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Dual Effect of Halides in the Stille Reaction: In Situ Halide Metathesis and Catalyst Stabilization

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Abstract: Halide anions can increase or decrease the transmetallation rate of the Stille reaction through in situ halide metathesis. Although the influence of the halogen present in oxidative addition complexes on the transmetallation rate with organostannanes was already known, the application of in situ halide metathesis to accelerate cross-coupling reactions with organometallic reagents is not described in the literature yet. In addition a second unprecedented role of halides was discovered. Halide anions stabilize the $[Pd^0(L)_2]$ catalyst in Stille reactions, by means of $[Pd^0X(L)_2]^-$ formation (X = Cl, I), hereby preventing its leaching from the catalytic cycle. Both arene (iodobenzene) and azaheteroarene (2-halopyridine, halopyrazine, 2-halopyrimidine) substrates were used.

Keywords: catalyst stabilization · halide metathesis · halides · palladium · transmetallation

Introduction

The Stille and the Suzuki reactions are among the most popular Pd-catalyzed cross-coupling reactions hitherto available for the bench chemist.[1] The popularity of the Stille reaction is based on the mild reaction conditions required to create carbon–carbon bonds. The high functional-group compatibility (neutral conditions) makes it a suitable tool to couple highly functionalized subunits in the synthesis of complex natural products and to perform efficient lead optimization in medicinal chemistry/agrochemistry programs.[2] In addition organostannanes can be easily synthesized in a variety of ways and stored without taking special precautions.[1,3] The mechanism of the Stille reaction focussing on the transmetallation step has been widely explored (Farina,[4] Espinet,[5] and Amatore and Jutand[6]). There have been several reports on the promotion of the transmetallation of Stille reactions by adding fluoride anions upon which more reactive hypervalent tin species are created (nucleophilic assistance).[7] Besides fluoride, chloride anions have also been reported to possess an enhancing effect, but in this case a direct effect on the oxidative addition step is described.[8,9] Stille, Farina, and Jutand described that when aryl triflates are used as substrates, stable neutral oxidative addition complexes are generated by adding chloride anions to the reaction mixture.[8] A distinct chloride effect was described by Amatore and Jutand, who clearly showed that the Pd^0 catalyst generated by in situ reduction of the precatalyst $[Pd^{II}Cl_2(L)_2]$ yields an anionic $[Pd^0Cl(L)_2]^-$ complex that is more nucleophilic than neutral $[Pd^0(L)_2]$ complex, thus facilitating the oxidative addition.[9] Halide effects in cross-coupling reactions were often neglected in the past, but more recently are the subject of detailed investigations as they can dramatically affect the selectivity and activity of a metal-mediated reaction.[10] In this paper we report an unprecedented dual role of halides in the Stille reaction: halide metathesis and catalyst stabilization.

Results and Discussion

When studying the Stille reaction on 2-chloro- (**1a**) and 2-iodopyridine (**1b**) under standard reaction conditions,[1c] we found that the reaction of **1a** with tributyl(2-thienyl)stan-

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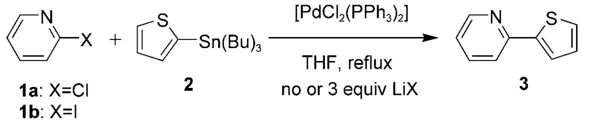
nane (**2**) was substantially faster than that of **1b** (Table 1, entries 3 and 8). Even with a catalyst loading of almost 10%, no full conversions were obtained within 24 h for substrates **1a** and **1b**. These results were quite unexpected, since aryl iodides are known to be more reactive than aryl chlorides in Pd-catalyzed reactions.[11] The determination of the rate constants of the oxidative addition of **1a** and **1b** (first step of the catalytic cycle) to $[Pd^0(PPh_3)_4]$ ($[Pd^0(PPh_3)_2]$ as the reactive species) by means of electrochemical techniques[12] revealed that, as expected, the oxidative addition of **1b** was considerably faster than **1a** by a factor 3×10^4 at 25 °C in THF. Consequently, the origin of the inversion of reactivity in the catalytic reactions must be found in the steps that follow the oxidative addition. Therefore, kinetic studies were undertaken on the influence of the concentration of **2** on the rate of formation of the coupling product **3**. The k_{obsd} values revealed that the transmetallation is the rate-limiting step of the catalytic cycle (first-order reaction for **2**). The only difference in the Stille reactions starting from **1a** and **1b** with **2** is the halide. There seems to be a serious difference in transmetallation rate between $[Pd^{II}Cl(2\text{-}Py)(PPh_3)_2]$ (**4a**) and $[Pd^{II}I(2\text{-}Py)(PPh_3)_2]$ (**4b**). Next, we tested if the transmetallation rate of chloride complex **4a** is indeed higher than that of the corresponding iodide complex **4b**. Therefore we added 29 equivalents of **2** to a solution of the complexes **4** in a 1:1 mixture of $CDCl_3$ and THF and followed the disappearance as a function of time at 50 °C with ^{31}P NMR spectroscopy. For **4a** a substantially faster transmetallation rate was observed than for **4b**, supporting our hypothesis (Figure S2 in the Supporting Information).[14]

