ORGANOMETALLICS
Article

Organometallics **2010,** *29,* 2815–2822 2815
DOI: 10.1021/om1003336

Copper(I) Iodide Polyphosphine Adducts at Low Loading for Sonogashira Alkynylation of Demanding Halide Substrates: Ligand Exchange Study between Copper and Palladium

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Received April 22, 2010

The prestabilization of copper iodide with a multidentate ferrocenyl phosphine ligand promotes the palladium-catalyzed cross-coupling of demanding halides with phenylacetylene in a selective way. Novel CuI-triphosphine adducts are described in the solid state and in solution. Their use allowed the introduction of the copper iodide cocatalyst in unprecedented low amounts (0.4 to 0.1 mol %) in systems also employing low amounts of "ligand-free" $[Pd^{II}(\eta^3\text{-allyl})Cl]_2$ precursor (0.2 to 0.05 mol %). The scope of substrates is reported, and electronically or sterically deactivated bromides were efficiently coupled. Concerning aryl chlorides, electron-poor activated substrates were also coupled using this innovative low-metal-content catalytic system. Some rarely tackled mechanistic aspects are discussed herein. In particular, the transfer of ligand from copper to palladium monitored by NMR was found to be different depending on the polyphosphine ligand. The inhibition of diyne formation was also an interesting feature provided by the prestabilized copper species used in low amount, contrary to the employment of 5 mol % CuI with palladium. Notably, the copper(I) iodide phosphine adduct **6**, formed from 1,2-bis(diphenylphosphino)-1′-(diisopropylphosphino)-4-*tert*-butylferrocene, also allowed under copper-only conditions the "palladium-free" coupling of the electron-rich deactivated 4-iodotoluene to phenylacetylene.

Introduction

Metal-catalyzed reactions to selectively yield valuable (aryl)-alkynes are mainly dependent on palladium chemistry for the alkynylation of demanding aryl halides by employing terminal alkynes.[1,2] One of the leading methods used to activate these appealing but demanding compounds (i.e., most aryl chloride substrates and sterically and/or electronically deactivated bromides) is the so-called Sonogashira reaction, which is based on the tandem catalytic use of a palladium complex with a copper salt (Scheme 1, left).[3] Recent reports often focus on water solvent, copper-free, or aerobic conditions.[4] Nevertheless, the cross-coupling of terminal alkynes to other organic fragments (aryls, amides, azides, etc.) catalyzed by palladium and/or copper often suffers from oxidative homocoupling of the terminal alkynes (Scheme 1, side reactions on the right).[5−7] This acetylenic coupling, when intended, is a powerful tool in molecular construction.[8] However, it could be significantly detrimental as a side-reaction,[5b] especially since it can be promoted by both copper(I) salts[8,9] and palladium(II) complexes.[10,11]

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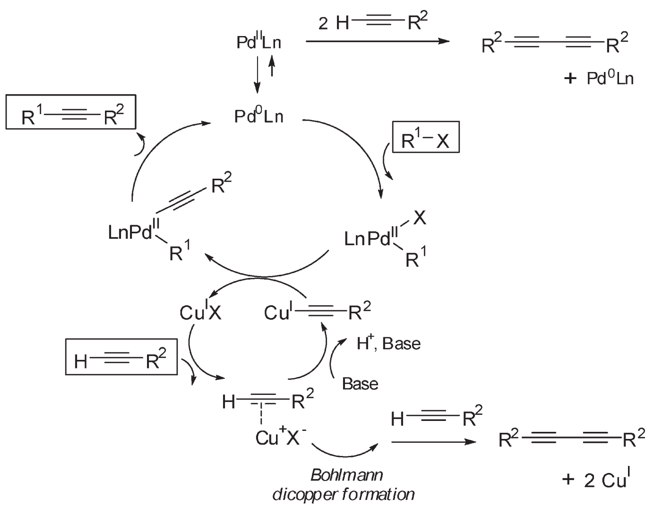
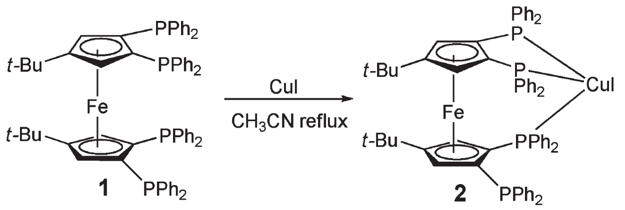
Scheme 1. Sonogashira Reaction and Alkyne Homocoupling Side-Reactions



Scheme 2. Synthesis of the Copper(I) Iodide Tetraphosphine Adduct 2

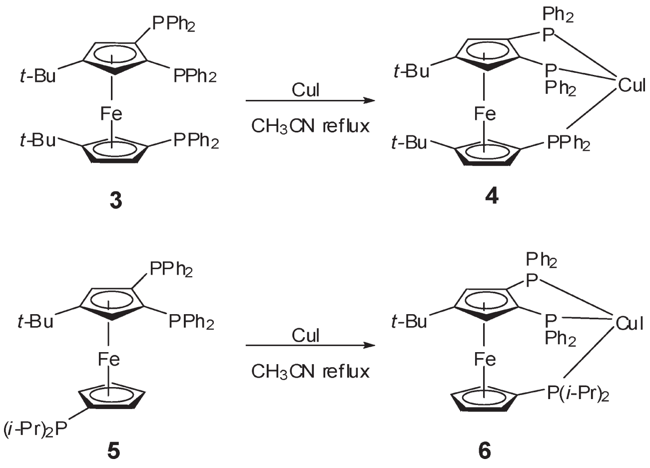


Typically, the Sonogashira reaction requires inert and oxygen-free conditions to restrain oxidative homocoupling of alkynes. On the other hand, more convenient handling conditions, for instance without the need of a glovebox or of deoxygenating the reagents (especially the liquid participants), are preferred for large-scale industrial applications.

