APPLIED ORGANOMETALLIC CHEMISTRY
*Appl. Organometal. Chem.* 2004; **18**: 574–582
Published online in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/aoc.742



*Review*

# Mechanism of Palladium-Catalyzed Reactions: Role of Chloride ions†

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Received 29 November 2003; Accepted 31 January 2004

**Chloride ions play a very important role in palladium-catalyzed reactions. This review illustrates how chloride ions modify: (i) the kinetics of the oxidative addition of aryl triflates, vinyl triflates, allylic acetates to palladium(0) complexes; (ii) the structure of the aryl-, vinyl- or allyl-palladium(II) complexes, generated in the oxidative addition, by formation of neutral aryl-, vinyl- or $\eta^1$-allyl-palladium(II) chloride complexes respectively, instead of cationic aryl-, vinyl- or ($\eta^3$-allyl)palladium(II) complexes; (iii) the mechanism of the second step of the catalytic cycle of the Stille reactions of aryl or vinyl triflates by formation of neutral aryl- or vinyl- chloride complexes able to react with the nucleophile; and (iv) the mechanism of the second step of the catalytic cycle of the Tsuji–Trost reactions, i.e. the nucleophilic attack on allyl-palladium(II) complexes (neutral $\eta^1$-allyl-PdCl versus cationic ($\eta^3$-allyl)palladium(II) complexes).** 

**KEYWORDS:** palladium; aryl triflates; vinyl triflates; cationic complex; chloride ions; oxidative addition; kinetics; mechanism

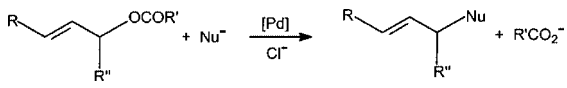
## INTRODUCTION

Many palladium-catalyzed reactions require additives to be efficient. Among them, chloride ions play a specific role; for a review, see Ref. 1. All palladium-catalyzed reactions involving aryl or vinyl triflates are sensitive to the presence of chloride ions, whose role may be positive or negative, depending on ligands and solvents, as in Stille reactions (cross-coupling of aryl or vinyl triflates with organostannanes):[2–11]

$$\mathrm{ROTf} + \mathrm{R'SnR''_3} \xrightarrow[\mathrm{Cl^-?}]{[\mathrm{Pd}]} \mathrm{RR'} + \mathrm{TfOSnR''_3} \qquad (1)$$

R = aryl, vinyl

Palladium-catalyzed nucleophilic substitution on allylic carboxylates (Tsuji–Trost reactions)[12–18] are also sensitive to the presence of chloride ions, which may affect the reactivity,[18–24] the regioselectivity[19–21] and the enantioselectivity[22–24] of the catalytic reactions:




(2)

Chloride ions may be voluntarily added to the catalytic mixture in large amounts or introduced in catalytic amounts via the catalytic precursor, usually $[\mathrm{Pd}(\eta^3\text{-allyl})(\mu\text{-Cl})]_2$.[19–24] In the latter case, the role of chloride ions is very often neglected as a consequence of their catalytic concentration.

This review shows how the role of chloride ions in catalytic reactions may be established, by finding out the species whose *structure* is affected by the chloride ions and then the mechanistic consequences in terms of *reactivity*.

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†Presented at the XV$^{th}$ FECHEM Conference on Organometallic Chemistry, held 10–15 August 2003, Zürich, Switzerland.

## STRUCTURAL AND KINETIC EFFECT OF CHLORIDE IONS IN PALLADIUM-CATALYZED REACTIONS OF ARYL TRIFLATES

As recalled in Eqn (3), Stille reactions involving aryl triflates are affected by the presence of chloride ions.[4–11]

$$\text{Ar-OTf} + \text{RSnR}'_3 \xrightarrow[\text{Cl}^-?]{[\text{Pd}]} \text{ArR} + \text{TfoSnR}'_3 \qquad (3)$$

The effect of chloride ions was first investigated by Echavarren and Stille.[4] Chlorides were supposed to be involved in the first step of the catalytic reaction, i.e. in the oxidative addition of aryl triflates to palladium(0) complexes. Undefined and unstable complexes $[ArPdL_n]^+$ ($n = 2$ or 3?) would be generated in toluene or tetrahydrofuran (THF; Scheme 1), whereas stable neutral complexes *trans*-$ArPdClL_2$ would be generated in the presence of chloride ions (Scheme 1) and would react with the nucleophile.

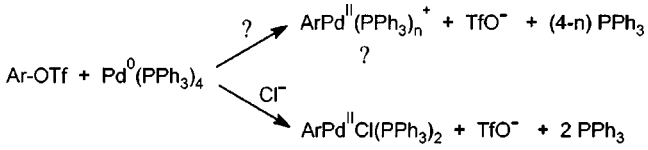
The oxidative addition was reinvestigated by Farina *et al.*[7] in 1993 in the more polar solvent *N*-methylpyrrolidone, but the complexes formed in the oxidative addition in the absence of added chlorides could not be characterized.

### Cationic *trans*-$[ArPdL_2(DMF)]^+,TfO^-$ complexes in the oxidative addition of aryl triflates to palladium(0) complexes in the absence of chloride

In 1995 we established that stable well-defined cationic complexes *trans*-$[ArPdL_2(DMF)]^+$ were generated as free ions in the oxidative addition of aryl triflates to $Pd^0(PPh_3)_4$ performed in the coordinated solvent dimethylformamide (DMF):[25]

$$\text{ArOTf} + \text{Pd}^0(\text{PPh}_3)_4 \xrightarrow[\text{DMF}]{k_{app}} \text{Ar–Pd(PPh}_3\text{)(PPh}_3\text{)(DMF)}^+ + \text{TfO}^- + 2\text{PPh}_3 \qquad (4)$$

The cationic character of *trans*-$[ArPd(PPh_3)_2(DMF)]^+$ complexes was established by conductivity measurements in DMF[25] (Fig. 1); for a review see Ref. 26, whereas their structure was given by $^{31}P$ NMR spectroscopy performed in DMF (one singlet representative of two magnetically equivalent




