Stille Coupling

Stille Coupling Made Easier—The Synergic Effect of Copper(I) Salts and the Fluoride Ion**

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The union of two trigonal carbon centers through the Stille coupling[1] is a versatile process which has found numerous applications in organic synthesis. However the reaction between an aryl or vinyl halide/triflate and an organostannane under palladium catalysis sometimes presents difficulties.[2] The choice of catalyst, ligands, additives, solvent, and temperature can substantially affect the outcome and yield of the reaction.

We encountered a difficult Stille reaction in the course of a recent natural product synthesis,[3] a reaction which was very low yielding under typical conditions. After extensive optimization studies we discovered a combination of co-reagents that has proven to be remarkably effective in promoting the Stille reaction, that is, a copper(I) salt in conjunction with fluoride ions.

The beneficial effect of Cu^I salts in the Stille coupling is well documented[4–7] and it is believed that the function

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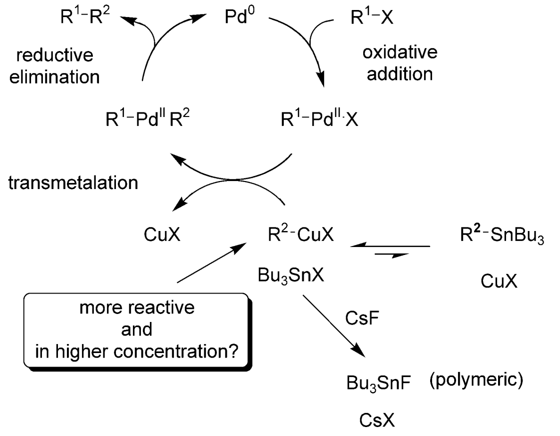
performed by the Cu^I salt in the catalytic cycle is solvent dependent.[5] In ethereal solvents such as THF and dioxane, the proposed role of Cu^I is as a scavenger for free neutral ligand that otherwise causes autoretardation of the rate-determining associative transmetalation.[5,6] However in highly polar solvents such as *N*-methylpyrrolidone (NMP) and DMF, the rate-accelerating effect of Cu^I has been attributed to a preliminary transmetalation reaction from the organostannane to generate a more reactive organocopper intermediate, which then takes part in the catalytic cycle.[6,7] Stille and Scott have observed previously that the fluoride ion increases the rate of the palladium-catalyzed coupling reaction between vinyl triflates and organostannanes.[8] It was also noted that the Bu_3SnCl by-product could be efficiently transformed into insoluble Bu_3SnF, which could be removed from the reaction mixture by filtration. More recently others have also employed the fluoride ion to enhance the Stille reaction.[9–11,16]

On this basis we hypothesized that if the preliminary transmetalation between the organostannane and CuI did exist and it was in equilibrium, then removal of the Bu_3SnI by-product as insoluble Bu_3SnF should favor the formation of the more reactive organocopper species, resulting in enhancement of the reaction (Scheme 1). To our knowledge, the tandem use of CuI and CsF to promote the Stille reaction has not been reported.

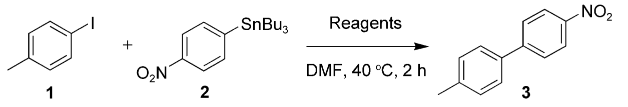


Scheme 1. Hypothesis leading to the investigation of the simultaneous use of copper(I) and fluoride in the Stille reaction.

We emphasize here that Scheme 1 presents an outline of our hypothesis. Detailed mechanistic studies will be required to determine the precise role of copper(I) and fluoride in the Stille reaction. This is beyond the scope of our current investigation; nonetheless the improvement they afford is significant however it comes about.

To investigate the effect of CuI and CsF on the Stille reaction we chose to couple 4-iodotoluene (**1**) and a deactivated electron-deficient aryl stannane, 4-(tri-*n*-butylstannyl)nitrobenzene (**2**), as a model reaction. Since **1** would be expected to undergo facile oxidative addition,[12] any variation in the rate and yield of this reaction should reflect the relative ease of the transmetalation step involving organostannane **2**. A series of reactions were carried out to determine the individual effects of CuI and CsF and then the combined effect of these two additives on this coupling reaction (Table 1).

Table 1: The individual and combined effects of CuI and CsF on the coupling of **1** and **2**.