We initiated a program aiming to develop air-stable, moisture- and temperature-resistant polydentate auxiliaries, which could allow efficient catalytic reactions in the presence of low amounts of metals (less than 1 mol %). For environmental and economical reasons the minimization of metal amounts in metal-catalyzed reactions is a crucial objective, and novel strategies to shore up this goal are highly desirable. In the course of this program, the first examples of copper(I)-ferrocenyltetraphosphine complexes have been reported (Scheme 2).[12]

Our investigations showed that 1 mol % of adduct **2** combined with 1 mol % of a "ligand-free" palladium(II) precursor was much more efficient and selective for Sonogashira coupling than the system combining the palladium complex coordinated to the same tetraphosphine metallo-ligand **1** in the presence of 5 mol % of CuI.[12] This was evidenced by the selective coupling of the deactivated 4-bromoanisole to phenylacetylene. The Cu^{I}L$_n$/Pd^{II} precursor system avoided the concurrent and deleterious consumption of phenylacetylene by formation of diyne or enynes. Additionally, the use of adduct **2** offered practical advantages since it was efficient in only 1 mol % amount and its stability to air allowed much easier storage and handling compared to anhydrous CuI. To the best of our knowledge, this was the first time that such high selectivity had been induced in Sonogashira alkynylation by initial ligand complexation to copper instead of palladium. With regard to the many environmental challenges attached to contemporary chemistry, the development of selective catalytic reactions under significantly lower metal contents is of high interest. Therefore, we decided to explore whether other benefits could be obtained from new CuI adducts in the alkynylation of organic halides.

Scheme 3. Synthesis of Copper(I) Iodide Triphosphine Adducts 4 and 6



Herein, synthesis of the first copper(I) iodide ferrocenyl triphosphine adducts is described together with their characterization in the solid state by single-crystal X-ray diffraction (XRD) and in solution by NMR. The catalytic performances reported focus on the alkynylation of deactivated aryl substrates (bromides and chlorides) since ligand-less systems are efficient with iodides or some activated aryl bromides (electron-poor).[1,13] Our efforts were also devoted to the minimization of metal content. Finally, a better mechanistic understanding was sought through the monitoring of ligand transfer from copper to palladium by ^{1}H and ^{31}P NMR at variable temperatures from 183 to 353 K.

Results and Discussion

Copper(I) Iodide-Triphosphine Adducts Characterization. In order to obtain a better knowledge of ferrocenyl polyphosphine coordination behavior toward copper salts, two new triphosphine adducts, **4** and **6**, were synthesized quantitatively from the triphosphines **3** and **5** (Scheme 3).

In the solid state, XRD studies confirmed the expected tridentate coordination of the ligand **3** or **5** to one copper iodide (Figures 1 and 2). The distorted tetrahedral environment for the copper center is analogous in **4** and **6** to the one found for the adduct **2**,[12] the main general difference being the uncoordinated phosphorus donor atom in the tetraphosphine adduct **2**.

A comparison of atom distances and angles is given in Table 1. A correlation is found between the ligand rigidity and the greater difference found within the three Cu−P bond distances in the complexes. Due to the total number of substituents on the ferrocene backbone, **2** is more hindered than **4**, which is in turn more hindered than **6**. For the most rigid adduct, **2**,

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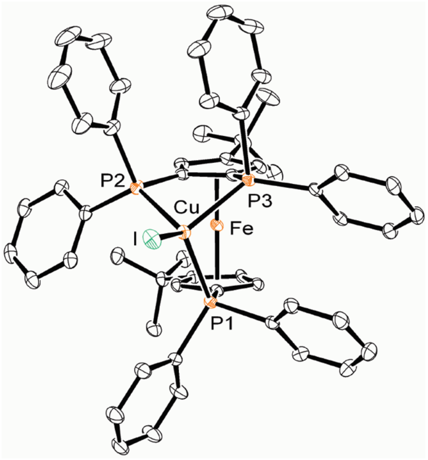

Figure 1. X-ray molecular structure of CuI-triphosphine adduct **4**.

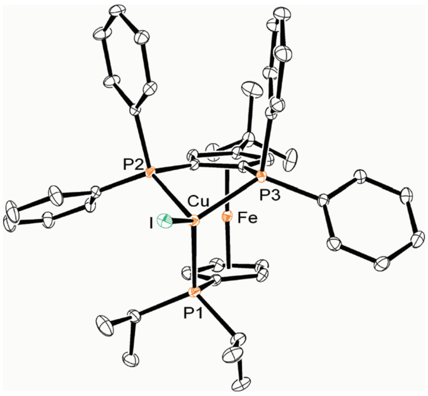

Figure 2. X-ray molecular structure of CuI-triphosphine adduct **6**.

Table 1. Structural Parameter Comparison for Copper Adducts 2, 4, and 6[a]

	2·$(CH_3CN)_2$	**4**·$(MeC_6H_5)_{1.5}$	**6**·$(MeC_6H_5)_{1.5}$
d $P_{(1)}$−Cu (Å)	2.273(2)	2.321(4)	2.281(1)
d $P_{(2)}$−Cu (Å)	2.355(2)	2.289(1)	2.296(4)
d $P_{(3)}$−Cu (Å)	2.310(3)	2.274(1)	2.296(8)
$P_{(1)}$−Cu−$P_{(2)}$ (deg)	103.8	109.8	101.4
$P_{(1)}$−Cu−$P_{(3)}$ (deg)	106.9	99.2	108.1
$P_{(2)}$−Cu−$P_{(3)}$ (deg)	85.9	86.2	87.3

[a] Crystal data for **2** are reported in ref 12.

a difference in the Cu−P bond distances of 0.037 to 0.082 Å is observed, which is reduced to 0.015 to 0.047 Å for **4** and is even smaller for **6** (0.015 Å difference or less).