**Scheme 1.**

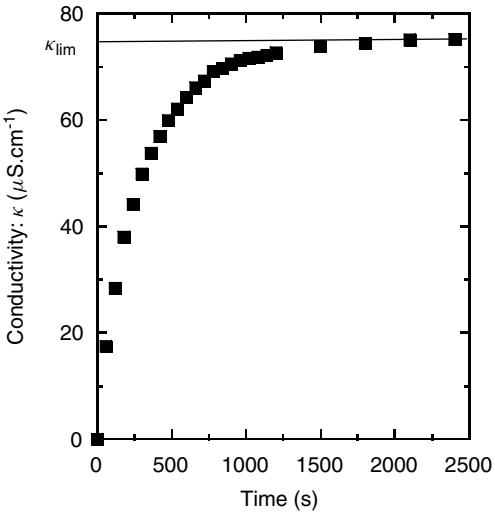


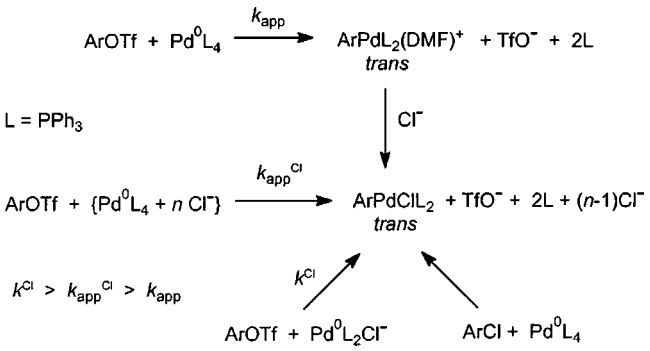

**Figure 1.** Kinetics of the formation of [*trans*-4-$NO_2$–$C_6H_4$–Pd$(PPh_3)_2(DMF)]^+,TfO^-$ in the oxidative addition of 4-$NO_2$–$C_6H_4$–OTf (10 mM) to $Pd^0(PPh_3)_4$ (2 mM) in DMF at 20 °C. Variation of the conductivity versus time. $\kappa = \kappa_{exp} - \kappa_0$ ($\kappa_{exp}$: experimental conductivity at $t$; $\kappa_0$: initial residual conductivity of 2 μS $cm^{-1}$).

$PPh_3$ in a trans position), by fast atom bombardment and electrospray mass spectrometry.[25]

### Neutral *trans*-$ArPdClL_2$ complexes in the oxidative addition of aryl triflates to palladium(0) complexes performed in the presence of chloride in DMF

Neutral complexes *trans*-$ArPdCl(PPh_3)_2$ are generated by addition of chloride ions as *n*-$Bu_4NCl$: (i) to *trans*-$[ArPd(PPh_3)_2(DMF)]^+$ complexes formed in the oxidative addition of aryl triflates; (ii) to the $Pd^0(PPh_3)_4$ complex before the introduction of the aryl triflates (Scheme 2).[25] Neutral complexes *trans*-$ArPdCl(PPh_3)_2$ are also generated in the oxidative addition of aryl triflates to $[Pd^0(PPh_3)_2Cl]^-$ generated in the reduction of $PdCl_2(PPh_3)_2$ (Scheme 2).[27]

Consequently, the *structure* of the aryl-palladium(II) complexes generated in the oxidative addition of aryl triflates




**Scheme 2.**

to palladium(0) complexes is affected by the presence of chloride ions: neutral complexes are formed instead of cationic ones.[25,27]

## Accelerating effect of chloride ions in the oxidative addition of aryl triflates to palladium(0) complexes

The kinetics of the oxidative addition of aryl triflates to $Pd^0(PPh_3)_4$ was monitored by amperometry at a rotating disk electrode, taking advantage of the fact that the oxidation current of $Pd^0(PPh_3)_4$ is at any time proportional to its concentration. The rate constant $k_{app}$ of the overall oxidative addition (Scheme 2) was then determined (Fig. 2, Table 1).[25]

The oxidative addition is faster in the presence of chloride ions added to $Pd^0(PPh_3)_4$ before the introduction of the aryl triflates. The values of the rate constants $k_{app}^{Cl}$ of the overall oxidative addition (Scheme 2) are gathered in Table 1. A large amount of chloride ions relative to $Pd^0(PPh_3)_4$ is required (as in catalytic reactions) to observe a significant accelerating effect with highly reactive aryl triflates, whereas the accelerating effect is more pronounced with poorly reactive aryl triflates.[25] This accelerating effect is due to the formation of anionic species $[Pd^0(PPh_3)_2Cl]^-$ when chloride ions are added to $Pd^0(PPh_3)_4$.[25,28] The rate constant $k^{Cl}$ (Scheme 2) which characterizes the intrinsic reactivity of $[Pd^0(PPh_3)_2Cl]^-$ generated by the reduction of $PdCl_2(PPh_3)_2$ in the absence of any phosphine is also determined (Table 1).[27] It is the most reactive complex due to its anionic structure and to the absence of extra phosphine.

Consequently, the chloride ions play a dual role in the oxidative addition of aryl triflates to $Pd^0(PPh_3)_4$ in DMF: (i) formation of neutral *trans*-$ArPdCl(PPh_3)_2$ instead of cationic *trans*-$[ArPd(PPh_3)_2(DMF)]^+$ and (ii) acceleration of the oxidative addition.[25]

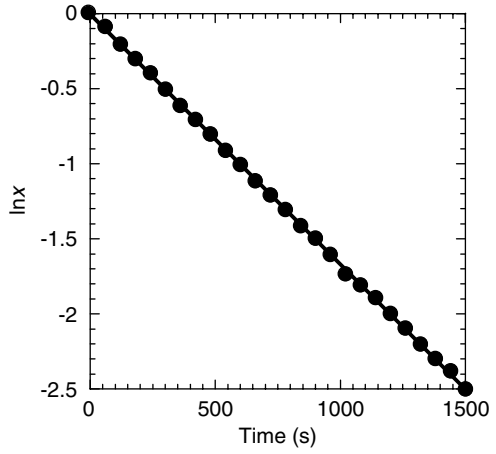



**Figure 2.** Kinetics of the oxidative addition of 4-EtOCO–$C_6H_4$–OTf (65 mM) to $Pd^0(PPh_3)_4$ (2 mM) in DMF (containing *n*-$Bu_4NBF_4$, 0.3 M) at 20 °C, monitored by amperometry at a rotating gold disk electrode polarized at +0.18 V versus SCE, on the oxidation wave of $Pd^0(PPh_3)_3$. Variation of ln *x* versus time ($x = [Pd^0]_t/[Pd^0]_0) = i_t/i_0$; *i*: oxidation current of $Pd^0(PPh_3)_3$ at *t*; $i_0$: initial oxidation current of $Pd^0(PPh_3)_3$).