Table 1. Conversions for the Stille reaction of **1** with **2** in the absence and presence of additives.[a]

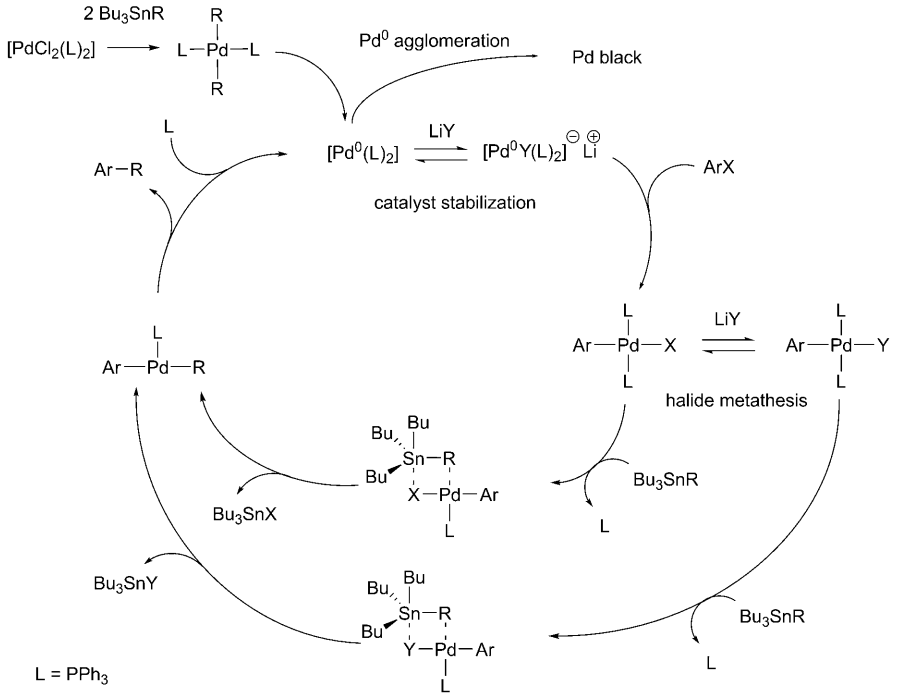


Entry	1	2 [M]	Additive [M]	k_{obsd}[b]	Reaction time [min] (% conversion to 3)
1	**1a**	0.583	–	–	480 (24), 1440 (36)
2	**1a**	0.875	–	4.3	480 (38), 1440 (48)
3	**1a**	1.166	–	6.7	1440 (75), 2880 (97)
4	**1a**	0.583	LiCl (1.275)	4.9	60 (36), 480 (93)
5	**1a**	0.875	LiCl (1.275)	9.7	60 (45), 480 (100)
6	**1a**	0.875	LiI (1.275)	3.1	480 (60),1440 (97)
7	**1b**	0.583	–	–	480 (7), 1440 (13)
8	**1b**	1.166	–	–	480 (21), 1440 (36)
9	**1b**	1.166	LiCl (1.275)	4.6	480 (56), 1440 (100)
10	**1b**	1.166	LiI (1.275)	3.6	480 (73), 1440 (100)

[a] **1a** (0.425 M), **2**, $[Pd^{II}Cl_2(PPh_3)_2]$ (9.4 mol%), dry THF (6 mL), reflux. [b] k_{obsd} values[13] are given in 10^{-3} min^{-1}.

