03), the Centre National de la Recherche Scientifique and the Ministère de la Recherche (Ecole Normale Supérieure) for supporting this work.

Notes and references

1 (*a*) F. Ullmann, *Ber. Dtsch. Chem. Ges.*, 1903, **36**, 2382; (*b*) I. Goldberg, *Ber. Dtsch. Chem. Ges.*, 1906, **39**, 1691–1692.

2 (*a*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; (*b*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337; (*c*) J. P. Corbet and G. Mignani, *Chem. Rev.*, 2006, **106**, 2651; (*d*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2008, **47**, 3096.

3 (*a*) M. Taillefer, H.-J. Cristau, P. P. Cellier and J.-F. Spindler, Fr 2833947-WO 0353225 (Pr. Nb. Fr 2001 16547), 2001; (*b*) S. L. Buchwald, A. Klapars, J. C. Antilla, G. E. Job, M. Wolter, F. Y. Kwong, G. Nordmann and E. J. Hennessy, WO 02/085838 (Pr. Nb. US 2001 0286268), 2001; (*c*) M. Taillefer, H.-J. Cristau, P. P. Cellier, J.-F. Spindler and A. Ouali, Fr 2840303-WO 03101966 (Pr. Nb. Fr 2002 06717), 2002.

4 (*a*) A. J. Paine, *J. Am. Chem. Soc.*, 1987, **109**, 1496; (*b*) H. L. Aalten, G. van Koten, D. M. Grove, T. Kuilman, O. G. Piekstra, L. A. Hulshof and R. A. Sheldon, *Tetrahedron*, 1989, **45**, 5565; (*c*) E. R. Streiter, D. G. Blackmond and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4120; (*d*) A. Ouali, J.-F. Spindler, A. Jutand and M. Taillefer, *Organometallics*, 2007, **26**, 65; (*e*) A. Ouali, J.-F. Spindler, A. Jutand and M. Taillefer, *Adv. Synth. Catal.*, 2007, **349**, 1906; (*f*) S.-L. Zhang, L. Liu, Y. Fu and Q.-X. Guo, *Organometallics*, 2007, **26**, 4546; (*g*) R. A. Altman, E. D. Koval and S. L. Buchwald, *J. Org. Chem.*, 2007, **72**, 6190; (*h*) H.-Q. Do and O. Daugulis, *J. Am. Chem. Soc.*, 2008, **130**, 1128; (*i*) L. M. Huffman and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 9196; (*j*) R. A. Altman, A. M. Hyde, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 9613; (*k*) J. W. Tye, Z. Weng, A. M. Johns, C. D. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2008, **130**, 9971.

5 (*a*) A. Kiyomori, J.-F. Marcoux and S. L. Buchwald, *Tetrahedron Lett.*, 1999, **40**, 2657; (*b*) H. B. Goodbrand and N. X. Hu, *J. Org. Chem.*, 1999, **64**, 670; (*c*) R. K. Gujadhur, C. G. Bates and D. Venkataraman, *Org. Lett.*, 2001, **3**, 4315; (*d*) H.-J. Cristau, A. Oualli, J.-F. Spindler and M. Taillefer, *Chem. Eur. J.*, 2005, **11**, 2483.

6 M. Meyer, A.-M. Albrecht-Gary, C. O. Dietrich-Buchecker and J. P. Sauvage, *Inorg. Chem.*, 1999, **38**, 2279.

7 A. J. Bard and L. R. Faulkner, *Electrochemical Methods. Fundamentals and Applications*, Wiley, New York, 2001, 2nd edn.

8 (*a*) W. J. Geary, *Coord. Chem. Rev.*, 1971, **7**, 81; (*b*) A. Jutand, *Eur. J. Inorg. Chem.*, 2003, 2017.

9 (*a*) We are conscious that we are not comparing standard potentials E^0 but peak potentials E^{p} which slightly differ from standard potentials[7]; (*b*) For comparison, the standard potentials E^0 of ArX determined in DMF are given in Table 1, see: R. J. Enemaerke, T. B. Christensen, H. Jensen and K. Daasbjerg, *J. Chem. Soc., Perkin Trans. 2*, 2001, 1620.

10 For a recent review, see: A. Jutand, *Chem. Rev.*, 2008, **108**, 2300.

11 For some examples, see: (*a*) T. Osaka, K. D. Karlin and S. Itoh, *Inorg. Chem.*, 2005, **44**, 410; (*b*) D. Maiti, A. A. N. Sarjeant, S. Itoh and K. D. Karlin, *J. Am. Chem. Soc.*, 2008, **130**, 5644.