## Mechanistic consequences

As recalled in the Introduction, the palladium-catalyzed Stille coupling of aryl triflates is very sensitive to the presence of chloride ions (Eqn (3)).[4–11] Espinet *et al*.[10] have observed that, in THF, the $Pd^0L_4$-catalyzed cross-coupling of vinyl(tributyl)tin ($CH_2$=CH–$SnBu_3$) with fluorinated aryl triflates, $Ar_F$–OTf ($Ar_F = C_6F_5$ or $C_6Cl_2F_3$), was slower in the presence of chloride ions when the ligand was $PPh_3$. On the contrary, the coupling was accelerated in the presence of chloride ions when the ligand was $AsPh_3$. This puzzling effect of chloride ions is rationalized as follows.[10] Whatever the ligand, *trans*-$Ar_F$–$PdClL_2$ (L = $PPh_3$ and $AsPh_3$) complexes are formed in the oxidative addition. When the ligand is $PPh_3$, the oxidative addition of $Ar_FOTf$ to $Pd^0(PPh_3)_4$ is fast (it is shown above that it is accelerated by the presence of chloride ions)[25] and the transmetallation (reaction of $CH_2$=CH–$SnBu_3$ with *trans*-$Ar_F$–$PdCl(PPh_3)_2$) becomes rate determining because *trans*-$Ar_F$–$PdCl(PPh_3)_2$ complexes are less reactive than the *trans*-$[Ar_F–Pd(PPh_3)_2(THF)]^+,TfO^-$ or $[Ar_F–Pd(PPh_3)_3]^+,TfO^-$ that would have been formed in the absence of any chloride ions.[10] This is why chloride ions have a negative effect on the catalytic reaction.

When the ligand is $AsPh_3$, the transmetallation is fast because of the easier exchange of $AsPh_3$ than $PPh_3$ by $CH_2$=CH–$SnBu_3$ from *trans*-$Ar_F$–$PdCl(AsPh_3)_2$ to generate the key intermediate $Ar_F$–Pd($\eta^2$-$CH_2$=CH–$SnBu_3$)Cl $(AsPh_3)$.[10] The oxidative addition of $Ar_FOTf$ to $Pd^0(AsPh_3)_4$ is then rate determining and is highly accelerated by chloride ions (as for $Pd^0(PPh_3)_4$).[25] This is why chloride ions have a positive effect on the cross-coupling.

**Table 1.** Accelerating effect of chloride ions on the rate of the oxidative addition of aryl triflates to palladium(0) complexes (2 mM) in DMF at 20 °C (Scheme 2)

| ArOTf | 4-$NO_2$–$C_6H_4$–Otf | | $C_6H_5$–OTf | | 1-naphthyl–OTf | |
|---|---|---|---|---|---|---|
| $Cl^-$ equiv.[a]/$Pd^0(PPh_3)_4$ | 0 | 150 | 0 | 150 | 0 | 150 |
| $k_{app}$ ($M^{-1}$ $s^{-1}$), $k_{app}^{Cl}$ ($M^{-1}$ $s^{-1}$) | 0.32 | 0.59 | $1.7 \times 10^{-3}$ | $33 \times 10^{-3}$ | 0.075 | 0.43 |
| $k^{Cl}$ ($M^{-1}$ $s^{-1}$)[b] | — | — | — | — | 5.5[b] | — |

[a] Added as *n*-$Bu_4NCl$.
[b] Reactivity of $[Pd^0(PPh_3)_2Cl]^-$ generated in the electrochemical reduction of $PdCl_2(PPh_3)_2$.

This is an illustration of the important role that chloride ions may play in catalytic reactions involving cationic palladium complexes by changing the rate-determining step of the catalytic cycle.

## STRUCTURAL AND KINETIC EFFECT OF CHLORIDE IONS IN PALLADIUM-CATALYZED REACTIONS OF VINYL TRIFLATES

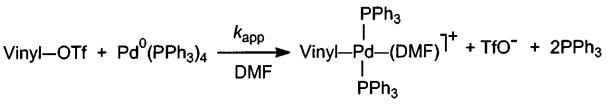
Whereas aryl triflates may react in palladium-catalyzed Stille reactions (Eqn (3)) in the absence of chloride ions, the latter are always required in Stille reactions involving vinyl triflates:[2,3,5–9]

$$\text{Vinyl–OTf} + \text{R–SnR}'_3 \xrightarrow[\text{Cl}^-]{[\text{Pd}]} \text{Vinyl–R} + \text{TfO–SnR}'_3 \qquad (5)$$

In 1986, Scott and Stille[3] investigated the mechanism of the oxidative addition of vinyl triflates to $Pd^0(PPh_3)_4$. Undefined unstable complexes, postulated as cationic $[\eta^1\text{-vinyl–Pd}^{II}(PPh_3)_n]^+,TfO^-$ ($n = 2$ or 3?), were supposed to be formed in THF, whereas stable, well-characterized neutral $\eta^1$-vinyl–$Pd^{II}Cl(PPh_3)_2$ complexes were generated in the presence of added chloride ions (Scheme 3).[3]

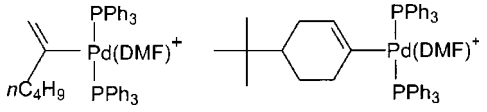
### Cationic *trans*-$[(\eta^1\text{-vinyl})Pd^{II}L_2(DMF)]^+,TfO^-$ complexes in the oxidative addition of vinyl triflates to palladium(0) complexes in the absence of chloride

In 2003 we reinvestigated the mechanism of the oxidative addition of vinyl triflates to $Pd^0(PPh_3)_4$ in DMF. Cationic *trans*-$[\eta^1\text{-vinyl–Pd}^{II}(PPh_3)_2(DMF)]^+,TfO^-$ is generated due to the good coordinating properties of DMF:[29]

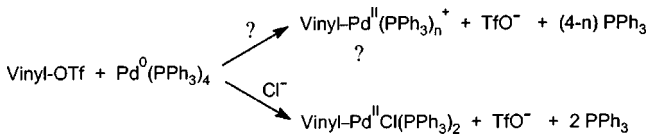



(6)

Two complexes, $\mathbf{1a}^+$ and $\mathbf{1b}^+$, have been unambiguously characterized by conductivity measurements[26,29] (Fig. 3), $^1H$, $^{31}P$ NMR spectroscopy and electrospray mass spectrometry, in oxidative additions performed under stoichiometric conditions.