The similar behavior of phenyl complexes $[Pd^{II}X(Ph)(PPh_3)_2]$ (**6a**: X=Cl; **6b**: X=I)[15] (**6a** more reactive than **6b**, see Figure S4 in the Supporting Information) confirm that $[PdCl(Ar)(PPh_3)_2]$ are generally more reactive than $[Pd^{II}I(Ar)(PPh_3)_2]$ complexes. Our observations are in agreement with the transmetallation rates of $(CH_2{=}CH)SnBu_3$ with $[Pd^{II}X(F_3Cl_2Ph)(AsPh_3)_2]$ (X=Cl, Br, I) studied by Espinet[5a] and DFT calculations on the transmetallation process of the same organostannane with $[Pd^{II}X(Ph)(PH_3)_2]$ (X=Cl, Br, I) published by Fairlamb.[16] We wondered if it would be feasible to perform an in situ halide metathesis with chloride ions, thus transforming **4b** into the more reactive **4a** (Scheme 1). Halide metathesis is a well-known process for the synthesis of Pd complexes, but it has, to the best of our knowledge, never been considered to play a role in Pd-catalyzed cross-coupling reactions with organometallic species.[17]

We therefore performed the coupling of **1b** with **2** in the presence of LiCl. Gratifyingly, we found a serious increase in reaction rate (Table 1, compare entries 8 and 9). When we added LiCl (32 equiv) to a solution of **4b** or **6b** in THF at 30 °C in an NMR tube, we gratifyingly observed the for-



Scheme 1. General mechanism of the Stille reaction taking into account in situ halide metathesis and catalyst stabilization by LiY.

mation of some **4a** or **6a**, respectively, which proves that halide metathesis is a realistic process. Moreover, a transmetallation experiment with **2** on **4b** and on **6b** (followed by ^{31}P NMR spectroscopy) in the presence of LiCl showed a rate acceleration in comparison with the experiments in the absence of LiCl, proving that halide metathesis is also a kinetically relevant process (Figures S5 and S6 in the Supporting Information). Complexes **4b** and **6b** are thermodynamically more stable, since halide metathesis on **4a** and **6a** in the presence of LiI (32 equiv) gave a complete conversion to **4b** and **6b**, respectively.

To further support our findings on the role of in situ halide metathesis in the acceleration of the reaction rate, the Stille reaction of **1a** was studied in the presence of LiI. A decrease of the initial k_{obsd} was observed (Table 1, compare entries 2 and 6) due to an in situ halide metathesis converting [Pd^{II}Cl(2-Py)(PPh$_3$)$_2$] (**4a**) into the less reactive [Pd^{II}I(2-Py)(PPh$_3$)$_2$] (**4b**) (Scheme 1, see Figures S7 and S8 in Supporting Information for the decelerating effect of LiI on the transmetallation of **4a** and **6a** by **2**). However, within 24 h in the presence of LiI a full conversion was achieved, while in its absence only 48% was obtained.[18] Additionally, an increase of the reaction rate was observed when LiCl was added to the Stille reaction of 2-chloropyridine (**1a**) (Table 1, compare entries 2 and 5) and when LiI was added to the Stille reaction of 2-iodopyridine (**1b**) (Table 1, compare entries 8 and 10), while no effect on the turnover limiting transmetallation was expected. Initially, the promotion of the transmetallation by the formation of a hypervalent stannane (=known as nucleophilic assistance) was considered to be responsible for the rate acceleration of these reactions.[7] Transmetallation experiments on [Pd^{II}Cl(2-Py)(PPh$_3$)$_2$] (**4a**) and [Pd^{II}I(2-Py)(PPh$_3$)$_2$] (**4b**) with **2** in the presence of LiCl and LiI, respectively, showed however no rate effect (Figures S9 and S10 in the Supporting Information). Therefore, the observed accelerations cannot be due to nucleophilic assistance at tin. The obtained results indicate that in situ halide metathesis does play a role in some cases, but cannot be the only effect of halides on the reaction rate. We then focused on the in situ reduction of [Pd^{II}Cl$_2$(PPh$_3$)$_2$] by **2**. This process delivers the actual Pd^0 catalyst at the very beginning of the catalytic reaction and a different concentration of catalyst will immediately influence the rate of the Stille reaction.[19]

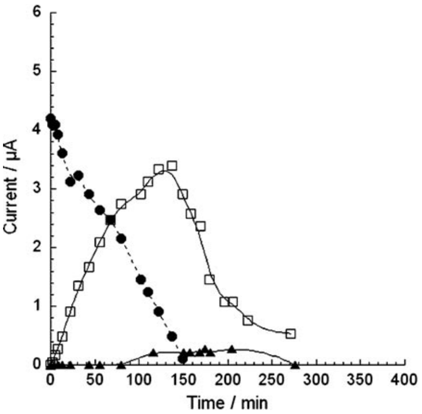


Figure 1. Cyclic voltammetry study of the reduction of [Pd^{II}Cl$_2$(PPh$_3$)$_2$] by **2**. Reactions performed in THF (containing nBu$_4$NBF$_4$, 0.3 M) at 20 °C. Peak currents were measured at a steady gold disk electrode (d=1 mm) at the scan rate of 0.5 Vs^{-1}. ●: Decrease of the reduction peak current of [Pd^{II}Cl$_2$(PPh$_3$)$_2$] (1.94 mM) with time after addition of **2** (38.8 mM). □: Evolution with time of the reduction peak current of the intermediate complex [Pd^{II}(Th)$_2$(PPh$_3$)$_2$]. ▲: Evolution with time of the oxidation peak current of the Pd^0 complex formed in situ from [Pd^{II}(Th)$_2$(PPh$_3$)$_2$].