Entry	Reagents[a]	Yield [%][b]
1	$[Pd(PPh_3)_4]$	2
2	$[Pd(PPh_3)_4]$, CsF	8
3	$[Pd(PPh_3)_4]$, CuI	46
4	$[Pd(PPh_3)_4]$, CsF and CuI	98
5	CsF and CuI	0

[a] $[Pd(PPh_3)_4]$ (10%), CuI (20%), CsF (2.0 equiv). [b] Yields are isolated yields of **3** and are the average of two repeat experiments. Remaining mass balance is recovered starting materials.

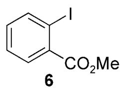
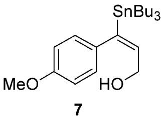
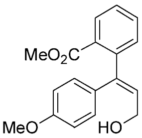
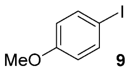
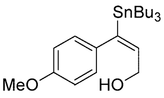
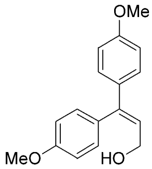
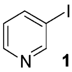
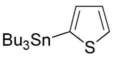
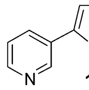
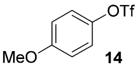
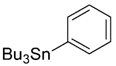
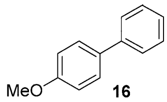
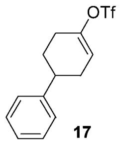
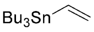
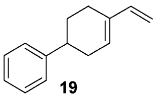
When the reaction between **1** and **2** was conducted at 40 °C for two hours using $[Pd(PPh_3)_4]$ as catalyst, only a trace of product **3** was isolated and most of the starting materials were recovered (Table 1, entry 1). The addition of CsF had a very minor positive effect on the yield of this reaction (Table 1, entry 2). A significant improvement in the yield of **3** was observed when CuI was included as an additive; the recovered starting materials again accounted for the remaining mass balance (Table 1, entry 3). When both CuI and CsF were present, the coupling reaction proceeded to completion with a near-quantitative yield of **3** (Table 1, entry 4). However no product formation was observed when the coupling between **1** and **2** was attempted with only CuI and CsF (Table 1, entry 5). This eliminated the possibility of CuI directly catalyzing the coupling of **1** and **2**.[13–15] It is clear that in the presence of palladium(0), CuI and CsF exert a synergic effect that promotes this reaction considerably.

Before exploring the scope of this combined effect, we evaluated the optimal conditions for the reaction. Variables investigated were: solvent, palladium source, ligands, fluoride source, and copper(I) source. We observed that aryl iodides and triflates undergo facile coupling with organostannanes using a mixture of $[Pd(PPh_3)_4]$/CuI/CsF in DMF (Conditions A). For the less reactive aryl bromides, the most effective reagent combination has proven to be $PdCl_2/P\textit{t}Bu_3$/CuI/CsF in DMF (Conditions B). However, in both cases these were not necessarily the only conditions that gave high yields. Highly polar solvents such as DMSO and NMP were also effective and tetrabutylammonium fluoride (TBAF) seemed comparable to CsF in enhancing the reaction, whereas other fluoride sources (LiF, NaF, KF) were less effective.

Recently Fu et al. reported a procedure for the Stille coupling that also makes use of $P\textit{t}Bu_3$.[16] To investigate whether our Conditions B provide an improvement over the procedure described by Fu et al. for the coupling of bromides, a series of reactions were carried out on the challenging coupling of electron-rich 4-bromoanisole (**4**) and electron-deficient 4-(tri-*n*-butylstannyl)nitrobenzene (**2**; Table 2).

The coupling of **4** and **2** under Conditions B afforded 92 % of the desired product **5** after 4 h at 45 °C (Table 2, entry 1). To demonstrate that CuI is necessary when using P*t*Bu$_3$ under Conditions B the coupling of **4** and **2** was repeated in the absence of CuI. After the same reaction time only 29 % of the coupled product **5** was isolated, with the remaining starting material being recovered (Table 2, entry 2). This indicates that even though Conditions B generate a coordinatively unsaturated catalytic system, CuI is still necessary to provide the highest yields. When the coupling of **4** and **2** was carried out using the reagent combination described by Fu et al.,[16] a 16 % yield of the coupled product **5** was isolated along with recovered starting materials (Table 2, entry 3). Interestingly when CuI was included in the same reaction there was a slight decrease in yield (Table 2, entry 4). This observation is supported by our optimization studies in which it was discovered that highly polar solvents are necessary to ensure the synergic effect of CuI and CsF. We also observed that PdCl$_2$ was a superior palladium source to [Pd$_2$(dba)$_3$] (dba = *trans,trans*-dibenzylideneacetone) when using DMF as the solvent.