$\mathbf{1a}^+$ $\mathbf{1b}^+$




**Scheme 3.**

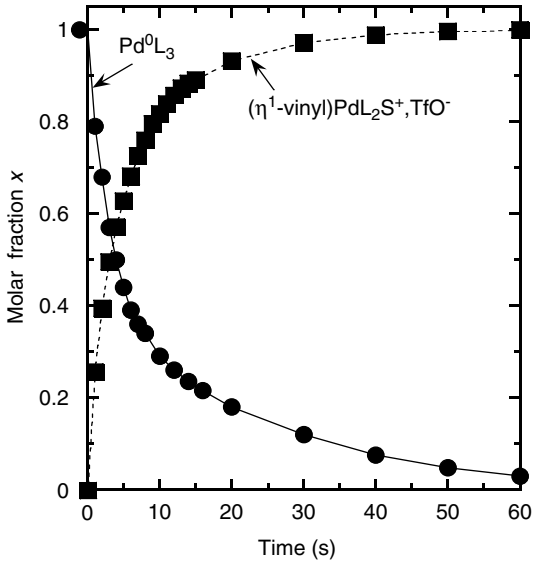
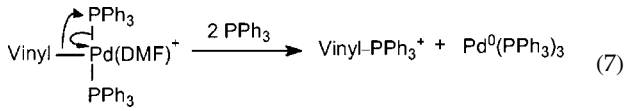



**Figure 3.** Kinetics of the oxidative addition of $CH_2{=}C(n\text{-Bu})–OTf$ (2 mM) to $Pd^0(PPh_3)_4$ (2 mM) in DMF at 10 °C: ■, variation of the molar fraction of the ionic complex $[CH_2{=}C(n\text{-Bu})–Pd(PPh_3)_2(DMF)]^+,TfO^-$ versus time, monitored by conductivity; ●, variation of the molar fraction of $Pd^0(PPh_3)_3$ versus time, monitored by amperometry at a rotating gold disk electrode.

However, the cationic *trans*-$[\text{Vinyl–Pd}(PPh_3)_2(DMF)]^+$, $TfO^-$ complexes are less stable than the cationic aryl ones, *trans*-$[\text{ArPd}(PPh_3)_2(DMF)]^+,TfO^-$, since a slow degradation takes place at room temperature with formation of the vinyl-phosphonium salt $[\text{vinyl–PPh}_3]^+,TfO^-$ (Eqn (7)). This reaction also gives a palladium(0) complex detected in $^{31}P$ NMR spectroscopy if the oxidative addition is performed under stoichiometric conditions (Eqn (7)). When the oxidative addition is performed with excess vinyl triflates (as in catalytic reactions), the palladium(0) complex generated in Eqn (7) undergoes a second oxidative addition as in Eqn (6). The subsequent formation of the vinyl-phosphonium and a palladium(0) complex occurs until the total conversion of $PPh_3$ to $[\text{vinyl–PPh}_3]^+$. The detection of a stable vinyl–palladium(II) complex is thus made impossible when the oxidative addition is performed with vinyl triflates in large excess.[29]




(7)

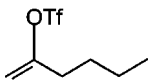
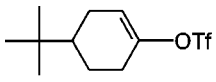
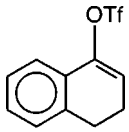
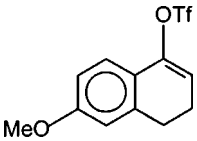
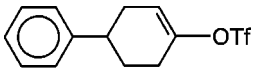
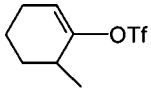
### Structural and kinetic effect of chloride in the oxidative addition of vinyl triflates to palladium(0) complexes in the presence of chloride: mechanistic consequences

Since Scott and Stille[3] have shown that neutral complexes *trans*-$\eta^1$-vinyl–$PdCl(PPh_3)_2$ are formed when the oxidative

addition is performed in the presence of added chloride ions, we have focused our research on the effect of chloride ions on the kinetics of the oxidative addition of vinyl triflates to $Pd^0(PPh_3)_4$ in DMF. In the absence of any chloride ions, the determination of the rate constant $k_{app}$ of the oxidative addition (Eqn (6)) by amperometry (Fig. 3, Table 2) shows that vinyl triflates are considerably more reactive than aryl triflates (compare Tables 1 and 2).[29] The oxidative additions were so fast that the kinetics were investigated in the presence of extra $PPh_3$ (10 equivalents) in order to decrease the rate of the reaction by decreasing the concentration of the reactive complex $Pd^0(PPh_3)_2$ relative to that of the unreactive complex $Pd^0(PPh_3)_3$.[30]

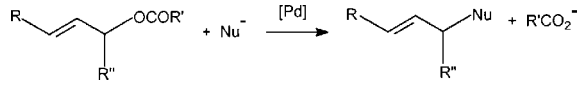
In the presence of a large amount of chloride ions (200 equivalents), the oxidative addition is slightly faster than that in the absence of chloride (Table 2, entries 2 and 3).[29] Consequently, since the accelerating effect of the chloride ions on the oxidative addition is very low, one can assume that the beneficial role of chloride ions in Stille reactions involving vinyl triflates is not due to a faster oxidative addition; rather, it is due to the stabilization of the cationic complex *trans*-[$\eta^1$-vinyl–$Pd^{II}(PPh_3)_2$(DMF)]$^+$ as the neutral complex *trans*-$\eta^1$-vinyl–$PdCl(PPh_3)_2$, in order to avoid the decomposition of the cationic complex into the phosphonium salt.[29]

**Table 2.** Kinetics of the oxidative addition of vinyl triflates to $Pd^0(PPh_3)_4$ (2 mM) in DMF at 30 °C (Eqn (6)). Effect of chloride ions added as *n*-$Bu_4NCl$

| Entry | Vinyl-OTF | Additive | $k_{app}$ ($M^{-1}$ $s^{-1}$) |
|---|---|---|---|
| 1 |  **2a** | — | 5300 |
| 2 |  **2b** | — | 530 |
| 3 | **2b** | $Cl^-$ (200 equiv) | 730 |
| 4 |  **2c** | — | 1530 |
| 5 |  **2d** | — | 3200 |
| 6 |  **2e** | — | 660 |
| 7 |  **2f** | — | 170 |