The molecular crystal structures obtained for **2**, **4**, and **6** have in common three substantially different P−Cu−P angles, each roughly lying within the same range of values: 85.9° to 87.3° (chelating homoannular phosphorus), 99.2° to 108.1°, and 101.4 to 109.8°. As shown in Figure 3, the molecular structure of **6** virtually displays a plane of symmetry, which is absent in the structures of **2** and **4**. The ferrocene backbone is orientated following a staggered conformation of the cyclopentadienyl rings.

In CD_2Cl_2 solution at 298 K, the ^{31}P NMR spectrum of **4** exhibits two broad signals at −22.8 and −30.9 ppm of respective intensity 2:1. The signal at lower field is thus attributed to the chelating pair of homoannular phosphorus atoms. In contrast to the case of tetraphosphine adduct **2**, the broadness of signals is not related to the fluxional behavior of the CuI moiety in dynamic exchange between the phosphorus atoms.[12] This is shown at low temperature by NMR measurements conducted between 298 and 182 K, where the appearance of signals, as well as their chemical shifts, is unchanged.[14] In contrast, for adduct **2** above 213 K the mutual location of phosphorus donors toward the copper atom is exchanged at a high rate, leading at 298 K to one averaged signal for the three bonded phosphorus atoms.[12,14] For **4** at 182 K the ^{1}H NMR signals corresponding to the five protons of the cyclopentadienyl rings are clearly distinguished at 4.61, 4.48, 4.24, 4.22, and 3.55 ppm. The chemical shift for the methyl protons of the two *tert*-butyl groups are also significantly different at 1.25 and 0.77 ppm.

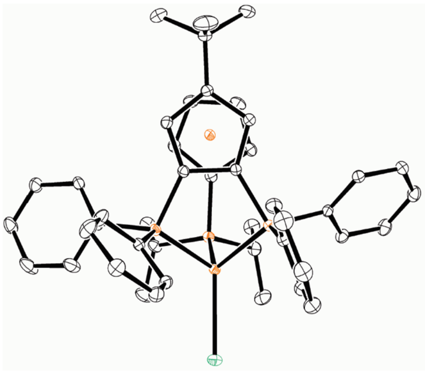

Figure 3. Molecular structure of **6** viewed from above.

The ^{31}P NMR spectrum of triphosphine adduct **6** also displays two broad signals, centered at −0.65 ppm (phosphorus atom holding isopropyl groups) and −28.0 ppm. Similarly to adduct **4**, upon cooling to 182 K, no changes in the NMR patterns were detected. In the ^{1}H NMR of **6** at 182 K three signals are observed for the six protons of the cyclopentadienyl rings at 4.83, 4.36, and 4.04 ppm, and the methyl protons of the *tert*-butyl group are observed at 1.32 ppm.

The characterization of the triphosphine adducts **4** and **6** has confirmed the preferred tridentate coordination adopted to stabilize copper(I) iodide. Spectroscopic studies have also revealed that the fluxional behavior evidenced from variable-temperature NMR measurements for adduct **2** is not observed in the case of **4** and **6**. With regard to the structural differences between the three compounds, dynamic exchange previously detected for **2** seems to be a direct consequence of the presence of four phosphorus donors. The distinction in structure and solution dynamic behavior between the polyphosphine adducts **2**, **4**, and **6** led us to test their performances in C(sp)−C(sp^2) bond coupling processes with metal catalysis.

Catalytic Performances in Sonogashira Alkynylation Reactions. The influence of the copper(I) iodide triphosphine adducts **4** and **6** in Sonogashira alkynylation of deactivated aryl halide substrates was investigated in light of the previously reported results obtained by employing **2**.[12] Table 2 summarizes the screening of catalytic performances in the coupling of the deactivated electron-rich 4-bromoanisole with phenylacetylene from various systems incorporating the copper iodide polyphosphine adducts.

In the absence of palladium, the systems incorporating only either CuI or the adduct **2** were inefficient (Table 2, entries 1 and 2). As known from the literature,[1,2] in the absence of ligand the

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[14] See the NMR spectra in the Supporting Information.

Table 2. Screening of Phenylacetylene Coupling to 4-Bromoanisole[a]

entry	copper source	palladium/ligand catalytic system	alkynylation product[b]	alkyne dimerization
1	5 mol % CuI		0	no
2	1 mol % **2**		0	no
3	5 mol % CuI	0.5% $[Pd(allyl)Cl]_2$	25%	moderate (40%[c])
4		0.5% $[Pd(allyl)Cl]_2$/ **1**	20%	no
5	5 mol % CuI	0.5% $[Pd(allyl)Cl]_2$/ **1**	10 to 30%	high (>60%[c])
6	5 mol % CuI	0.5% $[Pd(allyl)Cl]_2$/ **5**	40 to 65%	substantial (50%[c])
7	1 mol % **2**	0.5% $[Pd(allyl)Cl]_2$	80 to 90%	low (<10%[c])
8	1 mol % **4**	0.5% $[Pd(allyl)Cl]_2$	85%	traces
9	1 mol % **6**	0.5% $[Pd(allyl)Cl]_2$	99%	no
10	0.4 mol % **6**	0.2% $[Pd(allyl)Cl]_2$	96%	traces
11	0.1 mol % **6**	0.05% $[Pd(allyl)Cl]_2$	83%	traces

[a] Reaction conditions: 4-bromoanisole (3.38×10^{-3} mol), phenylacetylene (2 equiv), K_2CO_3 (2 equiv), and the catalytic system stirred at 120 °C over 20 h in 10 mL of DMF under argon. [b] GC yields average of two consistent runs or more. [c] Based on phenylacetylene consumption, determined by GC.

coupling of 4-bromoanisole is difficult (entry 3). In our case substantial amounts of alkyne dimerization were concurrently obtained. In the absence of a copper source, a low 20% yield of coupling was obtained from Pd/**1** with, however, no diyne or enyne formation (entry 4).[15] The use of copper adducts **2** and **6** in the presence of $[Pd(allyl)Cl]_2$ was more efficient in this coupling than a direct mixture of palladium with polyphosphine **1** or **5** and 5% CuI (entries 7 and 9 compared to 5 and 6), resulting in a significant inhibition of diyne formation. The use of the copper adducts **4** and **6** confirmed that the prestabilization of copper iodide with a multidentate ferrocenyl phosphine ligand promotes the palladium cross-coupling of demanding halides with phenylacetylene in a selective way (entries 8 and 9).