Table 3: Scope of the combined copper(I)/fluoride effect on a variety of cross coupling reactions of iodides and triflates.

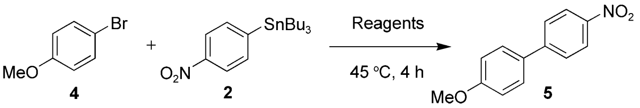
Entry	Iodide/Triflate	Stannane	Product	Conditions	Time [h]	Yield [%][a]
1	 **6**	 **7**	 **8**	A	8	92
2	 **9**	 **7**	 **10**	A	8	94
3	 **11**	 **12**	 **13**	A	1	99
4	 **14**	 **15**	 **16**	A	2	92
5	 **17**	 **18**	 **19**	A	1	98

Conditions A: [Pd(PPh$_3$)$_4$] (5 %), CuI (10 %), CsF (2 equiv), DMF, 45 °C. [a] Yields are isolated yields and are the average of two repeat experiments.

To investigate the efficiency of our new conditions we studied a number of different coupling reactions which are summarized in Table 3 and Table 4. Some of these examples were selected from the literature.

The coupling of hindered iodide **6** and hindered stannane **7** to give **8** has previously been achieved in an optimized yield of only 27 %, following reaction for 15 h at 80 °C.[17] When conducted under the new conditions, this same reaction delivered **8** in an excellent yield of 92 % (Table 3, entry 1). It is noteworthy that with Cu^I and CsF present, the reaction between **6** and **7** was complete after 6 h at just 45 °C. Similarly, reaction of iodide **9** and stannane **7** afforded **10** in 94 % yield (Table 3, entry 2), whereas the previously reported best yield of this reaction was a moderate 42 %.[17] Heterocycles are well tolerated under our coupling conditions, as demonstrated by the near-quantitative coupling of 3-iodopyridine (**11**) and 2-(tributylstannyl)thiophene (**12**; Table 3, entry 3). Organotriflates were also shown to be excellent substrates under the new conditions: reaction of deactivated triflate **14** with stannane **15** gave the coupled product **16** in 92 % yield (Table 3, entry 4), and diene **19** was obtained in 98 % yield from coupling of vinyl triflate **17** and stannane **18** (Table 3, entry 5).

Table 2: Evaluating alternative conditions on the coupling of **4** and **2**.

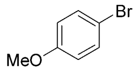
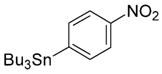
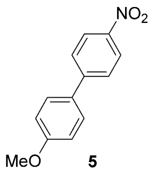
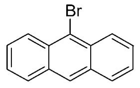
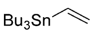
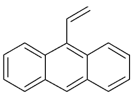
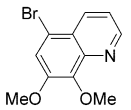
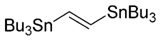
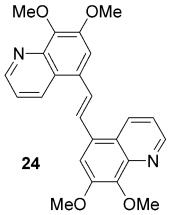
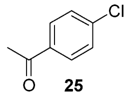
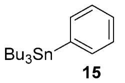
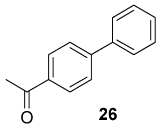
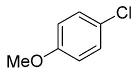
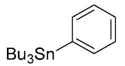
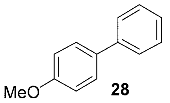


Entry	Reagents[a]	Yield [%][d]
1	PdCl$_2$, P*t*Bu$_3$, CuI, CsF, DMF[b]	92
2	PdCl$_2$, P*t*Bu$_3$, CsF, DMF	29
3	[Pd$_2$(dba)$_3$], P*t*Bu$_3$, CsF, dioxane[c]	16
4	[Pd$_2$(dba)$_3$], P*t*Bu$_3$, CuI, CsF, dioxane	10

[a] PdCl$_2$ (2 %) *or* [Pd$_2$(dba)$_3$] (1 %), P*t*Bu$_3$ (4 %), CuI (4 %), CsF (2.0 equiv). [b] Conditions B. [c] Reagent combination reported by Fu et al.[16]. [d] Yields are isolated yields and are the average of two repeat experiments. Remaining mass balance is recovered starting materials.