The effect of halide ions on the in situ reduction of [Pd^{II}Cl$_2$(PPh$_3$)$_2$] by **2** was studied by electrochemical techniques, taking the advantage of the fact that Pd^{II} and Pd^0 complexes can be detected and characterized by their reduction or oxidation potentials, respectively, and quantified since the reduction or oxidation peak currents are proportional to the concentration of electroactive species.[12] [Pd^{II}Cl$_2$(PPh$_3$)$_2$] exhibited a reduction peak at −0.87 V vs SCE in THF at 20 °C. The reduction peak slowly disappeared with time after addition of **2** (20 equiv), evidencing a reaction of [Pd^{II}Cl$_2$(PPh$_3$)$_2$] with **2** (Figure 1; ●). Concomitantly, a new reduction peak was observed at −1.67 V, the reduction peak current of which increased with time to reach a maximum value and then decreased (Figure 1; □). This peak was assigned to [Pd^{II}(Th)$_2$(PPh$_3$)$_2$] (Th = 2-thienyl) formed by double transmetallation of [Pd^{II}Cl$_2$(PPh$_3$)$_2$] with **2**. When the cyclic voltammetry was performed directly towards oxidation potentials, a tiny oxidation peak was observed at +0.12 V, which characterized a Pd^0 complex.[9] This small peak appeared about 90 min after addition of **2** to [Pd^{II}Cl$_2$(PPh$_3$)$_2$] and was generated from [Pd^{II}(Th)$_2$(PPh$_3$)$_2$]. The peak current of the oxidation peak of the Pd^0 species was very low (Figure 1; ▲) and the yellow solution first turned brown and then black. This indicates that the Pd^0 generated by reduction of [Pd^{II}Cl$_2$(PPh$_3$)$_2$] by **2** was quite unstable, owing to the lack of stabilizing ligands (no chlorides because quenched as ClSnBu$_3$). The reaction of **2** with [Pd^{II}Cl$_2$(PPh$_3$)$_2$] was also followed by ^{1}H and ^{31}P NMR spectroscopy at room temperature (CDCl$_3$). The ^{1}H NMR spectrum exhibited the three protons of a thienyl group located at higher field than in **2**, characteristic for aromatic groups ligated to a Pd^{II} center. No stable Pd^0 complex in the reductive elimination could be characterized by ^{31}P NMR spectroscopy, in agreement with its instability. An important modification appeared in the cyclic voltammetry measurements when the reaction of [Pd^{II}Cl$_2$(PPh$_3$)$_2$] with **2** was performed in the presence of chloride ions introduced as nBu$_4$NCl (9.3 equiv) before the addition of **2** (20 equiv). The reduction peak current of [Pd^{II}Cl$_2$(PPh$_3$)$_2$] again decreased with time, but the reaction was slower than in the absence of chlorides (compare Figures 1 and 2; ●) because [Pd^{II}Cl$_2$(PPh$_3$)$_2$] was in equilibrium with the less or non reactive anionic [Pd^{II}Cl$_3$(PPh$_3$)]$^-$.[20] Appearance of [Pd^{II}(Th)$_2$(PPh$_3$)$_2$] was again linked with the disappearance of [Pd^{II}Cl$_2$(PPh$_3$)$_2$] and its concentration exhibited a maximum value (Figure 2; □). Cyclic voltammetry performed concomitantly first towards oxidation potentials revealed an oxidation peak at +0.12 V, characteristic of a Pd^0 complex. This oxida-

