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Mechanism of the Copper-Free Palladium-Catalyzed Sonagashira Reactions: Multiple Role of Amines

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Abstract: Amines used as bases in copper-free, palladium-catalyzed Sonogashira reactions play a multiple role. The oxidative addition of iodobenzene with $[Pd^0(PPh_3)_4]$ is faster when performed in the presence of amines (piperidine > morpholine). Amines also substitute one ligand L in *trans*-$[PdI(Ph)(L)_2]$ ($L = PPh_3$, $AsPh_3$) formed in the oxidative addition. This reversible reaction, which gives $[PdI(Ph)L(R_2NH)]$, is favored in the order $AsPh_3 > PPh_3$ and piperidine > morpholine. Two mechanisms are proposed for Sonogashira reactions, depending on the ligand and the amine. When $L = PPh_3$, its substitution by the amine in *trans*-$[PdI(Ph)(PPh_3)_2]$ is less favored than that of the alkyne. A mechanism involving prior coordination of the alkyne is suggested, followed by deprotonation of the ligated alkyne by the amine. When $L = AsPh_3$, its substitution in *trans*-$[PdI(Ph)(AsPh_3)_2]$ by the piperidine is easier than that by the alkyne, leading to a different mechanism: substitution of $AsPh_3$ by the amine is followed by substitution of the second $AsPh_3$ by the alkyne to generate [PdI(Ph)(amine)(alkyne)]. Deprotonation of the ligated alkyne by an external amine leads to the coupling product. This explains why the catalytic reactions are less efficient with $AsPh_3$ than with PPh_3 as ligand.

Keywords: alkynes · amines · palladium · reaction mechanisms · Sonogashira reaction

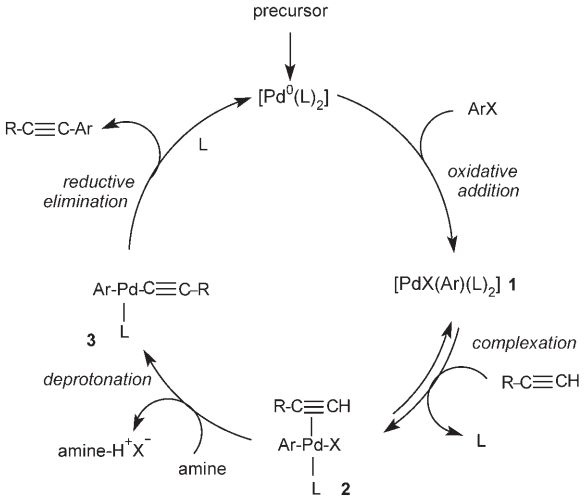
Introduction

Amines are often used as bases in copper-free, palladium-catalyzed Sonogashira reactions [Eq. (1)].[1] Specific amines are required, such as the secondary amines piperidine,[1a,d,f,g] morpholine,[1h] and diisopropylamine.[1f,h] The amines are usually used in large excess,[1c,d,f,g] or as the solvent.[1a,d,e]

$$ArX + R\text{-}C{\equiv}CH + amine \xrightarrow{[Pd^0]} R\text{-}C{\equiv}C\text{-}Ar + amine\text{-}H^+ + X^- \quad (1)$$

The mechanism of the copper-free Sonogashira reaction is not known. The mechanism proposed in Scheme 1 is derived from a related one.[1h] The key step is a complexation of the alkyne to the complex $[PdX(Ar)(L)_2]$ (**1**) formed in the oxidative addition, with release of one ligand L. This generates $[PdX(Ar)(PPh_3)(\eta^2\text{-alkyne})]$ (**2**), in which the proton of the ligated alkyne is more acidic than in the free alkyne.[2] Deprotonation of the ligated alkyne by the amine generates complex **3**, which is able to undergo a reductive elimination, affording the coupling product and the Pd^0 catalyst.

In a preliminary study, we established that amines (for example, piperidine, morpholine, diisopropylamine) react with *trans*-$[PdX(Ar)(PPh_3)_2]$ (**1a**) to generate new complexes $[PdX(Ar)(PPh_3)(amine)]$ (**4a**) in reversible reactions whose



Scheme 1.

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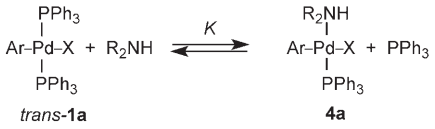
equilibrium constants K have been calculated [Eq. (2)].[3] The reversible substitution of one PPh_3 group by the amine may thus compete with the substitution of PPh_3 by the alkyne to generate [PdX(Ar)(PPh_3)(η^2-alkyne)] (**2**), a key step in the postulated mechanism of the copper-free Sonogashira reaction (Scheme 1). The fact that the amine is often used in large excess,[1c,d,f,g] or even as solvent,[1a,d,e] may favor the substitution of the phosphine by the amine.



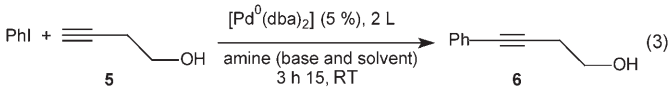
(2)

In other work related to the palladium-catalyzed Stille reaction (cross-coupling between iodobenzene and [CH_2=CH–$SnBu_3$]), it was established that $AsPh_3$ was a more efficient ligand than PPh_3.[4] This was rationalized by the fact that $AsPh_3$ was more easily substituted by CH_2=CH–$SnBu_3$ in *trans*-[PdI(Ph)($AsPh_3$)$_2$] (**1b**) to generate transient complexes [PdI(Ph)($AsPh_3$)(η^2-CH_2=CH–$SnBu_3$)] than PPh_3 in *trans*-[PdI(Ph)(PPh_3)$_2$] (**1a**).[4,5] In other words, $AsPh_3$ is a more labile ligand than PPh_3 in *trans*-[PdI(Ph)(L)$_2$] complexes.

This encouraged us to investigate the role of ligands and amines in copper-free Sonogashira reactions more deeply. We report herein that $AsPh_3$ is less efficient than PPh_3 in the catalytic reactions. The amine may be involved in three different steps of the catalytic cycle and two different mechanisms may operate according to the nature of the ligand and amine.

Results and Discussion

Comparative efficiency of PPh_3 and $AsPh_3$ in copper-free palladium-catalyzed Sonogashira reactions: The effect of the ligand PPh_3 or $AsPh_3$ was probed in the reaction of PhI with the alkyne **5** [Eq. (3)].



(3)

Such a reaction catalyzed by [Pd^0(PPh_3)$_4$] was reported by Linstrumelle et al., using piperidine as solvent (5% [Pd^0(PPh_3)$_4$], 25°C, 6 h, 96% yield).[1a,6] We have used [Pd^0(dba)$_2$] (dba = dibenzylidene acetone) as the catalytic precursor, in order to vary the nature of the ligand more easily. First we checked that no side reaction occurred between the amine (morpholine or piperidine) and the dba which would be released from the precursor [Pd^0(dba)$_2$] in the course of the catalytic reactions. The Sonogashira reactions were performed at room temperature with the amine as solvent. For comparison, the reagents and catalyst concentrations were the same as those of the reaction catalyzed by [Pd^0(PPh_3)$_4$].[1a,6] The reactions were voluntarily stopped after the same reaction time of 3 h 15 min, to compare the efficiency of the ligand $AsPh_3$ with that of PPh_3, as well as the efficiencies of the amines.

Table 1. Palladium-catalyzed Sonogashira reactions[a] (Scheme 4).

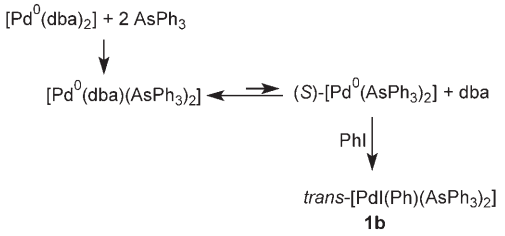
Entry	L	Amine	Recovered PhI [%][b]	Yield of **6** [%][b]
1	PPh_3	piperidine	0	94
2	$AsPh_3$	piperidine	47	44
3	PPh_3	morpholine	40	56
4	$AsPh_3$	morpholine	45	50

[a] PhI (1 mmol) and **5** (2 mmol) in amine (piperidine or morpholine; 3 mL). [b] Yields are relative to the initial PhI. They were determined in the crude after work-up, by ^{1}H NMR spectroscopy using $CHCl_2CHCl_2$ as an internal standard.