The near-quantitative conversion to (4-methoxyphenyl)phenylacetylene obtained from the system employing the adduct **6** (1 mol %) with 1 mol % Pd (entry 9) led us to focus our screening on the minimization of metal compounds employed in the catalytic reactions. A very high conversion of 96% to (4-methoxyphenyl)phenylacetylene was obtained in the presence of 0.4 mol % of copper and palladium (entry 10). From 0.1 mol % of the metals the conversion decreased to a still satisfactory 83% yield (entry 11). While the decrease of the quantity of palladium is rather common in cross-coupling reactions,[16] most of the Sonogashira reactions are reported with CuI amounts ranging between 5 and 10 mol %. In the experiments reported in Table 2, the use of 5 mol % CuI is always correlated to the formation of substantial amounts of alkyne dimerization products. In the recent rebirth of copper-catalyzed coupling reactions, attempts to formulate processes with lower loadings of copper catalysts are a desirable general goal.[17] Therefore, the use of 0.4 mol % of CuI (25 to 10 times less than common conditions) for coupling of demanding substrates would be a valuable achievement.

The scope of this system was further examined under low-metal-content conditions. Table 3 shows the performances obtained for the coupling of phenylacetylene with a variety of halide substrates. By employing 0.4 mol % of **6** and the palladium source, the electron-rich 4- and 3-bromoanisole were efficiently coupled in yields of over 90% (96% and 92%, respectively, Table 3 entries 1 and 2). Other deactivated electron-donating substituted aryl halides were tested, showing that the system tolerates either *para*-, *meta*-, or *ortho*-substitution. However, 2-bromotoluene gave only 80% conversion (entry 4) compared to the less hindered 3-bromotoluene, for which 96% conversion was obtained (entry 3). The sterically hindered *ortho*-substituted 2-bromonaphthalene was almost quantitatively converted into the desired product (entry 5). We were also pleased to see that a highly efficient bis-alkynylation was possible on 1,2-dibromobenzene (entry 6). The resulting product is of particular interest for further activation of the internal triple bonds toward fused-ring formation (through hydroamination, for instance). Under the successful conditions established for electronically or sterically demanding aryl bromides, the catalytic system was tested on aryl chlorides. The coupling of the deactivated 4-chloroanisole was ineffective (entry 7). However, electron-poor 4-chloroacetophenone and 4-chlorobenzonitrile were activated to yield moderate to good conversion to alkynylated aryls (entries 8−11). Using as low as 0.1 mol % of copper and palladium, 27% yield of coupling product was obtained (entry 8), and 46% in the presence of 0.4 mol % of catalysts (entry 9). Under the same catalytic conditions 4-chloroacetophenone was coupled in 36% yield (entry 11). By employing 2 mol % of copper adduct and palladium the yield with 4-chlorobenzonitrile increased above 65% (entry 10). The attempts to expand the scope of the system to C(sp)−C(sp^3) bond coupling with bromocyclohexane and bromooctane unfortunately failed (entries 12 and 13). To date, only few very catalytic systems exist to promote these couplings, all developed under glovebox conditions.[18] Finally, we were glad to see that copper adduct **6** in the absence of palladium promotes the coupling of electron-rich 4-iodotoluene to phenylacetylene in almost quantitative conversion. This performance matches some relevant "palladium-free" copper-based systems reported using nitrogen- or oxygen-containing ligands.[19]

In general, when the conversions of expected product were low, we observed that the triphosphine system was producing more alkyne dimerization than the tetraphosphine system. Having established some synthetic and practical advantages of using molecularly well-defined CuI-stabilized adducts in Sonogashira reactions (less metal involved, CuI adducts as air- and moisture-insensitive reagents for storage and handling), we were interested in obtaining more information on the interactions in solution between the polyphosphine ligands and the copper and the palladium centers. In

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(15) The sometimes deleterious effect of copper by nonproductive consumption of the alkynes has been noted by many authors; see for instance ref 5b.

(16) For reviews, see: (a) Hierso, J.-C.; Beaupérin, M.; Meunier, P. *Eur. J. Inorg. Chem.* **2007**, 3767. (b) Hierso, J.-C.; Smaliy, R.; Amardeil, R.; Meunier, P. *Chem. Soc. Rev.* **2007**, *36*, 1754.

(17) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096.

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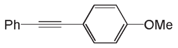
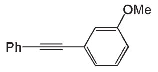
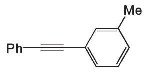
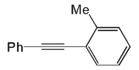
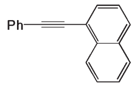
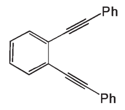
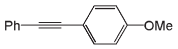
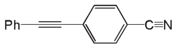
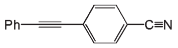
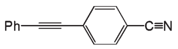
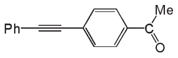
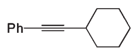
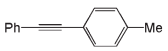
(19) See for instance: Monnier, F.; Turtaut, F.; Duroure, L.; Taillefer, M. *Org. Lett.* **2008**, *10*, 3203, and references therein.