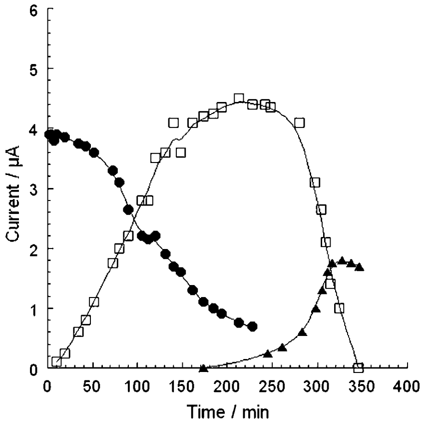


Figure 2. Cyclic voltammetry study of the reduction of $[Pd^{II}Cl_2(PPh_3)_2]$ by **2** in the presence of nBu_4NCl. Reactions performed in THF (containing nBu_4NBF_4, 0.3 M) at 20 °C. Peak currents were measured at a steady gold disk electrode ($d = 1$ mm) at the scan rate of 0.5 Vs^{-1}. ●: Decrease of the reduction peak current of $[Pd^{II}Cl_2(PPh_3)_2]$ (1.94 mM) with time in the presence of nBu_4NCl (18 mM) after addition of **2** (38.8 mM). □: Evolution with time of the reduction peak current of the intermediate complex $[Pd^{II}(Th)_2(PPh_3)_2]$ in the presence of nBu_4NCl (18 mM). ▲: Evolution with time of the oxidation peak current of the Pd^0 complex formed in situ from $[Pd^{II}(Th)_2(PPh_3)_2]$ in the presence of nBu_4NCl(18 mM).

tion peak appeared only 250 min after addition of **2** (Figure 2; ▲). The appearance of the Pd^0 complex was simultaneous with the disappearance of the intermediate complex $[Pd^{II}(Th)_2(PPh_3)_2]$. In contrast with the experiment performed in the absence of chlorides, the Pd^0 complex formed from $[Pd^{II}(Th)_2(PPh_3)_2]$ in the presence of chloride ions was generated in higher concentration and was more stable (compare Figures 1 and 2; ▲) owing to the stabilization by chloride ions as $[Pd^0Cl(PPh_3)_2]^-$.[9a] No significant decomposition was observed within the timescale investigated (Figure 2; ▲). Chloride ions therefore stabilized Pd^0 as an anionic species and prevented the formation of inactive palladium black, observed in the absence of chlorides. These cyclic voltammetry studies therefore indicate that the loading of palladium catalyst is higher in the presence of halide anions in the Stille reactions and therefore the cross-coupling reactions are faster. This rationalizes our data, which could not be explained based on halide metathesis (vide supra).

To further support the catalyst stabilization effect hypothesis in the cross-coupling experiments, theoretical conversions as a function of time were calculated using initial k_{obsd} values, derived from the experimental data points in the first 45 min of a reaction. The theoretical conversion versus time curves were then compared with the experimental ones. The reaction of **1a** with **2** was chosen as model. In Figure 3 both graphs for this reaction are shown. The curves for the same reaction but in the presence of LiCl are depicted in Figure 4. Comparison of Figures 3 and 4 clearly shows that catalyst decomposes in the absence of chloride, since experimental and theoretical curves only coincide in the presence of chloride. Given the fact that in this case LiCl has no rate effect on the transmetallation step, the observed acceleration was only due to catalyst stabilization. Similarly, for the reaction of substrate **1b** in the presence of LiI experimental and theoretical curves were also identical, further supporting the generality of the stabilizing role of halides (formation of $[Pd^0(PPh_3)_2I^-$ in this case).[9a] The higher initial value of k_{obsd} confirms that the initial concentration of Pd^0 is higher in the presence of halide.

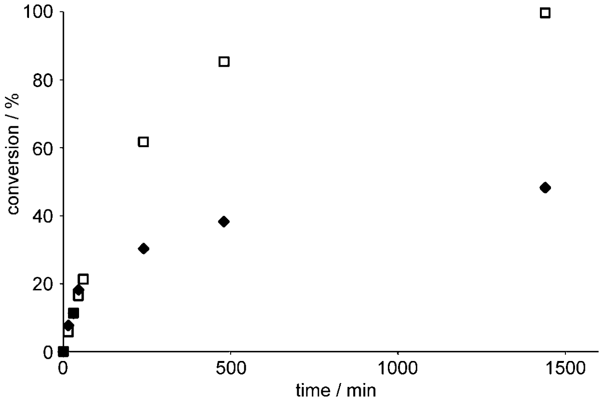


Figure 3. Experimental (◆) and theoretical (□) conversion curves for the cross-coupling reaction of **1a** with **2** using $[Pd^{II}Cl_2(PPh_3)]$ (Table 1, entry 2); $k_{obsd} = 4.3 \times 10^{-3}$ min^{-1}.