From the results of the catalytic reactions reported in Table 1, PPh_3 appears to be a better ligand than $AsPh_3$ for the palladium-catalyzed Sonogashira reaction, whatever the base (piperidine or morpholine). Piperidine was much more efficient than morpholine when PPh_3 was considered (entries 1, 3), whereas similar results were obtained for $AsPh_3$ whatever the base (entries 2, 4).

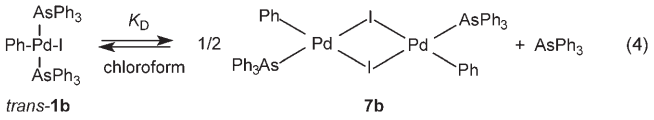
[Pd^0(dba)$_2$] associated with PPh_3 (2 equiv) proved to be more efficient than [Pd^0(PPh_3)$_4$][1a,6] (vide supra). We know from previous work that [Pd^0(PPh_3)$_4$] is more reactive than the Pd^0 complex generated from [Pd^0(dba)$_2$] + 2 PPh_3 in oxidative addition with PhI.[7] This indicates that the oxidative addition is not the rate-determining step of the Sonogashira reactions investigated here. A main difference between the two precursors is the concentration of free PPh_3, which is more important when starting from [Pd^0(PPh_3)$_4$] (that is, [Pd^0(PPh_3)$_3$] + PPh_3) than from [Pd^0(dba)$_2$] + 2 PPh_3 (that is, [Pd^0(dba)(PPh_3)$_2$] + dba; no free PPh_3).[7] This implies that PPh_3 is involved in the rate-determining step of the catalytic cycle by a decelerating effect. In other words, the rate-determining step involves the release of PPh_3 by a ligand substitution process. The fact that the catalytic reaction works better with piperidine than with morpholine when L = PPh_3 suggests that the amine also is involved in the rate-determining step. At the least, we need to understand why $AsPh_3$ is much less efficient than PPh_3, when piperidine is used as base and solvent.

Reaction of amines with *trans*-[PdI(Ph)($AsPh_3$)$_2$] (4b) formed in oxidative addition: The reaction of PhI with [Pd^0(dba)$_2$] associated with two equivalents PPh_3 gives *trans*-[PdI(Ph)(PPh_3)$_2$] (**1a**),[7] which is known to react with amines [Eq. (2)].[3] The reaction of PhI with [Pd^0(dba)$_2$] associated with two equivalents $AsPh_3$ gives *trans*-[PdI(Ph)($AsPh_3$)$_2$] (**1b**) (Scheme 2).[8]



Scheme 2.

As previously established, *trans*-[PdI(Ph)($AsPh_3$)$_2$] (**1b**) is in equilibrium with the dimeric complex [PhPd(μ-I)-($AsPh_3$)]$_2$ (**7b**) in chloroform [Eq. (4)].[5]



When morpholine (10 μmol) was added to an NMR tube containing *trans*-[PdI(Ph)($AsPh_3$)$_2$] (**1b**; 10 μmol) in $CDCl_3$ (0.75 mL), the NMR signals of the protons of the Ph group of **1b** disappeared partially to give new signals (Table 2) the magnitude of which increased at the expense of those of **1b** after successive addition of morpholine. New signals characteristic of a ligated morpholine were also observed (Table 2). Morpholine (5 equiv) was required to consume the **1b** completely. The complex **1b** was in part restored after further addition of $AsPh_3$ (1 equiv). Consequently, morpholine reacted with **1b** to generate a new complex **4bm** in a reversible reaction.

Table 2. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) spectrum of **4bm** (see Figure 1, bottom, for the attribution of protons).

Proton	δ
H_1	2.82 (d, d, d, d, J = 12.8, 12.8, 12.8, 3.7 Hz, 1H)
H'_4	2.99 (d, J = 12.8 Hz, 1H)
H'_1	3.16 (d, J = 12.8 Hz, 1H)
H_3	3.53 (d, d, J = 12.8, 12.8 Hz, 1H)
H_4	3.59 (d, d, J = 12.8, 12.8 Hz, 1H)
H'_3	3.74 (d, J = 12.8 Hz, 1H)
H'_2	3.82 (d, J = 12.8 Hz, 1H)
H_2	3.91 (d, d, d, d, J = 12.8, 12.8, 12.8, 3.7 Hz, 1H)
m-H, *p*-H of Ph	6.71 (m, 3H)
o-H of Ph	6.97 (d, J = 7.5 Hz, 2H)
H of $AsPh_3$	7.27 (m, 6H)
H of $AsPh_3$	7.35 (m, 9H)

When morpholine (10 μmol) was added to an NMR tube containing the dimer [PhPd(μ-I)($AsPh_3$)]$_2$ (**7b**; 5 μmol) in chloroform (0.75 mL), the solution turned from dark orange to yellow. The signals of **7b** disappeared partially to give the new signals mentioned in Table 2. Morpholine (3 equiv) was required to consume **7b** completely. Therefore, morpholine reacted more easily with the dimer **7b** to generate the new complex **4bm**, still in a reversible reaction. This new complex was crystallized and its formula deduced from its X-ray structure (Figure 1 (top) and Tables 3 and 4), attesting to the substitution of one $AsPh_3$ by one morpholine ligand, which is in a *trans* position relative to the remaining $AsPh_3$ ligand.

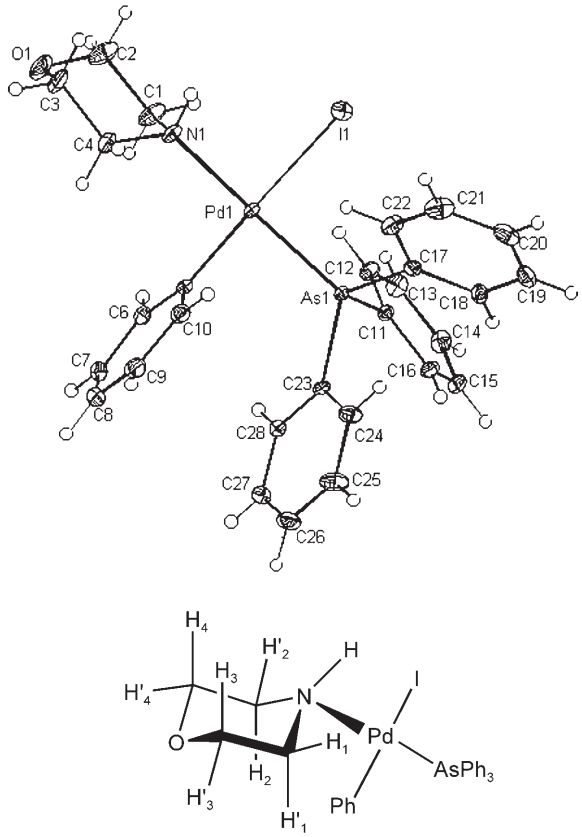


Figure 1. Complex [PdI(Ph)($AsPh_3$)(morpholine)] (**4bm**). Top: X-ray structure. Bottom: See Table 2 for the ^{1}H NMR characterization.

Table 3. Crystal data and structure refinement for [PdI(Ph)($AsPh_3$)(morpholine)] (**4bm**).

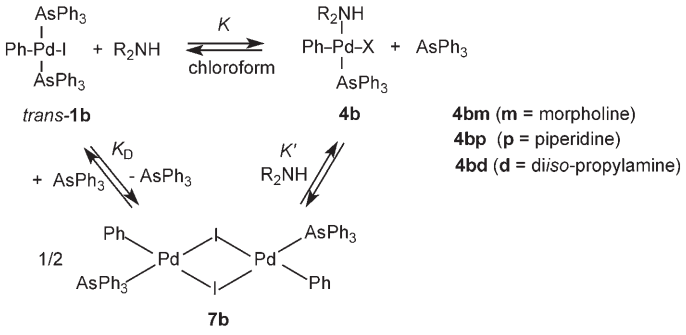
empirical formula	$C_{28}H_{29}AsINOPd$	crystal size [mm^3]	0.22 × 0.13 × 0.11
formula weight	703.74	θ range [°]	2.26–32.00
T [K]	293(2) K	index range	$-15 \le h \le 15$
λ [Å]	0.71069		$-17 \le k \le 17$
crystal system, space group	triclinic, $P\bar{1}$		$-18 \le l \le 18$
a [Å]	10.378(11)	collected/unique reflections	27797/8838 [R(int) = 0.0346]
b [Å]	11.464(7)	completeness to θ = 32.00 [%]	98.6
c [Å]	12.498(10)	refinement method	full-matrix least-squares on F^2
α [°]	87.982(6)	data/restraints/parameters	8838/0/299
β [°]	75.277(7)	goodness-of-fit on F^2	1.062
γ [°]	64.197(4)	final R indices [I > 2σ(I)]	$R1$ = 0.0568, $wR2$ = 0.1749
V [Å^3]	1289.86(16)	R indices (all data)	$R1$ = 0.0787, $wR2$ = 0.1892
Z/ρ_{calcd} [Mg m^{-3}]	2/1.812	extinction coefficient	0.0071(10)
μ [mm^{-1}]	3.210	largest diff. peak/hole [e Å^{-3}]	2.487/−4.486
F(000)	688		

Table 4. Relevant bond lengths [Å] and angles [°] for [PdI(Ph)-($AsPh_3$)(morpholine)] (**4bm**).