Table 3. Scope of [Pd/6] Catalytic Performances at Low Metal Loadings[a]

entry	**6** / Pd (mol)	aryl halide	coupling product	Yield[b]
1	0.4 % / 0.2%	4-bromoanisole		96%
2	0.4 % / 0.2%	3-bromoanisole		92%
3	0.4 % / 0.2%	3-bromotoluene		96%
4	0.4 % / 0.2%	2-bromotoluene		80%
5	0.4 % / 0.2%	2-bromonaphtalene		98%
6	0.4 % / 0.2%	1,2-dibromobenzene		99%
7	0.4 % / 0.2%	4-chloroanisole		0%
8	0.1 % / 0.05%	4-chlorobenzonitrile		27%
9	0.4 % / 0.2%	4-chlorobenzonitrile		46%
10	2.0% / 1.0%	4-chlorobenzonitrile		66%
11	0.4 % / 0.2%	4-chloroacetophenone		36%
12	0.4 % / 0.2%	bromocyclohexane		0%
13	0.4 % / 0.2%	1-bromooctane		0%
14	5% / 0%	4-iodotoluene		97%

[a] Reaction conditions: aryl halide (3.38×10^{-3} mol), phenylacetylene (2 equiv), K_2CO_3 (2 equiv), and the catalytic system stirred at 120 °C over 20 h in 10 mL of DMF under argon. [b] GC yields average of 2 runs or more; isolated yields range between 90% and 95% of these values.

particular, important questions arise concerning the adducts' stability and the possibility of ligand transfer from one metal to the other in the course of the tandem catalytic reaction.

Interactions of Copper(I) Adducts with Palladium(II). We investigated by ^{31}P and ^{1}H NMR experiments the interaction of copper adducts **2**, **4**, and **6** with palladium allyl chloride in various solvent ($CDCl_3$, CD_2Cl_2, DMF, toluene) at temperatures between 183 K (−90 °C) and 353 K (80 °C). We were particularly interested in evaluating the lifetime of copper interaction with phosphorus in the presence of palladium.

Upon mixing the triphosphine Cu adduct **6** in CD_2Cl_2 with 0.5 equiv of the dimeric palladium chloride at rt, a portion of the triphosphine ligand **5** is transferred to palladium, giving rise to the palladium complex **7**, clearly characterized in the ^{31}P NMR by two sharp singlets at 37.3 ppm (bonded $-PPh_2$) and 2.1 ppm (uncoordinated $-P(i\text{-}Pr)_2$) of respective intensity of about 2:1 (Figure 4). According to the subsequent ^{1}H NMR,[14] an equilibrium around 50:50 is obtained between copper adduct **6** and Pd complex **7**. This equilibrium is immediately obtained and was found to be stable after 30 min. Upon heating the mixture for 1 h at 323 K (50 °C), the equilibrium is almost not modified; however a novel palladium species is obtained, presumably due to allyl decoordination.[14] Upon heating at 353 K (80 °C) for 2 h, the presence of a phosphine bonded to copper is still detectable but in a very low concentration and is difficult to quantify.[14] These experiments were checked several times and in different solvents, and we were very surprised to observe that in $CDCl_3$ instead of CD_2Cl_2 the equilibrium between **6** and **7** is immediately and totally shifted toward **7** at rt.[14] This is a clear indication that in such intricate bimetallic systems the influence of solvent on the species formed and their equilibrium is of high importance.

The same kind of experiments were conducted with the triphosphine Cu adduct **4** in CD_2Cl_2. Analogous behavior was observed with this triphosphine, showing a partial transfer of ligand from copper to palladium. The ^{1}H NMR indicates after 10 min a ratio 80:20 in favor of palladium complexes.[14] However, the coordination to palladium is more complex in this case (Figure 5). Apparently the three phosphorus atoms are bonded to palladium (sharp signals as AB spin system at 35.9 and 34.1 ppm corresponding to a *cis* chelation and a singlet at 14.2 ppm corresponding to a monodentate *trans* P-bonding to Pd[20]). In addition a broader signal indicative of dynamic exchange is

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(20) Roger, J.; Mom, S.; Beaupérin, M.; Royer, S.; Meunier, P.; Ivanov, V. V.; Doucet, H.; Hierso, J.-C. *ChemCatChem* **2010**, *2*, 296.

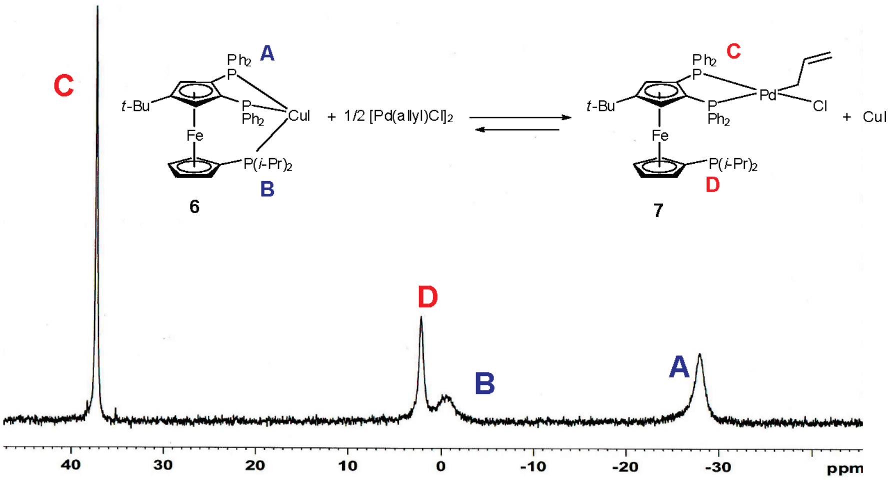

Figure 4. ^{31}P NMR of a 1:1 mixture of **6** to Pd^{II} in CD_2Cl_2 at 298 K.