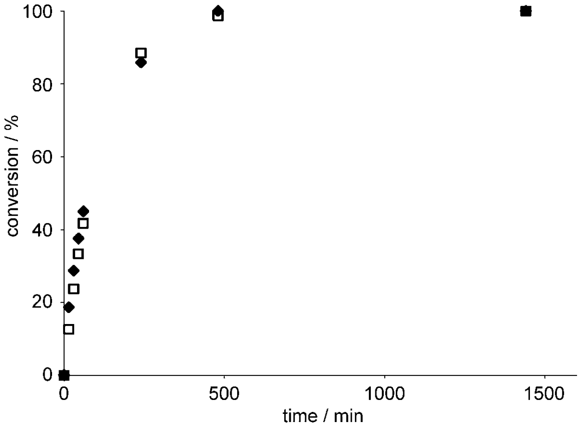


Figure 4. Experimental (◆) and theoretical (□) curves for the cross-coupling reaction of **1a** with 2 using $[Pd^{II}Cl_2(PPh_3)_2]$ in the presence of LiCl (Table 1, entry 5); $k_{obsd} = 9.7 \times 10^{-3}$ min^{-1}.

To find out if catalyst decomposition is only linked to the way palladium is introduced in the catalytic cycle, we used the intermediate **4a** as catalyst for the reaction of **1a** with **2** instead of precatalyst $[Pd^{II}Cl_2(PPh_3)_2]$. Interestingly, in the absence of chloride, similar behavior was seen as in the case when $[Pd^{II}Cl_2(PPh_3)_2]$ was used to feed the catalytic cycle (Figure 5). This indicates that loss of catalyst does not depend on the palladium feedstock used, it is not specifically linked to the initial reduction process of $[Pd^{II}Cl_2(PPh_3)_2]$ precatalyst and it occurs throughout the whole Stille reaction. The Pd^{II} present as oxidative addition complex is the main species (rate-limiting transmetallation) and $[Pd^0(PPh_3)_2]$ is expected to be only a small fraction of the total amount. Nevertheless agglomeration of Pd^0 seems to be still

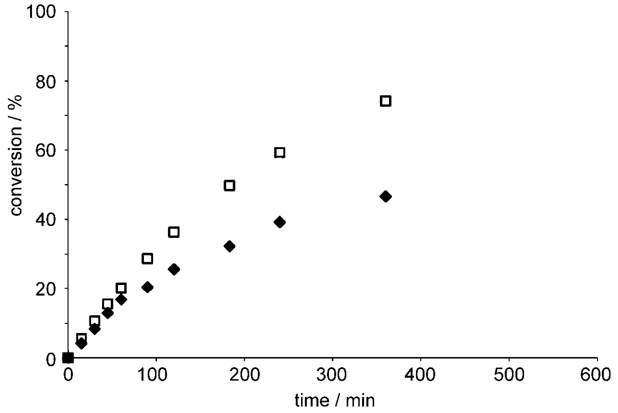
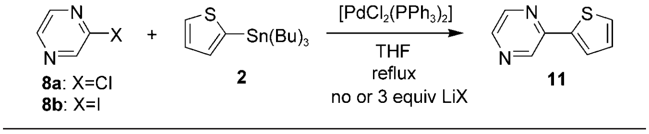


Figure 5. Experimental (◆) and theoretical (□) curves for the cross-coupling of **1a** with **2** using [Pd^{II}Cl(2-Py)(PPh$_3$)$_2$] (**4a**) as catalyst; k_{obsd} = 3.1×10^{-3} min^{-1}.[22]

an important process in the absence of halide.[21] Halide ions stabilize [Pd^0(PPh$_3$)$_2$] through the formation of stable [Pd^{0}X(PPh$_3$)$_2$]$^-$, which does not agglomerate to catalytically inactive Pd black due to coulombic repulsion. Based on the new insights a decrease of the Pd loading in the presence of halide is probably feasible. To test this we performed the reaction of **1a** with **2** in the presence of LiCl by using a smaller amount of [Pd^{II}Cl$_2$(PPh$_3$)$_2$]. In this case, even with a catalyst loading of only 1 mol %, full conversion can be achieved within 24 h. In order to get an idea of the generality of the identified halide effects, we also looked at other 2-haloazaheteroarenes and iodobenzene (**7**). A similar behavior was observed for halopyrazine (**8**) (Table 2) and 2-halopyrimidine (**9**) (Table 3) in a Stille reaction with **2**. The rate effect also occurs when 2-tributylstannylfurane (**10**) was selected as transmetallating agent in a reaction with **1** (Table 4). As an example of an arene the coupling of iodobenzene (**7**) with **2** was tested (Table 5). Also in this case the addition of LiCl and LiI had a similar rate enhancing effect.