Pd1−C5	1.999(6)	C10−C9	1.394(9)
Pd1−N1	2.128(5)	C10−C5	1.399(8)
Pd1−As1	2.3621(11)	C6−C5	1.385(9)
Pd1−I1	2.6728(15)	C6−C7	1.403(9)
O1−C3	1.388(11)	C4−C3	1.524(9)
O1−C2	1.437(13)	C8−C7	1.360(12)
N1−C4	1.484(9)	C8−C9	1.368(12)
N1−C1	1.492(8)	C1−C2	1.511(10)
C5-Pd1-N1	93.1(2)	C9-C10-C5	121.0(7)
C5-Pd1-As1	87.74(15)	C5-C6-C7	120.7(6)
N1-Pd1-As1	178.75(16)	N1-C4-C3	112.1(6)
C5-Pd1-I1	177.53(17)	O1-C3-C4	112.4(7)
N1-Pd1-I1	87.92(16)	N1-C1-C2	112.3(6)
As1-Pd1-I1	91.28(3)	C6-C5-C10	117.7(6)
C3-O1-C2	109.8(6)	C6-C5-Pd1	121.2(4)
C4-N1-C1	107.8(6)	C10-C5-Pd1	121.1(5)
C4-N1-Pd1	120.6(4)	O1-C2-C1	110.7(7)
C1-N1-Pd1	112.5(4)		

The complex **4bm** was also characterized by NMR spectroscopy (^1H, ^{13}C, and 2D), which revealed that the complexation of the morpholine on the Pd^{II} center resulted in a split of its eight protons which were then magnetically nonequivalent (Table 2).

Therefore, as for complexes ligated by PPh_3, the morpholine can substitute one $AsPh_3$ in *trans*-]PdI(Ph)($AsPh_3$)$_2$] (**1b**) to generate complexes **4b**. This reaction proceeds via the dimeric complex **7b** (Scheme 3).



Scheme 3.

The equilibrium constant K (Scheme 3) was determined from the value of K_D and K', with $K = K_D K'$ [Eqs. (5)–(7)].

$$K = \frac{[AsPh_3][\mathbf{4b}]}{[trans\text{-}\mathbf{1b}][R_2NH]} \quad (5)$$

$$K_D = \frac{[AsPh_3][\mathbf{7b}]^{1/2}}{[trans\text{-}\mathbf{1b}]} \quad (6)$$

$$K' = \frac{[\mathbf{4b}]}{[R_2NH][\mathbf{7b}]^{1/2}} \quad (7)$$

The value of K_D was determined by ^1H NMR spectroscopy from a solution (13.3 mM) of **1b** (10 μmol) in $CDCl_3$ (0.75 mL) using the integration of the doublet at $\delta = 7.1$ ppm (two *o*-H of Ph of **7b**) and the integration of the two triplets (one proton *p*-H and two protons *m*-H of Ph of **1b**): $K_D = 0.013$ ($CDCl_3$, 25 °C). The value of $K' = 333\ M^{-1/2}$ ($CDCl_3$, 25 °C) was determined by ^1H NMR spectroscopy performed on a solution of the dimer **7b** (5 μmol) in $CDCl_3$ (0.75 mL) after addition of various amounts of morpholine (in the range 0.5–3 equiv), by using the integration of the doublet of the two *o*-H of Ph of **7b** at $\delta = 7.1$ ppm and that of the doublet of the two *o*-H of Ph of **4bm** at $\delta = 6.95$ ppm (see Figure 2 for the determination of K'). The value of $K = K_D K' = 4.3$ ($CDCl_3$, 25 °C) was thus deduced.

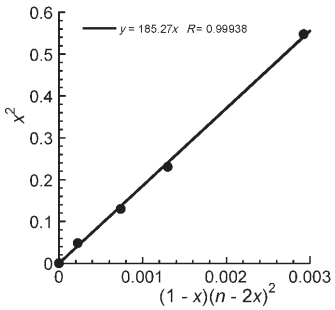


Figure 2. Determination of the equilibrium constant K' for the reaction between complex **7b** and **4bm** formed after addition of morpholine (n equiv) to complex **7b** ($C_0 = 6.67$ mM) in $CDCl_3$ at 25 °C. $K'' = [\mathbf{4bm}]^2/([R_2NH]^2[\mathbf{7b}]) = 4x^2/\{C_0(1-x)(n-2x)^2\}$ (x = molar fraction of **4bm**). Plot of x^2 versus $(1-x)(n-2x)^2$. The slope of the straight line gave $K'' = 110\,900\ M^{-1}$. $K' = K''^{1/2} = 333\ M^{-1/2}$ (Scheme 3).

Similar reactions were performed with piperidine. When piperidine (10 μmol) was added to the dimer **7b** (5 μmol) in $CDCl_3$ (0.75 mL), the signals of the dimer **7b** totally disappeared. Two new complexes **4bp** and **4′bp** (Figure 3, Scheme 3) were characterized by ^1H, ^{13}C, and 2D NMR spectroscopy. The structure of the major complex (63 %) was assigned to **4bp** (Figure 3) with the piperidine and the $AsPh_3$ in a *trans* position, by analogy to the structure of complex **4bm** (Figure 1, top). The structure of isomeric minor complex **4′bp** (37 %) could not be determined, through lack of crystals. However, the signals of the *o*-H of the minor complex are located at the lowest field (Table 5) in comparison with those of complexes **4bm**, **1b**, or **7b**, in which the Ph group is in a position *cis* to $AsPh_3$. This suggests that the Ph group and $AsPh_3$ are in a *trans* position in

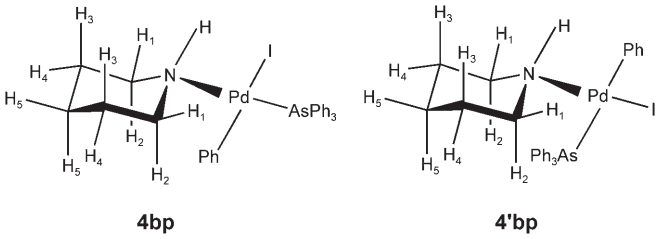


Figure 3. Proposed structures for **4bp** and **4′bp**.

Table 5. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 25 °C, TMS) of **4bp** and **4′bp** (see Figure 3).

Proton	δ [ppm]
4bp	
H_4, H_3, H_5	1.2–1.7 (m, 6H)
H_2	2.52 (dddd, J = 12.8, 12.8, 12.8, 2.7 Hz, 2H)
H_1	3.34 (d, J = 12.8 Hz, 2H)
N–H	3.49 (t, J = 12.4 Hz, 1H)
p-H	6.73 (t, J = 6 Hz, 1H)
m-H	6.75 (t, J = 6 Hz, 2H)
o-H	7.01 (d, J = 6 Hz, 2H)
H of $AsPh_3$	7.3–7.4 (m, 15H)
4′bp	
H_4, H_3, H_5	1.2–1.7 (m, 6H)
H_2	2.60 (pseudo q, 2H)
N–H	2.95 (t, J = 12.4 Hz, 1H)
H_1	3.24 (d, J = 13 Hz, 2H)
m-H and *p*-H	7.05 (t, J = 7 Hz, 1H)
m-H and *p*-H	7.09 (t, J = 7 Hz, 2H)
o-H	7.27 (m, 2H)
H of $AsPh_3$	7.3–7.4 (m, 15H)

complex **4′bp**. Therefore, from the two possible isomers, we propose the structure of **4′bp** in Figure 3.

The complex *trans*-**1b** reacted with piperidine to give complexes **4bp** and **4′bp** in a reversible reaction (Scheme 3). Two equivalents of piperidine were required to shift the equilibrium completely toward complexes **4bp** and **4′bp**. A minimum value of $K' = [\mathbf{4bp} + \mathbf{4'bp}]/([\mathbf{7b}]^{1/2}[\text{piperidine}]) > 850\ \text{M}^{-1/2}$ ($CDCl_3$, 25 °C) could be estimated from the reaction of dimer **7b** with piperidine (1 equiv) by using the ^{1}H NMR data. Since $K_D = 0.013$ (vide supra), a minimum value of $K = K_D K' > 11$ ($CDCl_3$, 25 °C) could be estimated (Table 6).

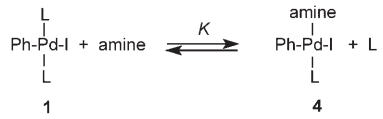
Table 6. Equilibrium constants K for the substitution of one ligand L by an amine in complexes *trans*-[PdI(Ph)$(L)_2$] (**1**) in chloroform at 25 °C [Eq. (8)].

Amine (pK_a)[a]	K	
	L = PPh_3[3]	L = $AsPh_3$
piperidine (11.12)	0.11	>11
morpholine (8.33)	0.014	4.3
tert-butylamine (10.83)	0.002	0.041
diisopropylamine (10.96)	0.00007	0.007

[a] In water (ref. [11]).

The complex **4bd** was formed by addition of a large excess of diisopropylamine to complex *trans*-**1b** in $CDCl_3$ (Scheme 3). Only after addition of 30 equivalents of diisopropylamine was complex **4bd** formed in a significant amount (46%). The complex was detected through the presence of the protons of the Ph group ligated to the Pd^{II} center. The ligated iPr$_2$NH could not be characterized because its signals overlapped those of the free iPr$_2$NH added in a large excess. The equilibrium constant K (Scheme 3) is given in Table 6. In addition, one $AsPh_3$ from complex *trans*-**1b** was substituted by a primary amine such as *tert*-butylamine to give the complex [PdI(Ph)$(AsPh_3)$(tBuNH$_2$)] (**4bt**) in a reversible reaction (see the K value in Table 6).

Therefore, one ligand $AsPh_3$ can be substituted by a secondary amine R_2NH (piperidine, morpholine, isopropylamine) or primary amine RNH_2 (*tert*-butylamine) in the complex *trans*-[PdI(Ph)$(AsPh_3)_2$] to give [PdI(Ph)$(AsPh_3)$-(R_2NH)] [Eq. (8)]. This reaction proceeds via the dimeric complex [PhPd(μ-I)$(AsPh_3)]_2$ (**7b**) (Scheme 3).[9] From the values of the equilibrium constants in Table 6, we deduce that $AsPh_3$ is much more labile than PPh_3, because the dimer [PhPd(μ-I)$(AsPh_3)]_2$ is generated easily from *trans*-[PdI(Ph)$(AsPh_3)_2$],[5] whereas [PhPd(μ-I)$(PPh_3)]_2$, even if known and synthesized independently,[10] has never been observed to be formed from *trans*-[PdI(Ph)$(PPh_3)_2$].



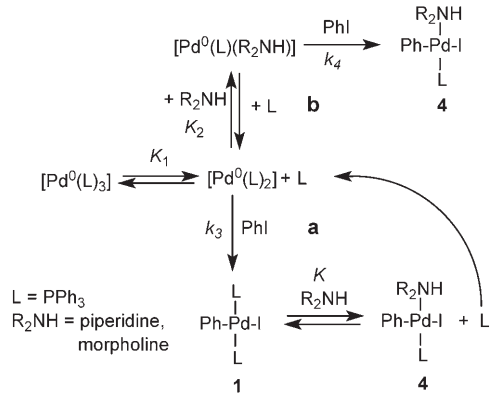
(8)

L = PPh_3, $AsPh_3$
amine = piperidine, morpholine, diisopropylamine, *tert*-butylamine

Whatever the ligand, the ability of the amine to substitute one $AsPh_3$ or one PPh_3 decreases in the order: piperidine > morpholine > *tert*-butylamine > diisopropylamine.

Piperidine is more basic than morpholine (Table 6)[11] and is thus a better ligand for the Pd^{II} center. Although diisopropylamine is more basic than morpholine, it is a poorer ligand for the Pd^{II} center. Thus the $AsPh_3$ substitution is also sensitive to the steric hindrance of the amine.

Role of the amine in the oxidative addition: Complexes *trans*-[PdX(Ar)$(L)_2$] (L = PPh_3 or $AsPh_3$) are formed in the first step of the catalytic cycle of the Sonogashira reaction by the oxidative addition of ArX with [$Pd^0(L)_2$] complexes. We have now established that secondary amines can coordinate *trans*-[PdX(Ar)$(L)_2$] complexes with the release of one ligand L, which can in turn react with [$Pd^0(L)_2$] to form unreactive [$Pd^0(L)_3$] complexes in the course of the oxidative addition. A decelerating effect of the amine in the rate of the overall oxidative addition might therefore be expected (path **a** in Scheme 4). It was thus of great interest to probe the effect of amine on the kinetics of the oxidative addition.



Scheme 4.

Moreover, the coordination of Pd^0 complexes by amines was recently under debate.[12]

$[Pd^0(PPh_3)_4]$ was selected because it was more easily available than $[Pd^0(AsPh_3)_4]$. The kinetics of the oxidative addition of PhI (2 mM) to $[Pd^0(PPh_3)_4]$ (2 mM) in DMF containing nBu_4NBF_4 (0.3 M) was monitored at 20 °C, by recording the decrease in the oxidation current of $[Pd^0(PPh_3)_3]$ (proportional to its concentration) measured at a rotating gold disk electrode polarized at +0.2 V versus SCE on the plateau of the oxidation wave of $[Pd^0(PPh_3)_3]$, first in the absence of amine and then in the presence of various amounts of piperidine or morpholine, added to the Pd^0 complex before PhI. The graph of the molar fraction x of the Pd^0 complex versus time shows that the oxidative addition was faster when performed in the presence of amine (piperidine or morpholine) (Figure 4 left). A ^{31}P NMR measurement at the end of the oxidative addition performed in the presence of piperidine (100 mM) did exhibit the singlet of *trans*-[PdI(Ph)(PPh_3)(piperidine)] at $\delta = 32.5$ ppm, as already characterized.[3] This proves that the oxidative addition worked well in the presence of the amine.[13] Although PPh_3 was released in the course of the oxidative addition performed in the presence of piperidine, the oxidative addition went faster. This indicates that the reactive species differed from $[Pd^0(PPh_3)_2]$ and would be the more reactive complex: $[Pd^0(PPh_3)(amine)]$ (path **b** in Scheme 4). Consequently, the decelerating effect due the release of PPh_3 by the amine (path **a** in Scheme 4) and the more effective accelerating effect due to the formation of a more reactive species $[Pd^0(PPh_3)(amine)]$ (path **b** in Scheme 4) must be in opposition to each other.

The accelerating effect was less important in the presence of morpholine than with piperidine added at the same concentration (Figure 4 left), suggesting that morpholine is a less good ligand for $[Pd^0(L)]$ than piperidine. The accelerating effect was more pronounced when the concentration of the piperidine was increased (Figure 4 middle). The kinetic law for the mechanism proposed in Scheme 4 (paths **a** and **b** operating in parallel) is given in Equations (9)–(11).

$$\text{rate} = k_3[\text{PhI}][Pd^0(L)_2] + k_4[\text{PhI}][Pd^0(L)(R_2NH)] \quad (9)$$

$$\frac{d[Pd^0]}{dt} = -\frac{(k_3 + k_4K_2[R_2NH]/[L])[\text{PhI}]}{[L]/K_1 + K_2[R_2NH]/[L]} \quad (10)$$

$$k_{app} = \frac{k_3 + k_4K_2[R_2NH]/[L]}{[L]/K_1 + K_2[R_2NH]/[L]} \quad (11)$$