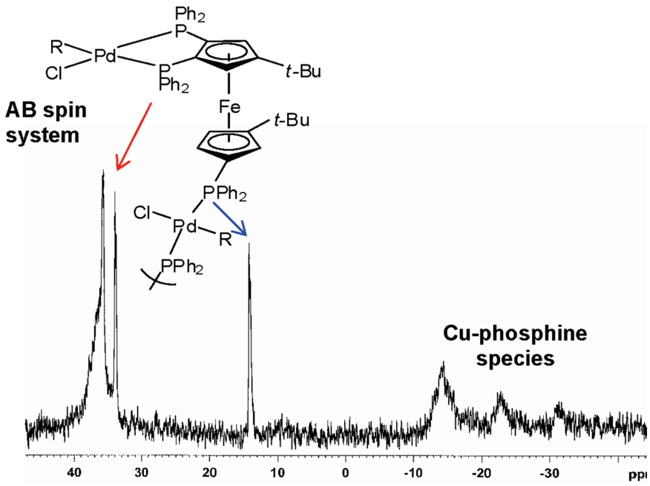

Figure 5. ^{31}P NMR of a 1:1 mixture of **4** with Pd^{II} in CD_2Cl_2 at 283 K.

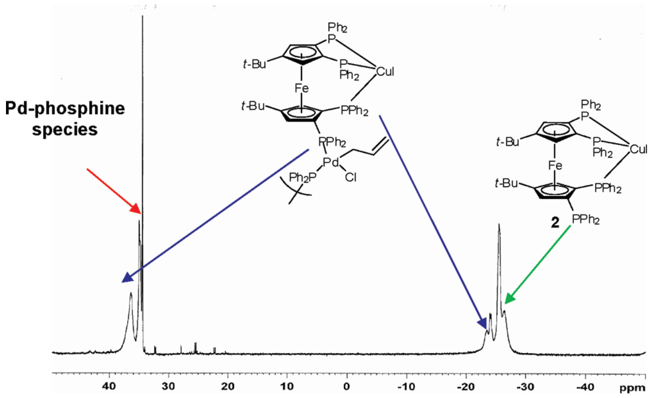

Figure 6. ^{31}P NMR of a 1:1 mixture of **2** with Pd^{II} in $CDCl_3$ at 298 K.

observed at 36 ppm, possibly due to a monodentate *cis* P-bonding to Pd. The presence of copper-phosphine-stabilized species is easier to detect at lower temperature (283 K) from broad signals centered at −10, −23, and −32 ppm. However, the nature of these species is unclear, and their chemical shifts are clearly different from those of adduct **4** (possibly clusters or dimeric species of Bohlmann type are formed,[8] due to the shortage of ligand after transfer to Pd). Upon heating to 353 K in CD_2Cl_2/toluene (1:1) for 2 h, both Pd and Cu species remain detectable in ^{31}P NMR.

The mixture of the Cu-tetraphosphine adduct **2** with 0.5 equiv of the dimeric palladium chloride at rt in $CDCl_3$ immediately reaches an equilibrium, which is conserved after 24 h at 277 K (Figure 6).

The presence of copper adduct **2** in more than 70% was estimated from ^{1}H NMR.[13] VT-^{31}P NMR at 190 K clearly ascertained that the two broad signals observed at −25.5 and −26.4 ppm relate to **2**. In addition, palladium-containing species are formed with the appearance of several peaks around 35 ppm. Interestingly, two broad signals of weaker intensity are found at −23.5 and −24.0 ppm, which seems to indicate the formation of other copper-phosphine species. Because of their deshielding and apparently 1:2 mutual intensity, they might be correlated to the broad signal found at 36.5 ppm in the palladium-bonded phosphine area and might correspond to a bimetallic species where the tricoordination of CuI is conserved and a fluxional monodentate *cis*-P bonding for the ligand appears (Figure 6). The exact attribution of the two other phosphorus signals at 34.6 and 34.9 ppm in the area corresponding to palladium coordination is more delicate but should correspond to palladium allyl species stabilized by phosphorus.[21] These signals after 24 h at 277 K are altered for a series of several superimposed multiplets probably due to allylic decoordination. Upon heating the mixture of adduct **2** to palladium chloride in $CDCl_3$/toluene (1:1) for 1 h at 353 K, it appears that mostly the palladium-phosphine area is changed (formation of bimetallic **1**·Pd_2Cl_4 and possibly monometallic **1**·$PdCl_2$), while copper-phosphine species are still detectable around −25.0 ppm. These results were similar in CD_2Cl_2/toluene (1:1),[13] showing that the Pd/**2** system is less sensitive to solvent than Pd/**6**.

In summary, CuI adducts stabilized by tridentate or tetradentate ligands lead to very different species when simply mixed with a palladium precursor at rt. Clearly, the CuI phosphine adduct **2** formed with the tetraphosphine **1** is more resistant to ligand transfer and higher temperatures. Concerning the triphosphine adducts the ligand transfer can be very fast, leading to palladium monometallic species from **6** and

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[21] Possibly bis-(P-chelating) bimetallic species [**1**·$Pd_2Cl_2(allyl)_2$] are formed; however doublets or multiplets are expected in this case. See ref 22a.

multimetallic from **4**. In general the equilibrium obtained between palladium and copper species at rt is conserved at 50 °C but slowly modified at 80 °C. To establish a rationale for the general catalytic behavior observed for the three species would be rather speculative at this stage; however the best results obtained from the system incorporating Pd/**6** might be related to the rather exclusive formation of **7** without variety of additional mononuclear or multinuclear phosphorus-stabilized metallic species. From the system incorporating Pd/**6**, when the conversion of coupling products was low, we observed that this triphosphine system was producing more alkyne dimerization than the tetraphosphine Pd/**2** system. Thus, better results were obtained concerning the inhibition of diyne formation over systems incorporating Pd/**2**, which might be related to the greater lifetime of copper adduct **2**. Further studies of interest would certainly concern the competitive kinetic studies between diyne formation and aryl/alkyne coupling. Nevertheless, the use of 0.4 mol % CuI adduct clearly led to much slower diyne formation than the use of 5 mol % CuI.

Conclusions

Several unprecedented CuI-polyphosphine adducts were quantitatively synthesized and are fully described in the solid state and in solution. We found that the prestabilization of copper iodide with a multidentate ferrocenylphosphine ligand promotes "ligand-free" palladium Sonogashira cross-coupling of deactivated aryl bromides and electron-poor chlorides. The system has some practical and economical advantages: (i) its efficient inhibition of alkyne oxidative homocoupling, (ii) the easiness of weighing and storing the CuI adducts, and (iii) the outstandingly low amount of copper needed (0.4 to 0.1 mol %) with also noticeable low amounts of palladium. The coordination behavior of polydentate ligands toward palladium and copper and, in particular, the transfer from one metal to the other are reported. These studies show that copper−ligand interactions might be very likely in traditional tandem Pd/Cu cross-coupling reactions, thus opening the way to new perspectives in mechanistic understanding.

Experimental Section

General Procedures. The reactions were carried out in oven-dried (115 °C) glassware under an argon atmosphere using Schlenk and vacuum-line techniques. The solvents were distilled over appropriate drying and deoxygenating agents prior to use, except for acetonitrile, which was deoxygenated by several nitrogen freezing/vacuum cycles. ^{1}H, ^{31}P, and ^{13}C NMR, including variable-temperature NMR experiments, were performed on a 600 MHz Bruker Avance II and a 300 MHz Bruker Avance. Elemental analyses and electrospray mass spectrometry (on a Bruker microOTOF-Q instrument) were performed at the PACSMUB of the "Institut de Chimie Moléculaire de l'Université de Bourgogne" (ICMUB-UMR CNRS 5260). GC and GC-MS analysis were done on a Supelco equity-5 capillary column on a Shimadzu GC-2014 for GC or from a hp-5 capillary column (30 m) for GC-MS. The synthesis and characterization of compounds **1**, **2**, and **5** were reported elsewhere.[22,12,23]

Synthesis of 1,1′,2-Tris(diphenylphosphino)-3′,4-di-*tert*-butylferrocene, 3. To a suspension of $FeCl_2$ (0.5 g, 3.93 mmol) in THF (50 mL) was added dropwise at −40 °C a solution of 1-diphenylphosphino-3-*tert*-butylcyclopentadienyllithium (1.08 g, 3.45 mmol) in THF (15 mL). The mixture was stirred for 2 h after reaching room temperature. A solution of 1,2-bis(diphenylphosphino)-4-*tert*-butylcyclopentadienyllithium (1.71 g, 3.45 mmol) in THF (15 mL) was dropwise added at −40 °C. After removal of THF under vacuum, toluene (100 mL) was added. The mixture was then refluxed for 15 h. After filtration, the resulting filtrate was concentrated to yield ferrocenes (2 g), which were separated first by chromatography on silica gel (toluene/hexane, 1:1) and then purified by thin-layer chromatography (ethyl acetate/hexane, 5:95) to yield pure **3** (880 mg, 32%). ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ 7.72−6.78 (m, 30H, Ph), 4.62 (s, 1H, Cp), 4.39 (s, 1H, Cp), 4.31 (s, 2H, Cp), 3.63 (s, 1H, Cp), 0.93 (s, 9H, *t*-Bu), 0.71 (s, 9H, *t*-Bu). ^{31}P NMR ($CDCl_3$, 121.4 MHz, 298 K): δ −20.6 (s, 1P), −25.4 (AB q, 2P). ^{13}C ($CDCl_3$, 75 MHz, 298 K): δ 127.1−142.8 (m, 36C, Ph), 107.4 (s, 1C, 4-Fc), 107.0 (s, 1C, 3′-Fc), 82.1 (d, 1C, $^{1}J_{CP} = 20$ Hz, 1-Fc,), 80.1 (d, 1C, $^{1}J_{CP} = 15$ Hz, 2-Fc,), 76.7 (d, 1C, $^{1}J_{CP} = 13.5$ Hz, 1′-Fc,), 75.9 (dd, 1C, $^{2}J_{CP} = 28$ Hz, $^{3}J_{CP} = 4.5$ Hz, 3-Fc,), 72.5 (s, 1C, 5′-Fc), 70.9 (s, 1C, 4′-Fc), 70.3 (dd, 1C, $^{2}J_{CP} = 4.5$ Hz, $^{3}J_{CP} \leq 1$ Hz, 5-Fc,), 68.5 (d, 1C, $^{2}J_{CP} = 4.5$ Hz, 2′-Fc,), 31.9, 31.7 (s, 3C each, *t*-Bu*C*H_3), 30.4, 30.0 (s, 1C, each, *t*-Bu*C*CH_3). Anal. Found for $C_{54}H_{53}FeP_3$ (MW 850.78): C 75.80; H 6.82. Calcd: C 76.25, H 6.28 (fractional amount of solvent is retained). Exact mass (ESI): *m*/*z* 850.27040 (M^+), $\sigma = 0.043$, err[ppm] = 2.61.