## STRUCTURAL AND KINETIC EFFECT OF CHLORIDE IONS IN PALLADIUM-CATALYZED ALLYLIC SUBSTITUTIONS

Palladium complexes are efficient catalysts of nucleophilic substitutions on allylic carboxylates (Tsuji–Trost reactions):[12–24]

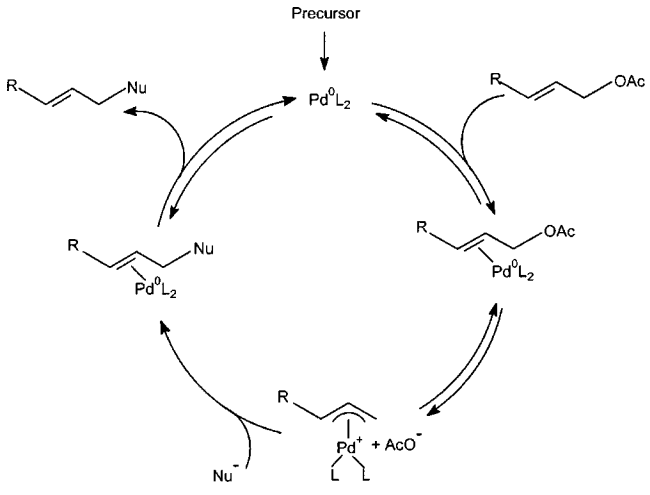


(8)

Whatever the catalytic precursor ($Pd^0L_4$, $Pd^0(dba)_2 + nL$, [$Pd(\eta^3$-allyl)($\mu$-Cl)]$_2$ + 4L, etc.) (dba is *trans*, *trans*-dibenzylideneacetone), the mechanism of the Tsuji–Trost reactions is supposed to involve cationic complexes [($\eta^3$-allyl)$PdL_2$]$^+$ with $AcO^-$ as the counter anion (free ions in DMF, ion pairs in THF) generated in a reversible oxidative addition (Scheme 4).[31,32]

However, the efficiency, regioselectivity and enantioselectivity of the Tsuji–Trost reactions may be affected by the catalytic precursor or by the presence of chloride ions purposely added in the reaction, as evidenced by the groups of Bäckvall,[19,20] Hayashi,[21] Lloyd-Jones[22,23] and Trost.[24]

In 1968, Powell and Shaw[33] established that dimeric [$Pd(\eta^3$-allyl)($\mu$-Cl)]$_2$ complexes led to neutral $\eta^1$-allyl–$PdClL_2$ complexes when four equivalents of $PPh_3$ were added to [$Pd(\eta^3$-allyl)($\mu$-Cl)]$_2$. In 1981, Åkermark *et al.*[34] reported a difference in reactivity and regioselectivity in the reaction of dimethylamine with the neutral complex $\eta^1$-$CH_3$–CH=CH–$CH_2$–$PdCl(PPh_3)_2$ (supposedly generated *in situ* by reaction of [$Pd(\eta^3$-$CH_3$–CH–CH–$CH_2$)($\mu$-Cl)]$_2$




**Scheme 4.**

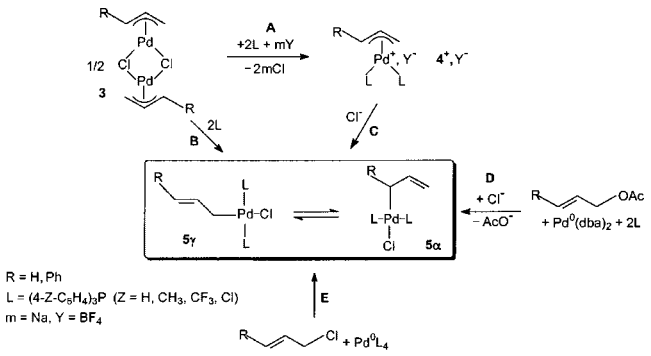
with four equivalents of $PPh_3$) when compared with its reaction with an isolated cationic complex $[(\eta^3\text{-}CH_3\text{–}CH\text{–}CH\text{–}CH_2)Pd(PPh_3)_2]^+BF_4^-$.

This strongly suggested that voluntarily added chloride ions or chloride ions introduced via the dimeric precursor $[Pd(\eta^3\text{-allyl})(\mu\text{-Cl})]_2$ may affect the structure and reactivity of the allyl-palladium(II) complex that has supposedly been involved in the nucleophilic attack.

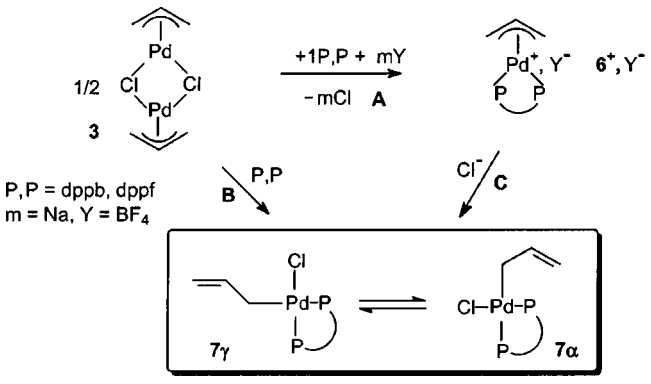
## Formation of neutral $\eta^1$-allyl-palladium chloride complexes

In 2001 and 2003, we established that neutral $\eta^1$-allyl–$PdClL_2$ (**5α**) and (**5γ**) (L = monophosphine) were generated in chloroform, acetone, THF and DMF: (i) by addition of four equivalents of L to $[Pd(\eta^3\text{-allyl})(\mu\text{-Cl})]_2$ in the absence of any chloride scavenger (route **B** in Scheme 5); (ii) by addition of chloride ions (as $n$-$Bu_4NCl$) to cationic complexes $[(\eta^3\text{-allyl})PdL_2]^+$ (route **C**); (iii) in the oxidative addition of allylic acetates to $Pd^0(dba)_2 + 2PPh_3$ when it is performed in the presence of $Cl^-$ (route **D**), the oxidative addition then becoming irreversible; (iv) in the oxidative addition of allylic chlorides to $Pd^0L_4$ complexes (route **E**), as summarized in Scheme 5.[35,36]