At low $[R_2NH]$, $K_2[R_2NH]/[L] < [L]/K_1$, then k_{app} simplifies to Equation (12); under stoichiometric conditions ($[\text{PhI}] = [Pd^0L_4] = C_0$), so Equation (13) is obtained, in which x = molar fraction of $[Pd^0(PPh_3)_3]$; $x = i/i_0$; i = oxidation current of $[Pd^0(PPh_3)_3]$ at time t; i_0 = initial oxidation current of $[Pd^0(PPh_3)_3]$.[14]

$$k_{app} = \frac{k_3K_1}{[L]} + \frac{k_4K_1K_2[R_2NH]}{[L]^2} \quad (12)$$

$$\frac{1}{x} = k_{app}C_0t + 1 \quad (13)$$

The plots of $1/x$ versus time were linear, in agreement with Equation (13) (Figure 4 middle). The values of k_{app} were determined from the slope of the straight lines. The plot of k_{app} versus piperidine concentration was linear (Figure 4 right) in agreement with Equation (12). From the intercept, one obtains $k_3K_1 = 0.11\ s^{-1}$ (DMF, 20 °C), which characterizes the reactivity of $[Pd^0(PPh_3)_4]$ alone (this value is similar to that determined in previous work).[7] From the slope of the straight line, $k_4K_1K_2 = 0.013\ s^{-1}$ (DMF, 20 °C) was determined.[15]

Role of the amine in the step involving the alkyne: It is now well established that *trans*-[PdI(Ph)$(L)_2$] complexes (L = PPh_3 or $AsPh_3$) react with a secondary amine (morpholine or piperidine) to generate [PdI(Ph)L(amine)] complexes in reversible reactions. Consequently, the amine may compete with the alkyne for the complexation of the Pd^{II} center in *trans*-[PdI(Ph)$(L)_2$] complexes.

Experiments were undertaken to characterize such competition, starting from *trans*-[PdI(Ph)$(AsPh_3)_2$] (**1b**) but mainly from the dimer $[PhPd(\mu\text{-}I)(AsPh_3)]_2$ (**7b**), since the complexation of the amine proceeds via **7b** (vide supra). Moreover, the complexation of the alkyne must also go by the same route, via **7b**. It is worth noting that alkynes (HC≡

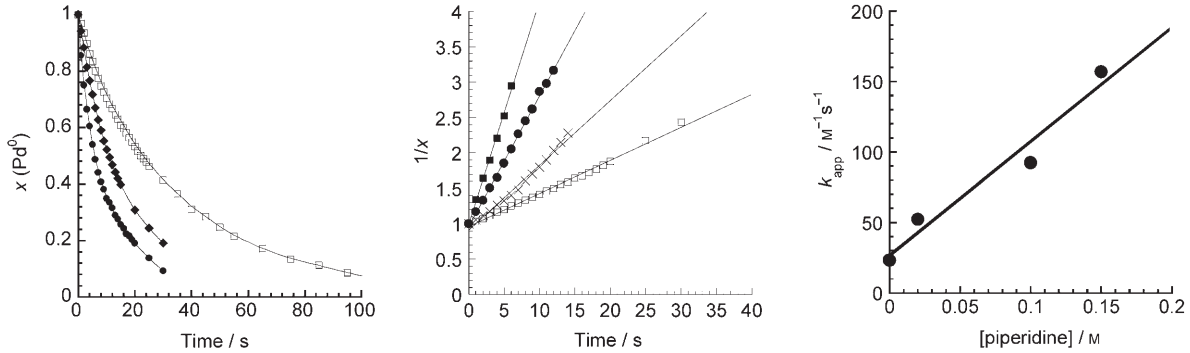
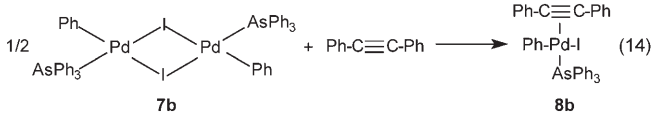


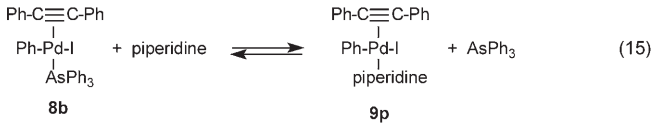
Figure 4. Kinetics of the oxidative addition of PhI (2 mM) to $[Pd^0(PPh_3)_4]$ (2 mM) in DMF containing nBu_4NBF_4 (0.3 M) at 20 °C. Left: Molar fraction x of the Pd^0 complex versus time ($x = i/i_0$; i = oxidation current of $[Pd^0(PPh_3)_3]$ at time t; i_0 = initial oxidation current of $[Pd^0(PPh_3)_3]$); (□) without any amine: (♦) in presence of morpholine (100 mM); (●) in presence of piperidine (100 mM). Middle: $1/x$ versus time: (□) without any amine; in presence of piperidine [(×) 10 mM, (●) 100 mM, (■) 150 mM]. Right: k_{app} versus piperidine concentration [see Eq. (12)].

C–R) may react with *trans*-[PdI(Ph)$(L)_2$] complexes in the absence of base in a carbopalladation step, leading to [Ph–CH=CH(R)–PdI$(L)_2$] complexes,[16] or even undergo multicarbopalladation steps.[16c] Carbopalladation is favored with electron-deficient alkynes (for example, R = CO_2Et).[16] Our present investigation mainly concerns the electron-rich alkyne **5**, which has been used in catalytic Sonogashira reactions (Scheme 1). Alkyne **5** did not react with piperidine or morpholine, as monitored by ^{1}H NMR spectroscopy in $CDCl_3$.

The alkyne **5** was added to an NMR tube containing the dimer **7b** (0.5 μmol) in $CDCl_3$ (0.75 mL; **7b**/**5** = 1:2). The protons of the Ph group attached to the Pd^{II} center remained unchanged, but broad signals were observed for the CH_2–CH_2 protons of **5**. The resulting complex could not be characterized any better. Under similar conditions, stoichiometric amounts of piperidine and **5** (**7b**/piperidine/**5** = 1:2:2) were introduced to an NMR tube containing **7b**. At short times the ^{1}H NMR signals of complexes **4bp** and **4′bp** and of the free **5** were exhibited. The competition between **5** and piperidine (used at the same concentration) for the coordination of the Pd^{II} center is thus in favor of the piperidine. Such an effect will be amplified if the amine is used as solvent, as in the present catalytic reactions [Eq. (3)]. The stability order, with R = CH_2–CH_2–OH could thus be established as:[17] [PdI(Ph)$(AsPh_3)$(piperidine)] > [PdI(Ph)-$(AsPh_3)(\eta^2$-RC≡CH)]. At longer times, a more complex ^{1}H NMR spectrum was obtained as in the reaction of isolated **4bp** and **4′bp** with **5** (vide infra) but the coupling product **6** was not formed.

PhC≡CPh was selected for another experiment, reaction of the dimer **7b** (6.67 mM in $CDCl_3$) with PhC≡CPh (**7b**/PhC≡CPh = 1:2), because it cannot react in a Sonogashira reaction and moreover it is supposed to undergo a slow carbopalladation after coordination of the Pd^{II} atom of a Ph–Pd^{II} complex. The first ^{1}H NMR spectrum recorded exhibited the signals of **7b** and those of a new complex **8b**. After 1 h 30 min, only **8b** was observed [Eq. (14)], characterized by ^{1}H NMR spectroscopy and FAB^+ MS. After further addition of piperidine (1 equiv) to complex **8b**, new signals appeared together with some free piperidine (56%). The complex **4bp**, which might have been formed by substitution of PhC≡CPh by piperidine in complex **8b**, was not present; this fact proves that PhC≡CPh is a better ligand than piperidine for the Pd^{II} in complex **8b**. Signals characteristic of a ligated piperidine were present together with free $AsPh_3$. This suggests the formation of complex **9p** [Eq. (15)].