Copper-Triphosphine Adduct 4. To a solution of triphosphine **3** (190 mg, 2.22×10^{-4} mmol) in CH_3CN (15 mL) was added anhydrous CuI (42 mg, 2.21×10^{-4} mmol). The mixture was refluxed for 3 h. After cooling, the orange solution was evaporated under reduced pressure to give complex {*P*,*P*′,*P*″-[1,1′,2-tris(diphenylphosphino)-3,4′-di-*tert*-butylferrocene]iodocopper(I)}, **4** (230 mg, 99% yield). ^{1}H NMR (CD_2Cl_2, 600 MHz, 298 K): δ 8.22−6.80 (m, 30H, Ph), 4.60 (s, 1H, Cp), 4.56 (s, 1H, Cp), 4.24 (s, 2H, Cp), 3.70 (s, 1H, Cp), 1.35 (s, 9H, *t*-Bu), 0.95 (s, 9H, *t*-Bu). ^{31}P NMR (CD_2Cl_2, 242.9 MHz, 298 K): δ −22.77 (s, br, 2P), −30.93 (s, br, 1P). ^{13}C NMR (CD_2Cl_2, 125.75 MHz, 298 K): δ 138.5, 134.6, 133.9 (m, 2C each, *ipso*-C_6H_5), 134.0−127.0 (m, 30C, C_6H_5), 111.6 (s, 1C, 4-Fc), 106.5 (s, 1C, 3′-Fc), 84.9 (d, 1C, $^{1}J_{CP} =$ 32.5 Hz, 1-Fc), 79,3 (d, 1C, $^{1}J_{CP} = 21.25$ Hz, 2-Fc,), 76.7 (s, 1C, 1′-Fc), 73.1 (d, 1C, $^{2}J_{CP} = 10$ Hz, 5′-Fc), 72.1 (s, 1C, 4′-Fc), 68.5 (s, 1C, 5-Fc), 67.7 (s, 1C, 2′-Fc), 66.3 (s, 1C, 3-Fc) 30.9, 30.3 (s, 3C each, *t*-Bu*C*H_3), 30.2, 29.4 (s, 1C each, *t*-Bu*C*CH_3). Anal. Found for $C_{54}H_{53}CuFeIP_3$ (MW 1041.23): C 61.74; H 5.39. Calcd: C 62.29, H 5.13. Exact mass (ESI): *m*/*z* 913.20001 ($M - I^+$), $\sigma = 0.030$, err[ppm] = 2.68.

Copper-Triphosphine Adduct 6. To a solution of 1,2-bis(diphenylphosphino)-1′-(diisopropylphosphino)-4-*tert*-butylferrocene, **5** (99 mg, 1.08×10^{-4} mmol), in CH_3CN (10 mL) was added anhydrous CuI (20.5 mg, 1.08×10^{-4} mmol). The mixture was refluxed for 3 h. After cooling, the orange solution was evaporated under reduced pressure to give complex {*P*,*P*′,*P*″-[1,2-bis(diphenylphosphino)-1′-(diisopropylphosphino)-4-*tert*-butylferrocene]iodocopper(I)}, **6** (100 mg, 99% yield). ^{1}H NMR (CD_2Cl_2, 600 MHz, 298 K): δ 8.00−6.80 (m, 20H, Ph), 4.88, 4.38, 4.12 (s, 2H each, Cp), 2.02 (s, 2H, CH *i-Pr*), 1.44−1.41 (m, 6H, CH_3 *i-Pr*), 1.40 (s, 9H, *t*-Bu), 1.20−1.09 (m, 6H, CH_3 *i-Pr*). ^{31}P NMR (CD_2Cl_2, 242.9 MHz, 298 K): δ −0.65 (s, br, 1P), −28.05 (s, br, 2P). ^{13}C NMR (CD_2Cl_2, 125.75 MHz, 298 K): δ 135.9 (s, 4C, *ipso*-C_6H_5), 134.0−128.0 (m, 20C, C_6H_5), 110.2 (s, 1C, 4-Fc), 82.9 (s, 1C, 1′-Fc), 80.3 (s, 2C, 1, 2-Fc), 74.4 (s, 2C, 2′, 5′-Fc), 71.8 (s, 2C, 3, 5-Fc), 69.8 (s, 2C, 3′, 4′-Fc), 31.8 (s, 3C, *t*-BuCH_3), 31.5 (s, 1C, *t*-Bu*C*CH_3), 28.1 (s, 2C, CH *i*-Pr), 21.3, 20.0 (s, 2C each, CH_3 *i*-Pr). Anal. Found for $C_{44}H_{49}CuFeIP_3$ (MW 917.09): C 56.38; H 5.64. Calcd: C 57.63, H 5.39 (fractional amount of solvent is retained). Exact mass (ESI): *m*/*z* 789.16871 ($M - I^+$), $\sigma = 0.033$, err[ppm] = 2.22.

Sonogashira Catalytic Reactions. The reaction of aryl halide (3.38×10^{-3} mol), phenylacetylene (0.75 mL, 6.76×10^{-3} mol,

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(23) (a) Hierso, J.-C.; Ivanov, V. V.; Amardeil, R.; Richard, P.; Meunier, P. *Chem. Lett.* **2004**, *33* (10), 1296. (b) Hierso, J.-C.; Fihri, A.; Amardeil, R.; Meunier, P.; Doucet, H.; Santelli, M.; Ivanov, V. V. *Org. Lett.* **2004**, *6*, 3473.

2 equiv), and K_2CO_3 (0.935 g, 6.76×10^{-3} mol, 2 equiv) with 0.4 mol % of copper adduct **6** (13.5 μmol, 12.4 mg) in the presence of 0.2 mol % $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (6.8 μmol, 2.5 mg), at 120 °C over 20 h in DMF (10 mL), under argon, affords the coupling products. Pure products were obtained after addition of water, extraction with organic solvents, separation, drying, concentration, and chromatography on silica gel.

Acknowledgment. This work was supported by the "Conseil Régional de Bourgogne". M.B. and A.J. thank the CNRS for a grant. The ANR program "Chimie Pour le Développement Durable" is sincerely acknowledged for supporting this research via the project ANR-09-CP2D-03 CAMELOT.

Supporting Information Available: Crystal data and structure refinement for **4** and **6**, exact-mass data, ^1H, ^{31}P, and ^{13}C NMR spectra for **3**, **4**, and **6**, organic product characterization, and details of catalytic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.