Similarly, neutral complexes $\eta^1$-allyl–PdCl(P,P) (**7α**) and (**7γ**) were generated with bidentate P,P ligands (Scheme 6).[36]




**Scheme 5.**




**Scheme 6.**

Whatever the ligand, monodentate or bidentate, the neutral complexes $\eta^1$-$CH_2$=CH–$CH_2$–$PdClL_2$ (**5**) or $\eta^1$-$CH_2$=CH–$CH_2$–PdCl(P,P) (**7**) exhibit similar $^1H$ NMR patterns consisting of a doublet ($J_{HH} = 10$ Hz) integrating for four protons and a quintet ($J_{HH} = 10$ Hz) integrating for one proton, suggesting a fast equilibrium between (**5α**) (R = H) and (**5γ**) (R = H) (Scheme 5) and (**7α**) and (**7γ**) (Scheme 6).[36]

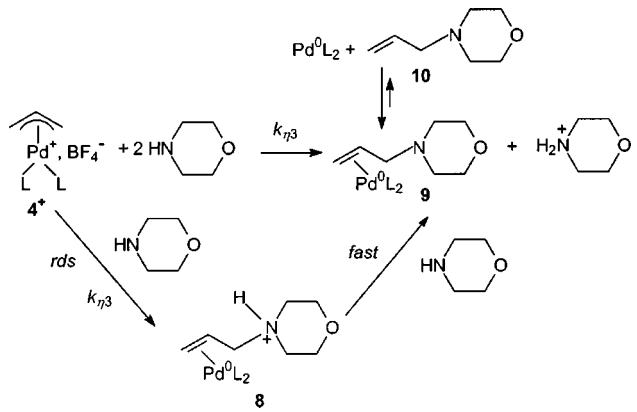
In 2001, Braunstein *et al.*[37] reported the characterization of an $\eta^1$-allyl–$Pd^{II}Cl(P,N)$(P,N = bis(oxazoline)phenylphosphonite) complex. In 2002, Kollmar and Helmchen[38] reported the synthesis of an $\eta^1$-allyl–PdCl(P,N) (P,N = phosphinooxazoline) complex. The $\eta^1$-allyl–PdCl complexes were obtained in both cases by treating a dimeric $[Pd(\eta^3\text{-allyl})(\mu\text{-Cl})]_2$ with two equivalents of the corresponding P,N ligand, in the absence of any chloride scavenger.

This is further evidence that the presence of chloride ions strongly favors the $\eta^1$-allyl structure, and it emphasizes the crucial role of presumably 'innocent' ligands, such as chloride ions, that do not behave as simple counter anions of cationic $[(\eta^3\text{-allyl})PdL_2]^+$ complexes but may modify their structure. It is shown in the following that they also modify the reactivity of allyl-palladium(II) complexes with nucleophiles.

## Reactivity of cationic complexes $[(\eta^3\text{-}CH_2\text{–}CH\text{–}CH_2)Pd(PAr_3)_2]^+,BF_4^-$ with morpholine in DMF in the absence of chloride ions

The reaction of morpholine with $[(\eta^3\text{-}CH_2\text{–}CH\text{–}CH_2)Pd\{P(4\text{-Cl–}C_6H_4)\}_3]^+BF_4^-$ (**4a**$^+$,$BF_4^-$) or $[(\eta^3\text{-}CH_2\text{–}CH\text{–}CH_2)Pd\{P(4\text{-}CH_3\text{–}C_6H_4)\}_3]^+BF_4^-$ (**4b**$^+$, $BF_4^-$), performed in DMF at room temperature, gives the substitution product **10**, which remains ligated to $Pd^0(PAr_3)_2$ complex as in complexes **9**, as identified by UV spectroscopy (Scheme 7).[36]

The kinetics of the reaction of morpholine with cationic complexes **4a**$^+$,$BF_4^-$ and **4b**$^+$,$BF_4^-$ was then monitored by UV spectroscopy by recording the increase of the absorbance of complexes **9a** (Fig. 4a) or **9b** with time. The limiting value of the absorbance of **9a** observed in the presence of morpholine in large excess (Fig. 4a) was reached only after addition of two




**Scheme 7.**

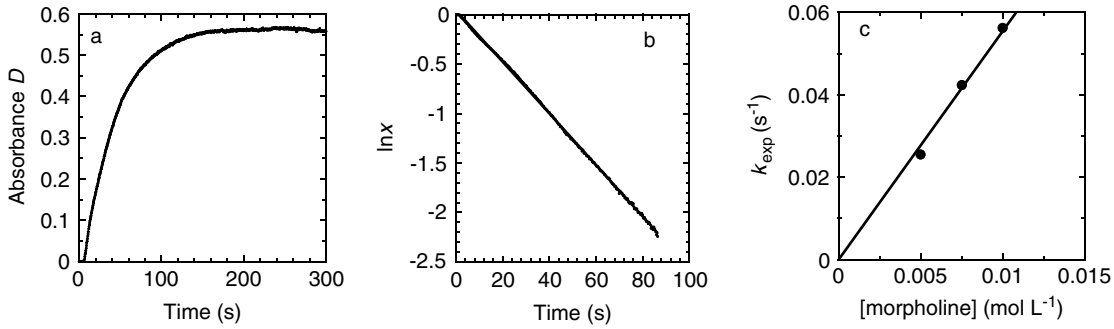



**Figure 4.** Kinetics of the reaction of morpholine with the cationic complex $[(\eta^3\text{-}CH_2\text{–}CH\text{–}CH_2)Pd(PAr_3)_2]^+,BF_4^-$ (Ar = 4-Cl–$C_6H_4$) (**4a**$^+$,$BF_4^-$) (0.5 mM) in DMF containing *n*-$Bu_4NBF_4$ (0.3 M) at −25 °C, monitored by UV spectroscopy. (a) Absorbance at 323 mm of the palladium(0) complex (**9a**) versus time, after addition of 10 equivalents of morpholine. (b) Variation of ln *x* versus time ($x = ([\mathbf{9a}]_{lim} - [\mathbf{9a}])/[\mathbf{9a}]_{lim} = (D_{lim} - D)/D_{lim}$ with *D* the absorbance of **9a** at *t* and $D_{lim}$ the final absorbance of **9a** determined in Fig. 4a). $\ln x = -k_{exp}t$. (c) Reaction order in morpholine: plot of $k_{exp}$ versus the morpholine concentration. $k_{exp} = k_{\eta^3}$[morpholine].