We have seen above that the reaction of the dimer **7b** with a stoichiometric amount of piperidine and alkyne **5** (**7b**/piperidine/**5** = 1:2:2) did not deliver the coupling product. However, when the amount of piperidine was doubled (**7b**/piperidine/**5** = 1:4:2), the coupling product Ph–C≡C–CH_2–CH_2–OH (**6**) was formed in approximately 50% yield, as determined by ^{1}H NMR spectroscopy with CH_2Cl_2 as an internal standard (Figure 5). Just after mixing, the free

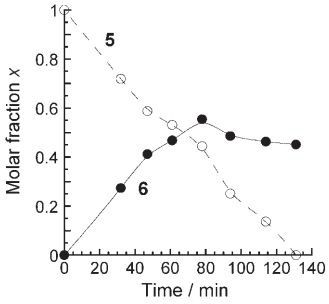
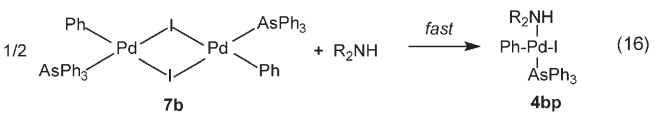
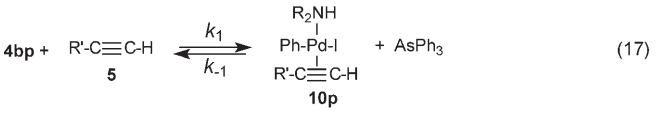


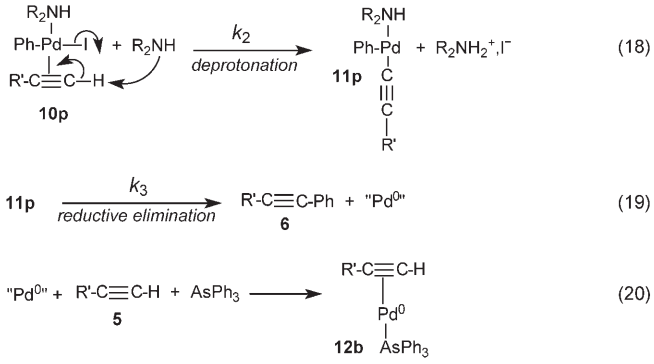
Figure 5. Concentration profiles of alkyne **5** (○) and coupling product **6** (●) in the reaction of dimer **7b** with piperidine and alkyne **5** (**7b**/piperidine/**5** = 1:4:2) in $CDCl_3$ at 25 °C.

alkyne **5** was observed together with complexes **4bp** and **4′bp** and free piperidine in an almost stoichiometric amount: piperidine/(**4bp**+**4′bp**) = 1.08:1, in agreement with the results established above: that is, **4bp** and **4′bp** were formed quantitatively from **7b** as soon as **7b**/piperidine = 1:2. This again shows that piperidine is more reactive than **5** in the cleavage of the iodide bridges of **7b** to generate complexes **4bp** and **4′bp**. The coupling product **6** then appeared over time (Figure 5), but its formation was not quantitative. The complexes **4bp** and **4′bp**, always in the same ratio as initially, were still detected (57%) at the end of the reaction, whereas the starting alkyne **5** was no longer observed (Figure 5).

From the concentration profiles of **5** and **6** shown in Figure 5 and the information obtained in Equations (14) and (15), a mechanism is proposed in Equations (16)–(20), in which R_2NH = piperidine, for the formation of the coupling product **6**. To simplify the discussion, the proposed mechanism involves only complex **4bp**. A similar mechanism may involve the isomer **4′bp** as well. After the fast formation of complex **4bp**, the ligand $AsPh_3$ is substituted by the alkyne **5** (R′ = CH_2CH_2OH) to give complex **10p** [Eq. (17)]. The ligated alkyne is more acidic than the free alkyne and can be deprotonated by an extra piperidine [Eq. (18)] to complex **11p**, which gives the coupling product **6** by reductive elimination [Eq. (19)].





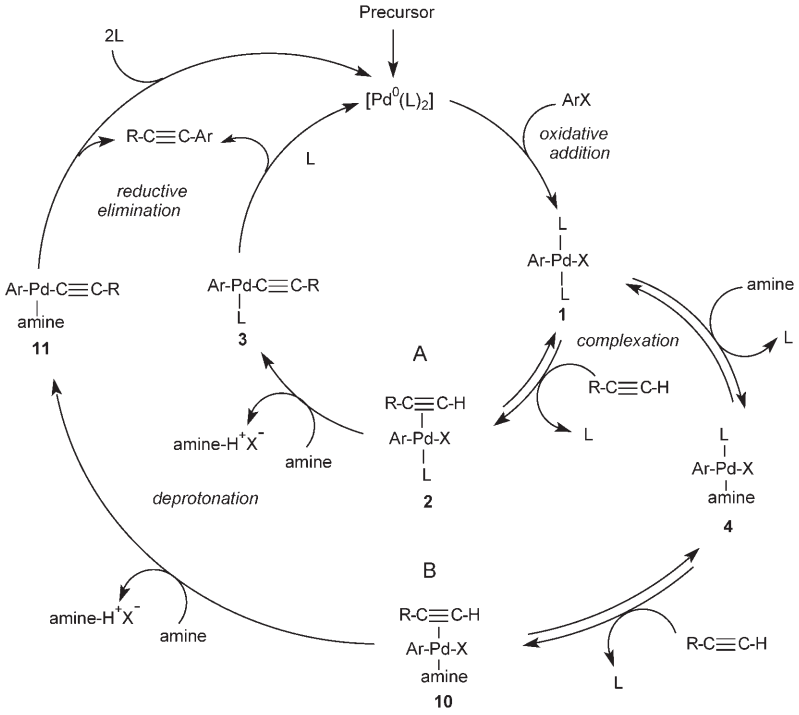


Early in the reaction ($t<60$ min, Figure 5), the rates of formation of **6** and disappearance of **5** follow a similar kinetic law. This means that the reductive elimination [Eq. (19)] is faster than the rate-determining reaction consisting of the equilibrium in Equation (17) shifted by the reaction in Equation (18). After 80 min, the decrease in **5** is more pronounced than during the first part of the reaction, and the formation of **6** nearly stops. The fact that **4bp** and **4′bp** were recovered in about 56% yield while **5** was totally consumed suggests that **5** was involved in a reaction competing with the reaction given in Equation (17). The alkyne **5** must be involved in the coordination of the Pd^0 complex formed in the reductive elimination [Eq. (20)].[18] This is why the reaction of **4bp** and **4′bp** with **5** was not quantitative. Such a competitive reaction will be less efficient in catalytic reactions since the Pd^0 complex will always be stabilized by the two $AsPh_3$ introduced with the Pd^0 precursor.

The feasibility of the reaction given in Equation (17) was tested by reaction of a mixture of isolated **4bp** and **4′bp** (62:38) with a stoichiometric amount of alkyne **5**. The reaction was monitored by ^{1}H NMR spectroscopy. A very complicated spectrum was obtained in which we could distinguish some unreacted **4bp** and **4′bp** by their respective ligated piperidine groups (Table 5). The signals of free alkyne **5** disappeared slowly. New signals assigned to a ligated piperidine ($\delta_1=2.98$ ppm (d, $J=14$ Hz, 1H), $\delta_2=3.16$ ppm (t, $J=12.5$ Hz, 2H)) could be distinguished from those of the ligated piperidine of **4bp** and **4′bp**, located at higher field as in complex **9p** [Eq. (15)]. Consequently, a new complex was formed which also contained a ligated piperidine. The detection of free $AsPh_3$, which turned to arsine oxide with time, was interesting. Even if complex **10p** could not then be fully characterized, because its ^{1}H NMR spectrum is too complicated due to the protons of three different ligated piperidines, the release of $AsPh_3$ is nevertheless indicative of the reaction given in Equation (17).

Mechanism of the copper-free palladium-catalyzed Sonogashira reaction: Having to hand the mechanism of Equations (16)–(20) established for aryl–Pd^{II} complexes ligated by $AsPh_3$, we can rationalize the results of the catalytic Sonogashira reactions reported in Table 1. The fact that the catalytic reactions involving the same precursor $[Pd^0(dba)_2]$ were more efficient when the ligand PPh_3 was used instead of $AsPh_3$, although $AsPh_3$ was more easily substituted than PPh_3 by an amine in *trans*-$[PdI(Ph)(L)_2]$ complexes, indicates that two different catalytic cycles can operate, according to the ligand and the amine. The two mechanisms (paths **A** and **B** in Scheme 5) are branched at the level of *trans*-$[PdI(Ph)(L)_2]$ complexes generated in the fast oxidative addition step.

When $L=PPh_3$, its substitution by the amine in *trans*-$[PdI(Ph)(PPh_3)_2]$ is not favored (see the K values for morpholine and piperidine in Table 6) because of the low concentration of the dimer $[\{Pd(\mu\text{-}I)(Ph)(PPh_3)\}_2]$; consequently the path **A** is dominant. According to path **A**, we under-



Scheme 5. Mechanism of the copper-free palladium-catalyzed Sonogashira reaction ($R=CH_2$–CH_2–OH). Path **A**: the amine is a less good ligand than the alkyne for the Pd^{II} center in $[PdX(Ar)(L)_2]$ ($L=PPh_3$ with amine = piperidine or morpholine). Path **B**: the amine is a better ligand than the alkyne for the Pd^{II} center in $[PdX(Ar)(L)_2]$ ($L=AsPh_3$, amine = piperidine).

stand why $[Pd^0(PPh_3)_4]$ is less efficient than $[Pd^0(dba)_2]+2PPh_3$: the excess of free ligand in the former case inhibits the substitution of PPh_3 by the alkyne. In the case of PPh_3, piperidine was more efficient than morpholine (entries 1 and 3 in Table 1), because it is more basic and consequently more reactive in the deprotonation step.[19]

When $L=AsPh_3$, its substitution in *trans*-$[PdI(Ph)(AsPh_3)_2]$ by the piperidine is quite easy (via the dimer $[\{Pd(\mu\text{-}I)(Ph)(AsPh_3)\}_2]$) and more efficient than the substitution by the alkyne **5** (present work, vide supra). Consequently, the mechanism of path **B** established in this work is dominant. In presence of piperidine, yields were lower when $AsPh_3$ was used instead of PPh_3 (entries 1 and 2 in Table 1). This means that path **B** is less efficient than path **A**. In the case of $AsPh_3$, piperidine appears to be slightly less efficient than morpholine (entries 2 and 4 in Table 1). This may be rationalized by the fact that the substitution of one $AsPh_3$ by morpholine in *trans*-$[PdI(Ph)(AsPh_3)_2]$ is less easy than the substitution by piperidine. The mechanism in path **A** may thus operate partially when morpholine is used.[17] It is worth noting that one may easily pass from path **A** to path **B**, and vice versa, by changing the relative concentrations of the alkyne and amine.

Conclusion

Amines used as bases in copper-free palladium-catalyzed Sonogashira reactions play a very important and multiple roles. Besides their expected function as deprotonating agents, amines (morpholine, piperidine) may be involved in two different steps preceding the deprotonation: 1) they interfere in the oxidative addition by an accelerating effect due to the formation of more reactive $[Pd^0L(amine)]$ complexes; and 2) amines can substitute one ligand in *trans*-$[PdI(Ph)(L)_2]$ complexes formed in the oxidative addition step, the substitution of $AsPh_3$ being more favored than that of PPh_3. Depending on the rate of the competition between amine and alkyne in the substitution of one L in *trans*-$[PdI(Ph)(L)_2]$, two different mechanisms may operate (path **A** or **B** in Scheme 5). Consequently, the amine does not react as a simple base in Sonogashira reactions, but it is also involved as a ligand of aryl–Pd^{II} complexes.

Experimental Section

General: ^{31}P NMR spectra were recorded on a Bruker spectrometer (101 MHz) in DMF containing 10% of $[D_6]$acetone. ^1H NMR spectra were recorded on a Bruker spectrometer (250 or 400 MHz). Cyclic voltammetry and amperometry were performed at gold disk electrodes with a home-made potentiostat and a Tacussel GSTP4 waveform generator. The voltammograms were recorded on a Nicolet 301 oscilloscope.

Chemicals: DMF was distilled from calcium hydride under vacuum and kept under argon. $CDCl_3$, PhI, $AsPh_3$, morpholine, piperidine, diisopropylamine, *tert*-butylamine, HC≡C–CH_2–CH_2–OH, and PhC≡CPh were commercial products. $[Pd(dba)_2]$,[20] $[Pd(PPh_3)_4]$,[21] *trans*-$[PdI(Ph)(AsPh_3)_2]$ (**1b**),[5] and $[PhPd(\mu\text{-}I)(AsPh_3)]_2$ (**7b**)[5] were synthesized according to published procedures.

General procedure for the palladium-catalyzed synthesis of Ph–C≡C–CH_2–CH_2–OH (6) [Eq. (3)]: The procedure was similar to that reported for $[Pd^0(PPh_3)_4]$ as catalyst,[1a,6] by using the same amount and concentration of the pre-catalyst and reagents to allow comparison. $[Pd(dba)_2]$ (28.7 mg, 0.05 mmol) was introduced under an argon atmosphere in piperidine (3 mL), followed by $AsPh_3$ (31 mg, 0.1 mmol). PhI (110 μL, 1 mmol) was then added, followed by HC≡C–CH_2–CH_2–OH (**5**) (152 μL, 2 mmol). The solution was stirred at room temperature for 3 h 15 min. It was then hydrolyzed with aqueous NH_4Cl, extracted with diethyl ether, and dried on $MgSO_4$. After evaporation of the solvent, $CHCl_2CHCl_2$ (75 μL) was added as internal standard. The yield of **6** and the unreacted PhI was determined from the ^1H NMR spectrum of the crude product after calibration (Table 1). Similar experiments were performed using morpholine (3.5 mL) instead of piperidine and PPh_3 (26.2 mg, 0.1 mmol) instead of $AsPh_3$ during the same reaction time (Table 1). ^1H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta=2.03$ (t, $^3J(H,H)=2.5$ Hz, 1H), 2.69 (t, $^3J(H,H)=6.3$ Hz, 2H), 3.81 (t, $^3J(H,H)=6.3$ Hz, 2H), 7.26–7.30 (m, 3H), 7.40–7.43 ppm (m, 2H), similar to an authentic sample.[1a,6]

General procedure for the reaction of amines with the dimer $[PhPd(\mu\text{-}I)(AsPh_3)]_2$ (7b), as monitored by ^1H NMR spectroscopy: Various amounts of amines: piperidine (2 equiv) or morpholine (1, 2, and 3 equiv) or diisopropylamine (2, 4, 10, and 60 equiv) (n = total number of equivalents added) were added to dimer **7b** (6.1 mg, 5 μmol) in $CDCl_3$ (0.75 mL). The ^1H NMR spectrum was recorded after each addition of amine to detect the formation of $[PhPd(AsPh_3)_2(amine)]$ (**4b**).

General procedure for the reaction of amines with *trans*-$[PdI(Ph)(AsPh_3)_2]$ (1b), as monitored by ^1H NMR spectroscopy: The procedure was the same as above, starting from a solution of **1b** (9.2 mg, 10 μmol) in $CDCl_3$ (0.75 mL) to which were added various amounts of amines: piperidine ($n=1$, 2 and 3 equiv) or morpholine (0.5, 1, 1.5, 2, 3, and 6 equiv) or diisopropylamine ($n=1$, 6 and 30 equiv) or *tert*-butylamine ($n=1$, 2, and 5 equiv) (n = total number of equivalents added).

Synthesis of $[PdI(Ph)(AsPh_3)(morpholine)]$ (4bm) by reaction of morpholine with $[PhPd(\mu\text{-}I)(AsPh_3)]_2$ (7b): Morpholine (3.5 μL, 40 μmol) was added to a solution of dimer **7b** (6.1 mg, 5 μmol) in chloroform (0.75 mL). Single crystals of **4bm** were obtained by diffusion of pentane into the chloroform solution. ^1H NMR (400 MHz, $CDCl_3$): see Table 2; ^{13}C NMR (63.3 MHz, $CDCl_3$, 25 °C, TMS): $\delta=48.65$, 53.81, 127.98, 128.40, 129.78, 133.45, 133.93, 134.76 ppm; X-ray structure: see Figure 1 (top) and Tables 3 and 4.

Synthesis of $[PdI(Ph)(AsPh_3)(piperidine)]$ (4bp) and (4′bp) by reaction of piperidine with $[PhPd(\mu\text{-}I)(AsPh_3)]_2$ (7b): Piperidine (40 μL, 0.4 mmol) were added to a suspension of the dimer **7b** (123 mg, 0.1 mmol) in chloroform (10 mL). After 30 min, the solution was filtered and the solvent eliminated under vacuum. Yellow-green crystals were formed. Two successive crystallizations from chloroform/pentane gave yellow crystals (93 mg, 67% yield), as a mixture of complexes **4bp** and **4′bp** that could not be separated. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): see Table 5. ^{13}C NMR (63.3 MHz, $CDCl_3$, 25 °C, TMS): $\delta=23.59$ (23.79), 27.68 (27.79), 50.01 (52.06), 127.68, 128.32, 128.58, 129.63, 133.66, 133.97, 134.23, 134.98 ppm; elemental analysis calcd (%) for $C_{29}H_{31}AsINPd$ (700.98): C 49.63, H 4.45, N 2.00; found C 49.29, H 4.51, N 1.74.