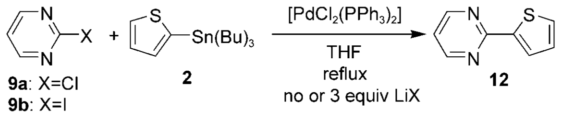
Table 2. Conversions for the Stille reaction of **8** with **2** in the absence and presence of additives.[a]



Entry	8	2 [M]	Additive [M]	Reaction time [min] (% conversion to **11**)
1	**8a**	0.583	–	480 (51), 1440 (95), 2880 (100)
2	**8a**	1.166	–	480 (93), 1440 (100)
3	**8a**	0.583	LiCl (1.275)	480 (88), 1440 (100)
4	**8a**	0.583	LiI (1.275)	480 (84), 1440 (100)
5	**8b**	0.583	–	480 (19), 1440 (49), 2880 (74)
6	**8b**	1.166	–	480 (29), 1440 (60), 2880 (100)
7	**8b**	0.583	LiCl (1.275)	480 (59), 1440 (100)
8	**8b**	0.583	LiI (1.275)	240 (56), 480 (100)

[a] **8** (0.425 M), **2**, [Pd^{II}Cl$_2$(PPh$_3$)$_2$] (9.4 mol %), dry THF (6 mL), reflux.

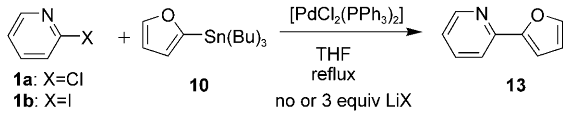
Table 3. Conversions for the Stille reaction of **9** with **2** in the absence and presence of additives.[a]



Entry	9	2 [M]	Additive [M]	Reaction time [min] (% conversion to **12**)
1	**9a**	0.583	–	480 (21), 1440 (60), 2880 (86)
2	**9a**	1.166	–	480 (43), 1440 (88), 2880 (100)
3	**9a**	0.583	LiCl (1.275)	480 (86), 1440 (100)
4	**9a**	0.583	LiI (1.275)	480 (51), 1440 (83)
5	**9b**	0.583	–	480 (9), 1440 (17), 2880 (34)
6	**9b**	1.166	–	480 (12), 1440 (20)
7	**9b**	0.583	LiCl (1.275)	480 (37), 1440 (68), 2880 (100)
8	**9b**	0.583	LiI (1.275)	480 (67), 1440 (100)

[a] **9** (0.425 M), **2**, [Pd^{II}Cl$_2$(PPh$_3$)$_2$] (9.4 mol %), dry THF (6 mL), reflux.

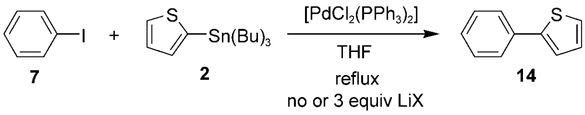
Table 4. Conversions for the Stille reaction of **1** with **10** in the absence and presence of additives.[a]



Entry	1	10 [M]	Additive [M]	Reaction time [min] (% conversion to **13**)
1	**1a**	0.583	–	60 (47), 480 (81), 1440 (97)
2	**1a**	1.166	–	60 (65), 480 (97)
3	**1a**	0.583	LiCl (1.275)	60 (84), 480 (100)
4	**1a**	0.583	LiI (1.275)	60 (41), 480 (67)
5	**1b**	0.583	–	60 (13), 480 (23), 1440 (37)
6	**1b**	1.166	–	60 (17), 480 (31), 1440 (53)
7	**1b**	0.583	LiCl (1.275)	60 (50), 480 (100)
8	**1b**	0.583	LiI (1.275)	60 (56), 480 (100)

[a] **1** (0.425 M), **10**, [Pd^{II}Cl$_2$(PPh$_3$)$_2$] (9.4 mol %), dry THF (6 mL), reflux.

Table 5. Conversions for the Stille reaction of **7** with **2** in the absence and presence of additives.[a]



Entry	7	2 [M]	Additive [M]	k_{obsd}[b]	Reaction time [min] (% conversion to **14**)
1	**7**	0.583	–	5.1	60 (34), 240 (80)
2	**7**	1.166	–	9.1	60 (50), 240 (100)
3	**7**	0.583	LiCl (1.275)	13.1	60 (55), 240 (100)
4	**7**	0.583	LiI (1.275)	22.8	60 (65), 240 (100)

[a] **7** (0.425 M), **2**, [Pd^{II}Cl$_2$(PPh$_3$)$_2$] (9.4 mol %), dry THF (6 mL), reflux. [b] k_{obsd} values are given in 10^{-3} min^{-1}.