equivalents of morpholine, which shows that the complete substitution on **4a**$^+$ to give the palladium(0) complex **9a** requires two equivalents of morpholine (Scheme 7). The overall reaction may then be decomposed into two successive steps: the rate-determining nucleophilic reaction, followed by the fast deprotonation of complex **8** (Scheme 7). The kinetics of formation of the palladium(0) complex **9** monitored by UV spectroscopy (Fig. 4a) is thus indicative of the kinetics of the nucleophilic attack. The value of the rate constant $k_{\eta^3}$ was determined from Fig. 4b and c (Table 3): $\ln x = -k_{\eta^3}$[morpholine]$t$.[36]

The effect of the ionic strength on this reaction was tested by addition of *n*-$Bu_4NBF_4$ (0.3 M) to anticipate its effect were the reaction to be performed in the presence of *n*-$Bu_4NCl$. The effect of the ionic strength is to accelerate (by 30%) the nucleophilic attack slightly (compare the values of $k_{\eta^3}$ determined in DMF at −25 °C, Table 3).[36]

From the respective values of $k_{\eta^3}$ in Table 3, one observes that the cationic complex ligated by 4-Me–$C_6H_4)_3P$ is less reactive than that ligated by 4-Me–$C_6H_4)_3P$. The ligand (4-Me–$C_6H_4)_3P$ of the cationic palladium(II) center is more electron rich than (4-Cl–$C_6H_4)_3P$, which disfavors the external nucleophilic attack on the allyl ligand.

**Table 3.** Comparative intrinsic reactivity of cationic $[(\eta^3\text{-allyl})PdL_2]^+$ and neutral $\eta^1$-allyl–$PdClL_2$ complexes with morpholine in DMF at 25 °C (Scheme 8)

| L | (4-Cl–$C_6H_4)_3P$ | (4-$CH_3$–$C_6H_4)_3P$ |
|---|---|---|
| $k_{\eta^3}$ ($M^{-1}$ $s^{-1}$) | 94[a] | 1 |
| $k_{\eta^1}$ ($M^{-1}$ $s^{-1}$) | 0.91 | 0.29 |
| $K_{Cl}$ ($M^{-1}$) | $58 \times 10^3$ | $2.4 \times 10^3$ |

[a] $k_{\eta^3} = 4.2\ M^{-1}\ s^{-1}$ at −25 °C. $k_{\eta^3} = 5.6\ M^{-1}\ s^{-1}$ at −25 °C in the presence of *n*-$Bu_4NBF_4$ (0.3 M).

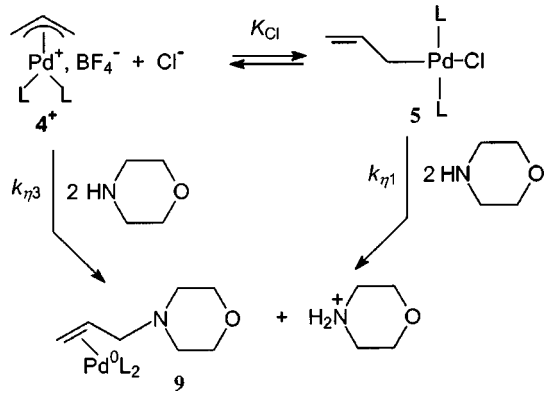
## Effect of chloride ions on the reactivity of cationic $[(\eta^3\text{-allyl})PdL_2]^+$ complexes with morpholine: comparative reactivity of neutral $\eta^1$-allyl–$PdClL_2$ chloride complexes versus cationic $[(\eta^3\text{-allyl})PdL_2]^+$ complexes

The nucleophilic attack of morpholine on the cationic complexes **4a**$^+$,$BF_4^-$ and **4b**$^+$,$BF_4^-$ was found to become slower and slower in the presence of increasing amounts of chloride ions added as *n*-$Bu_4NCl$ in the concentration range 4.9–8.8 mM to minimize any effect of the variation of the ionic strength.[36] This decelerating effect cannot be interpreted as a consequence of the increasing ionic strength, since the effect of the ionic strength was to accelerate the nucleophilic attack slightly (*vide supra*). A specific effect of *n*-$Bu_4NCl$ is thus involved.

The addition of $Cl^-$ to the cationic complexes $[(\eta^3\text{-}CH_2\text{–}CH\text{–}CH_2)Pd(PAr_3)_2]^+BF_4^-$ led to the formation of the neutral complexes $\eta^1$-$CH_2$=CH–$CH_2$–$PdCl(PAr_3)_2$.[36] The fact that the rate of the nucleophilic attack on the cationic complexes depends on the $Cl^-$ concentration indicates that the two complexes are in equilibrium with the $Cl^-$ (Scheme 8) with $K_{Cl}[Cl^-] >> 1$. Indeed, the cationic complexes were no longer detected in the presence of one equivalent of $Cl^-$ ($C_0 = 0.5$ mM).

The cationic complexes **4**$^+$ might remain the reactive complex even in the presence of a large excess of $Cl^-$, or both complexes **4**$^+$ and **5** might react in parallel with morpholine to give the same palladium(0) complex **9** (Scheme 8).[36] The reaction of morpholine with **4**$^+$ is known as an external attack onto the $\eta^3$-allyl ligand,[12–24] whereas reaction of morpholine with **5** would be an $S_N2'$ substitution at the $\eta^1$-allyl ligand, as proposed by Åkermark *et al*.[34]

According to Scheme 8, the kinetic law is given by Eqn (9), with an apparent rate constant $k_{app}$ expressed in Eqn (10) ($x = ([\mathbf{9}]_{lim} - [\mathbf{9}])/[\mathbf{9}]_{lim} = (D_{lim} - D)/D_{lim}$ with *D* the absorbance of **9** at *t* and $D_{lim}$ the final absorbance of **9**




**Scheme 8.**

determined as in Fig. 4a).

$$\ln x = [\text{morpholine}]\left(k_{\eta^1} + \frac{k_{\eta^3}}{K_{Cl}[Cl^-]}\right)t \quad (9)$$

$$k_{app} = k_{\eta^1} + \frac{k_{\eta^3}}{K_{Cl}[Cl^-]} \quad (10)$$

The plot of $k_{app}$ versus the reciprocal of the $Cl^-$ concentration is linear (Fig. 5) with a positive intercept, thus confirming the mechanism proposed in Scheme 8 and establishing that the neutral complex **5** reacts in parallel with the cationic complex $\mathbf{4}^+$.

The values of $k_{\eta^1}$ and $k_{\eta^3}/K_{Cl}$ are determined from the intercept and the slope of the straight line respectively, thus allowing the determination of $K_{Cl}$ (Table 3).[36] From

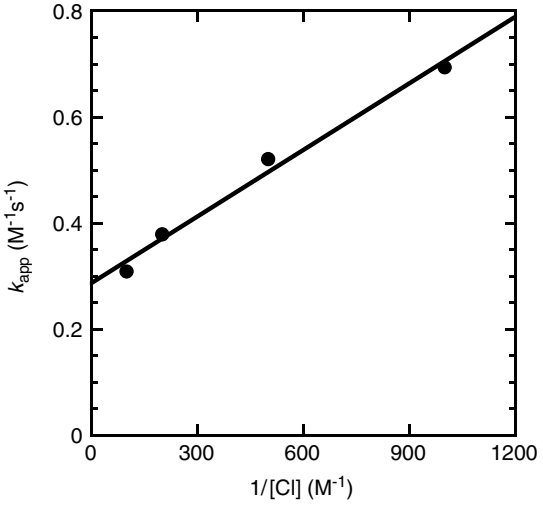



**Figure 5.** Kinetics of the reaction of morpholine (2 mM) with $[(\eta^3\text{-}CH_2\text{–}CH\text{–}CH_2)Pd(PAr_3)_2]^+,BF_4^-$ (Ar = 4-Me–$C_6H_4$) ($\mathbf{4b}^+,BF_4^-$, $C_0 = 1$ mM) in DMF, in the presence of various amount of $Cl^-$ ions added as *n*-$Bu_4NCl$, monitored by UV spectroscopy in DMF at 25 °C. Variation of $k_{app}$ versus the reciprocal of $Cl^-$ concentration (Eqn (10)).

the comparative values of $k_{\eta^1}$ and $k_{\eta^3}$, it is observed that, for the same ligand, the cationic complex $\mathbf{4}^+$ is intrinsically considerably more reactive than the neutral complex **5**. However, in the presence of $Cl^-$, the concentration of $\mathbf{4}^+$ may be very low and the neutral complex **5** may become the main reactive complex. If $[Cl^-] = 5 \times 10^{-3}$ M, then the contribution of the cationic complex $\mathbf{4a}^+$ will only be 0.35 of that of the neutral complex **5a**, which then plays the essential role in the reaction with morpholine.[36]

Consequently, one may switch from a nucleophilic attack on the $\eta^3$-allyl ligand of the cationic complex to an $S_N2'$ substitution on the $\eta^1$-allyl ligand of the neutral complex when increasing the chloride concentration, thus affecting the rate and probably the regioselectivity of the reaction. As recalled in the Introduction, this double effect was observed by Åkermark *et al*.[34] However, in that study, neither the equilibrium between the cationic and the neutral complexes was considered, nor the effect of the chloride concentration.[34]

Comparison of the $k_{\eta^1}$ values in Table 3 indicates that the neutral $\eta^1$-allyl–$PdCl(PAr_3)_2$ complex is only slightly less reactive when the electron-rich (4-Me–$C_6H_4)_3P$ is considered compared with (4-Cl–$C_6H_4)_3P$, whereas a stronger difference was observed for the cationic complexes (compare $k_{\eta^3}$ in Table 3). This suggests an $S_N2'$ mechanism with $Pd(PAr_3)_2$ as the leaving group located far from the impact of the nucleophilic attack, as proposed by Åkermark *et al*.[34]

## CONCLUSIONS

It is shown that chloride ions play a very important role in palladium-catalyzed reactions, since they are involved in several steps of the catalytic cycles. They affect the *structure* and *reactivity* of key intermediates in palladium-catalyzed reactions.

Indeed, chloride ions modify the kinetics of the first step of catalytic cycles, i.e. the oxidative addition of aryl triflates,[25] vinyl triflates,[29] and allylic acetates[35] to palladium(0) complexes (acceleration of the oxidative addition of aryl and vinyl triflates and irreversibility of the oxidative addition of allylic acetates).

Chloride ions modify the structure of the aryl-, vinyl- or allyl-palladium(II) complexes, generated in the oxidative addition, by formation of neutral aryl-, vinyl- or $\eta^1$-allyl-palladium(II) chloride complexes respectively,[25,29,35,36] instead of cationic aryl-, vinyl- or ($\eta^3$-allyl)palladium(II) complexes.

Chloride ions modify the mechanism of the second step of the catalytic cycle of the Stille reactions involving aryl or vinyl triflates by the formation of neutral aryl- or vinyl-palladium(II) chloride complexes[10,25,29] which then react with the organostannane derivative.[10]

Chloride ions also modify the mechanism of the second step of the catalytic cycle of the Tsuji–Trost reactions, i.e. the nucleophilic attack on allyl-palladium(II) complexes (neutral $\eta^1$-allyl- versus cationic ($\eta^3$-allyl)palladium(II) complexes).

At high chloride concentrations, the neutral $\eta^1$-allyl–PdCl complex may become the major reactive complex.[36] The catalytic precursors of Tsuji–Trost reactions, i.e. $[Pd(\eta^3\text{-allyl})(\mu\text{-Cl})]_2 + 4PAr_3$ or $[(\eta^3\text{-allyl})Pd(PAr_3)_2]^+BF_4^-$ are not equivalent, since in the presence of chloride ions delivered by the precursor the intermediate which reacts with the nucleophile might not be only the cationic complexes $[(\eta^3\text{-allyl})Pd(PAr_3)_2]^+$, as usually considered, but also the neutral complexes $\eta^1$-allyl–$PdCl(PAr_3)_2$.[36] The regioselectivity and enantioselectivity of the catalytic reactions may then be affected by the presence of chloride ions purposely added or introduced by the precursors.

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