$[PdI(Ph)(AsPh_3)(diisopropylamine)]$ (4bd): This was formed by reaction of *trans*-$[PdI(Ph)(AsPh_3)_2]$ (**1b**) (9.2 mg, 10 μmol) with diisopropylamine (42 μL, 0.3 mmol) in $CDCl_3$ (0.75 mL). ^1H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta=6.66$ (m, 3H; *m-H* and *p*-H of Ph–Pd), 7.00 (d, $^3J(H,H)=5$ Hz, 2H; *o*-H of Ph–Pd), 7.2–7.4 ppm (m; H of $AsPh_3$). The ligated iPr_2NH could not be characterized due to the overlapping of its signals with those of the free iPr_2NH added in excess. The complex **4bd** was not isolated because it formed a mixture (46:54) with the starting complex **1b**.

$[PdI(Ph)(AsPh_3)$(*tert*-butylamine)$]$ (4bt): *tert*-Butylamine (5.5 μL, 50 μmol) was added to a solution of *trans*-$[PdI(Ph)(AsPh_3)_2]$ (**1b**) (9.2 mg, 10 μmol) in $CDCl_3$ (0.75 mL). The complex **4bt** was not isolated because it formed a mixture (2.2:10) with the starting complex **1b**, but it

was characterized in situ. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 1.18 (s, 9H; *t*Bu), 6.66 (m, 3H; *m*-H and *p*-H of Ph–Pd), 6.92 (m, 2H; *o*-H of Ph–Pd), 7.2–7.4 ppm (m; H of $AsPh_3$).

Determination of the equilibrium constant *K′* between 7b and 4bp (see main text and Scheme 3): Various amounts of morpholine (0.5–3 equiv) were added to a solution of dimer **7b** (6.1 mg, 5 μmol, 6.67 mM) in $CDCl_3$ (0.75 mL). The ^{1}H NMR (250 MHz) spectrum was recorded after each addition of morpholine. See Figure 2 for the calculation of *K′*.

Formation of [PdI(Ph)(η^2-PhC≡CPh)(AsPh$_3$)] (8b) by reaction of PhC≡CPh with the dimer 7b: PhC≡CPh (1.8 mg, 10 μmol) was added to the dimer **7b** (6.1 mg, 5 μmol) in $CDCl_3$ (0.75 mL). The ^{1}H NMR spectrum was recorded with time. The first spectrum revealed a mixture of **7b** and **8b**. After 1 h 30 min, only **8b** was observed. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 6.50 (m, 1H; *p*-H of Ph–Pd), 6.59 (m, 2H; *m*-H of Ph–Pd), 6.87 (m, 6H; H of PhC≡CPh), 6.97 (m, 4H; H of PhC≡CPh), 7.19 (d, ^3J(H,H) = 5 Hz, 2H; *o*-H of Ph–Pd); 7.25 (m; H of $AsPh_3$), 7.32 ppm (m; H of $AsPh_3$); FAB$^+$ MS: *m*/*z*: 667 [M^+–I], 591 [M^+–I–Ph].

Formation of [PdI(Ph)(η^2-PhC≡CPh)(piperidine)] (9p) by reaction of piperidine with complex (8b): Piperidine (1 μL, 10 μmol) was added to an NMR tube containing **8b** formed as described above. The reaction was followed by ^{1}H NMR spectroscopy. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 1.0–1.5 (m, 4H), 2.12 (t, ^3J(H,H) = 10.8 Hz, 1H), 2.31 (d, ^3J(H,H) = 12.5 Hz, 1H), 2.58 (t, ^3J(H,H) = 12.5 Hz, 2H), 3.00 (t, ^3J(H,H) = 12.5 Hz, 1H), 3.19 (pseudo q, ^3J(H,H) = 13 Hz, 2H), 6.12 (m, 2H), 6.72–7.11 (m, 13H), 7.23–7.40 ppm (m; H of $AsPh_3$). Free $AsPh_3$ at $\delta =$ 7.33 ppm was also observed as a singlet.

Kinetics of formation of the coupling product Ph–C≡C–CH$_2$–CH$_2$–OH (6) from 7b and HC≡C–CH$_2$–CH$_2$–OH (5) in the presence of piperidine, as monitored by ^{1}H NMR spectroscopy (Figure 5): Piperidine (2 μL, 20 μmol), followed by **5** (0.8 μL, 10 μmol), was added to the dimer **7b** (6.1 mg, 5 μmol) in $CDCl_3$ (0.75 mL). A known amount of CH_2Cl_2 was added as an internal standard. The reaction was monitored by ^{1}H NMR spectroscopy. The amounts of **6** and unreacted **5** were determined by comparing the integration of their respective protons C≡C–CH_2 versus those of CH_2Cl$_2$ (Figure 5).

Electrochemical procedure for cyclic voltammetry and for the kinetics of the oxidative addition of PhI to [Pd^0(PPh$_3$)$_4$] in the presence of piperidine or morpholine: Experiments were carried out in a three-electrode thermostated cell (20 °C) connected to a Schlenk line. The reference was a saturated calomel electrode (Radiometer) separated from the solution by a bridge filled with DMF (3 mL) containing nBu$_4$NBF$_4$ (0.3 M). The counter electrode was a platinum wire, apparent surface area ≈1 cm^2. DMF (15 mL) containing nBu$_4$NBF$_4$ (0.3 M) was introduced to the cell followed by [Pd(PPh$_3$)$_4$] (34.7 mg, 0.03 mmol). Cyclic voltammetry was performed at a steady gold disk electrode (d = 2 mm) at a scan rate of 0.2 V s^{-1} in the absence of amine and then in the presence of an increasing amount (5–75 equiv) of amine (piperidine or morpholine).

The kinetic measurements for the oxidative addition of PhI were performed at a rotating gold disk electrode (Radiometer, EDI 65109, d 2 mm, angular velocity: 105 rad s^{-1}) polarized at +0.2 V versus SCE. PhI (3.4 μL, 0.03 mmol) was added and the decrease in the oxidation current was recorded versus time until conversion was complete. Other experiments were performed similarly in the presence of piperidine (148 μL, 1.5 mmol) or morpholine (131 μL, 1.5 mmol), added before the PhI.

CCDC 605796 contains the supplementary crystallographic data for complex **4bm**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[13] a) It is reported that [Pd^0(L)$_n$] complexes may react with amines R$_2$NH in oxidative addition leading to palladium(II) complexes [R$_2$N–Pd–HL$_{n'}$] (L = PCy$_3$) (references [13b,c]). When increasing amounts of morpholine or piperidine were added to [Pd^0(PPh$_3$)$_4$], its oxidation peak did not disappear but was slightly shifted to more positive potentials. It became broader while the oxidation peak current increased. This indicates that the new complex(es) formed in solution were still palladium(0) complexes involved in equilibrium with the amine. Work is in progress to characterize such species better. Consequently, no oxidative addition of the amine with the Pd^0 complex occurred during the timescale investigated here (10 min between each addition of amine), which is much longer than the time required for the oxidative addition (Figure 4 left); b) T. Yamamoto, K. Sano, A. Yamamoto, *Chem. Lett.* **1982**, 907–910; c) A. I. Siriwardana, M. Kamada, I. Nakamura, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 5932–5937.

[14] In the absence of excess PPh$_3$, the concentration of PPh$_3$ varies from C_0 to 3C_0 during the course of the oxidative addition due to its continuous release in the three equilibria (K_1, K, and K_2). Consequently, the variation of the concentration of L should have been considered in the integration of the kinetics law with [L] = (3–2x)C_0. Due to the complexity of the kinetics law, a constant value of [L] was con-

sidered for the integration of the kinetics law, equal to its average value of $2C_0$ ($C_0 = 2$ mM).

[15] a) From the expression for k_{app} given in Equation (11), we should observe a limit value at high R_2NH concentrations ($K_2[R_2NH]/[L] > [L]/K_1$,) with $k_{app} = k_4$, that is, when the equilibrium between $[Pd^0(L)_2]$ and $[Pd^0(L)(amine)]$ is totally shifted to the formation of $[Pd^0(L)(amine)]$, which would then be the unique reactive complex. However, the reactions went too fast at high piperidine concentrations (for example, $t_{1/2} = 3.5$ s for [piperidine] = 150 mM), preventing accurate data at 20 °C being obtained.

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