Conclusion

In conclusion, we report a hitherto unprecedented dual role of halide anions in Stille reactions. First, halide ions can increase or decrease the transmetallation rate of the Stille reaction through in situ halide metathesis. Although the influence of the halogen present in oxidative addition complexes on the transmetallation rates with organostannanes (Cl > I) is already known, the effect of in situ halide metathesis in the oxidative addition complexes on the transmetallation rate and its application to accelerate cross-coupling reactions with organometallic reagents was not shown yet. The second role of halide ions is the stabilization of the [$Pd^0(PPh_3)_2$] catalyst. No reports on the prevention of leaching of catalyst from the catalytic cycle by [$Pd^0X(PPh_3)_2$]$^-$ formation have been published yet. While the rate of cross-coupling reactions is hitherto typically altered by modifying the ligands of the catalyst, our results clearly show that keeping the concentration of Pd^0 catalyst in the catalytic cycle high is at least as important for the overall rate, but has been hitherto largely neglected in ligated catalyst systems.

Experimental Section

Typical procedure for the kinetic experiments: A two-necked round-bottomed flask was charged with 2-haloazine or iodobenzene (2.54 mmol), [$PdCl_2(PPh_3)_2$] (0.168 g, 0.24 mmol), organostannane (3.5 mmol), LiCl or LiI (7.65 mmol) and dry THF (6 mL). After flushing with nitrogen for 5 min at room temperature, the reaction mixture was heated under reflux in a preheated oil bath under vigorous magnetic stirring (oil bath temperature 85 °C; N_2 atmosphere). A sample was taken at appropriate time intervals with a GC syringe. Herewith 10 µL fluid was taken from the flask through a septum, brought into a 10 mL volumetric flask and immediately diluted with acetonitrile (HPLC grade solvent). The solutions were filtered (0.2 mm; Nylon) and subsequently analyzed with HPLC-UV. The percentage reaction product was determined by dividing the HPLC peak area of the reaction product by the sum of the peak areas of the starting material and reaction product (after a correction factor on the peak areas, based on the difference in extinction coefficient of the starting material and reaction product at the used wavelength (254 nm), has been taken into account). The k_{obsd} values were determined in the first 45 min of the reactions. Remark: kinetic data were very sensitive to precatalyst quality. When using a different batch of precatalyst, even from the same supplier, different experimental data were obtained. It is therefore essential to compare only data obtained using precatalyst from the same lot.

Chromatographic conditions: The analytical column (Econosphere, C18, 5 µm particles, 250 mm × 4.6 mm) was purchased from Grace (Alltech). The HPLC analysis was executed using a gradient elution of 50:50 (v/v) H_2O/CH_3CN to 100 % CH_3CN in 23 min at a flow rate of 1 mL min^{-1}.

Calculation of theoretical conversion versus time curves: Theoretical conversion curves were calculated by using the k_{obsd} value, derived from the experimental data points of the first 45 min of the reaction. ($X_{A,t}$ = experimental molar fraction of starting material A at time t; $X_{B,t}$ = theoretical molar fraction of reaction product B at time t; see chart).

$$A \xrightarrow{k_{obsd}} B$$

$$\ln X_{A,t} = -k_{obsd}\, t \xRightarrow[\substack{\text{conversion vs. time}\\ \text{in first 45 min}}]{\text{experimental data}} k_{obsd} \xRightarrow[\substack{\text{conversion vs time}\\ \text{with } k_{obsd}}]{\text{calculate}} X_{B,t} = 1\text{-}e^{-k_{obsd}\, t}$$

General procedure for the cyclic voltammetry: Experiments were carried out in a three-electrode thermostated cell (20 °C) connected to a Schlenk line. The reference was a saturated calomel electrode separated from the solution by a bridge filled with THF (1.5 mL) containing $n\mathrm{Bu_4NBF_4}$ (0.3 M). The counter electrode was a platinum wire of about 1 cm^2 apparent surface area. THF (12 mL) containing $n\mathrm{Bu_4NBF_4}$ (0.3 M) was introduced into the cell followed by [$PdCl_2(PPh_3)_2$] (16.3 mg, 0.023 mmol). Cyclic voltammetry was performed at a steady gold disk electrode (d = 1 mm) at a scan rate of 0.5 V s^{-1}. Compound **2** (147.4 µL, 0.465 mmol) was then added to the cell. Cyclic voltammetry was performed as a function of time towards reduction potentials to observe the evolution of [$PdCl_2(PPh_3)_2$] and [$Pd(Th)_2(PPh_3)_2$]. Concomitantly, cyclic voltammetry was performed towards oxidation potentials to observe the in situ formation of Pd^0 complex. Similar experiments were performed but in the presence of $n\mathrm{Bu_4NCl}$ (60 mg, 0.216 mmol) added to [$PdCl_2(PPh_3)_2$] before **2**.

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