Coupling reactions with aryl bromides or chlorides warranted the use of PdCl$_2$/P*t*Bu$_3$/CuI/CsF (Conditions B) (Table 4). These reactions were carried out overnight for convenience, but did not necessarily require this extended reaction time. For example the electronically disfavored coupling of electron-rich bromide **4** and electron-deficient stannane **2** afforded the product **5** in 97 % yield overnight (Table 4, entry 1), however it was essentially complete after 4 h (92 %) as demonstrated above in Table 2 (entry 1). The sterically unfavorable coupling of di-*ortho*-substituted bromide **20** and stannane **18** gratifyingly provided the coupled product **21** in 96 % yield (Table 4, entry 2). This is substantially higher than the previous reported yield of 66 %,[16] although our reaction was carried out at higher temperature and for a longer time. In our hands the coupling of **20** and **18**

Table 4: Scope of the combined copper(I)/fluoride effect on a variety of cross coupling reactions of bromides and chlorides.

Entry	Bromide/Chloride	Stannane	Product	Conditions	Time [h]	Yield [%][c]
1	 **4**	 **2**	 **5**	B	15	97
2[a]	 **20**	 **18**	 **21**	B	15	96
3	 **22**	 **23**	 **24**	B	15	93
4[b]	 **25**	 **15**	 **26**	B	15	81
5[b]	 **27**	 **15**	 **28**	B	15	40–60

Conditions B: $PdCl_2$ (2%), $PtBu_3$ (4%), CuI (4%), CsF (2 equiv), DMF, 45 °C. [a] 1.3 equivalents of organostannane. [b] Reaction temperature: 100 °C. [c] Yields are isolated yields and are the average of two repeat experiments (entry 5 shows the range).

under the conditions applied by Fu and co-workers ($[Pd_2(dba)_3]$, $PtBu_3$, toluene, RT, 3 h) gave 54% of the product **21**, whereas when the reaction was repeated using our catalytic system under identical conditions (RT, 3 h) a 68% yield of the product **21** was isolated. In both cases the remaining mass balance was largely recovered starting materials. As an example of a double Stille coupling, the quinoline derivative **22** and stannane **23** were subjected to our conditions, and delivered the desired product **24** in 93% yield (Table 4, entry 3).

We have also investigated the coupling of aryl chlorides under the Cu^I/CsF conditions. With these substrates we observed that the electronic effect of the substituents on the aromatic ring of the aryl chloride has a considerable influence on the reactivity of the substrate. Reaction of electron-deficient aryl chloride **25** with stannane **15** using Conditions B at 100 °C provided **26** in a respectable 81% yield (Table 4, entry 4). However the coupling of the electron-rich chloride **27** to stannane **15**, proceeded in lower yields of 40–60% (Table 4, entry 5). In both cases, coupling of the aryl chlorides did not proceed to completion even with extended reaction times, suggesting that the catalytic system may be decomposing under the more forcing conditions. Thus our new conditions appear effective for the coupling of electron-deficient aryl chlorides, but less effective when it comes to electron-rich aryl chlorides.[18]

In summary, we have demonstrated that the combination of copper(I) iodide and cesium fluoride can significantly enhance the Stille reaction. We found that the $PdCl_2/PtBu_3$ catalytic system with copper(I) iodide and cesium fluoride in DMF is most effective for coupling aryl bromides, while $[Pd(PPh_3)_4]$ in combination with copper(I) iodide and cesium fluoride is optimal when coupling iodides and triflates. Furthermore, our conditions are mild and compatible with a variety of functional groups. This combination of copper(I) iodide and cesium fluoride should widen the scope of the Stille reaction, allowing synthesis of sterically hindered systems and promote electronically disfavored coupling reactions.[19]

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[17] F. Liron, M. Gervais, J.-F. Peyrat, M. Alami, J.-D. Brion, *Tetrahedron Lett.* **2003**, *44*, 2789–2794.

[18] For an effective method of Stille coupling using aryl chlorides, see reference [16].

[19] General experimental: A mixture of the organohalide (or triflate) (0.840 mmol) and the organotin reagent (0.930 mmol) was dissolved in DMF (2 mL), then cesium fluoride (256 mg, 1.685 mmol) was added. The palladium catalyst and copper(I) iodide [Conditions A: $[Pd(PPh_3)_4]$ (5 %), CuI (10 %); Conditions B: $PdCl_2$ (2 %), $PtBu_3$ (4 %), CuI (4 %)] were added and the flask was evacuated and refilled with argon five times. The mixture was stirred at 45 °C for the specified duration, then diluted with CH_2Cl_2 (50 mL) and water (20 mL). After vigorous shaking the mixture was filtered through celite with CH_2Cl_2/EtOAc (200 mL, 1:1). The organic layer was separated, dried over Na_2SO_4/$MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography.