

Palladium(0)-Catalyzed Amination, Stille Coupling, and Suzuki Coupling of Electron-Deficient Aryl Fluorides

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During the course of our studies on the chemistry of vascular endothelial growth factor (VEGF) inhibitors, we observed what appeared to be palladium-catalyzed amination of an aryl fluoride. Aryl fluorides, however, have long been considered inert to Pd(0)-catalyzed coupling reactions.¹ A search of the primary literature yielded only one relevant study. In 1999, Widdowson and co-workers demonstrated that η^6 -Cr(CO)₃-fluorobenzene underwent Stille and Suzuki couplings in the presence of Pd₂(dba)₃ and PMe₃ in good yields.² In this communication, we would like to report our studies on the Pd(0)-catalyzed amination, Stille coupling, and Suzuki coupling of electron-deficient aryl fluorides.

Palladium-catalyzed amination was chosen as the initial reaction for investigation, because it is a well-studied transformation³ and known to be Pd(0) catalyzed. The major drawback of this choice is the background reaction, that is, the amination via the thermal nucleophilic aromatic substitution. Gratifyingly, it was found that the reaction between 4-*tert*-butylaniline and 2-fluoronitrobenzene was a good system for investigation, because the thermal S_NAr reactivity was low in the temperature range from 60 to 80 °C. Under these conditions, the S_NAr reaction gave no more than 7% of the product in a 24 h period, the mass balance being the recovered starting materials. This opened a window to study the palladium-catalyzed amination.

Accordingly, 4-*tert*-butylaniline (1.5 equiv), 2-fluoronitrobenzene (1.0 equiv), and Cs₂CO₃ (1.4 equiv) were heated at 65 °C in DMF in the presence of a variety of palladium catalyst systems for 24 h, and the HPLC integration percentage areas of the product as well as the unreacted starting material(s) were recorded and examined. As shown in Figure 1, it can be seen that the extent of the amination was dependent on the presence and identity of the palladium catalyst system. For instance, in the presence of Pd(PPh₃)₄ or Pd₂(dba)₃/2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)-biphenyl,^{3a} the reactions showed facile conversion to diarylamines, while in the absence of the catalyst, only very little conversion had occurred. These results indicated that this amination is both Pd(0) catalyzed and ligand-dependent.

To gain more insight into the matter, a set of control experiments was required. As shown in Figure 2, the palladium-catalyzed amination was conducted in parallel with four controls, that is, (i) the thermal reaction (neither Pd nor the ligand was present), (ii) in the presence of the ligand alone (no Pd was present), (iii) in the presence of the Pd(0) source alone (no ligand was present), and (iv) in the presence of Pd(II). As can be easily seen from the graphs, PPh₃ alone or Pd(II) alone did not effectively promote the amination. Pd(0) in the form of Pd₂(dba)₃ did promote the amination, although far less effectively than Pd(PPh₃)₄. Among the five experiments conducted, Pd(PPh₃)₄ stood out as the most effective catalyst for the amination reaction. These results suggest that the amination is not Pd(II) catalyzed. Rather, it is Pd(0) catalyzed, and the catalyst performs best when an appropriate ligand is present.

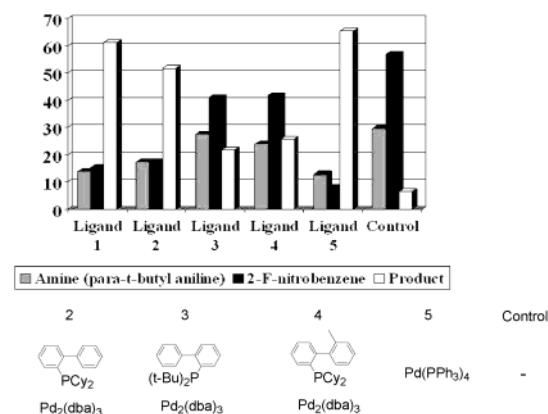
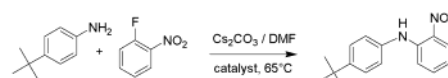


Figure 1. Amination in the presence of different catalysts (HPLC yields).

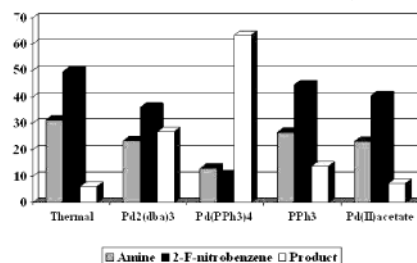
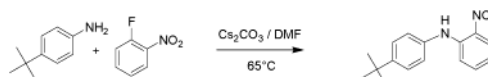
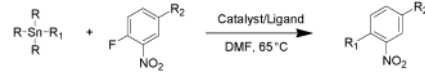


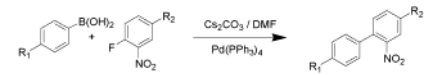
Figure 2. Amination under control conditions (HPLC).

Another Pd(0)-mediated coupling reaction investigated was the Stille coupling.⁴ Unlike amination or Suzuki coupling, where the presence of a base (such as Cs₂CO₃) is required, Stille coupling is normally conducted under neutral conditions. When the highly reactive trimethylphenyltin and 2-fluoronitrobenzene were heated at 65 °C in DMF in the presence of 10% Pd(PPh₃)₄, no Stille coupling product was detected.⁵ However, when both the ortho- and the para-positions of the fluorobenzene were occupied by electron-withdrawing groups, the Stille coupling proceeded smoothly even with the less reactive (also less toxic) tributyltin compounds. As shown in Table 1, when the activated aryl fluorides (entries 2, 4–6)⁶ were heated with tributylphenyltin or tributylvinyltin at 65 °C in the presence of Pd(PPh₃)₄, the expected Stille coupling products formed in moderate yields. In the absence of palladium, PPh₃ alone did not catalyze the reaction, and no coupling product was detected (see entry 3 in Table 1). Considering that the reaction conditions were not optimized, the ease of these reactions is

Table 1. Stille Coupling of Aryl Fluorides^a


#	R	R ₁	R ₂	catalyst/ligand	isolated yield
1	methyl	phenyl	H	Pd(PPh ₃) ₄ , 10%	—
2	butyl	phenyl	CN	Pd(PPh ₃) ₄ , 10%	56
3	butyl	phenyl	CN	PPh ₃ , 40%	—
4	butyl	vinyl	CN	Pd(PPh ₃) ₄ , 10%	28
5	butyl	phenyl	CHO	Pd(PPh ₃) ₄ , 10%	65
6	butyl	vinyl	CHO	Pd(PPh ₃) ₄ , 10%	45

^a The reactions were carried out using 2.7 mmol of the tin compound, 4.0 mmol (1.5 equiv) of aryl fluoride, and 10 mol % Pd(PPh₃)₄ in 25 mL of DMF. The reaction mixtures were degassed three times by alternately connecting to the house vacuum and nitrogen prior to heating.

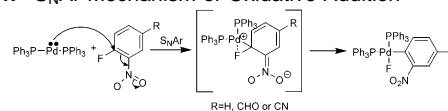
Table 2. Suzuki Coupling of Aryl Fluorides^a


#	R ₁	R ₂	ligand	catalyst	temp (°C)	isolated yield
1	H	CN		Pd(PPh ₃) ₄ , 10%	80	64
2	H	CHO		Pd(PPh ₃) ₄ , 10%	80	86
3	H	CHO			80	—
4	H	CHO	PPh ₃ , 40%		80	—
5	H	CHO		Pd ₂ (dba) ₃ , 5%	80	—
6	OMe	CN		Pd(PPh ₃) ₄ , 10%	65	49
7	OMe	CHO		Pd(PPh ₃) ₄ , 10%	65	33
8	OMe	CHO			65	—
9	OMe	CHO	PPh ₃ , 40%		65	—
10	OMe	CHO		Pd ₂ (dba) ₃ , 5%	65	—

^a The reactions were carried out using 2.7 mmol of boronic acid, 4.0 mmol (1.5 equiv) of aryl fluoride, 3.7 mmol of Cs₂CO₃ in 25 mL of DMF; the amounts of the catalyst, ligand, and temperature are indicated in the table. The reaction mixtures were degassed three times by alternately connecting to the house vacuum and nitrogen prior to heating.

remarkable. In these reactions, the palladium was introduced as Pd(0). Because it has been well documented in the literature that in Stille couplings organotin compounds reduce Pd(II) to Pd(0),⁴ the presence of Pd(II) in these reactions is unlikely. Consequently, the Stille couplings listed in Table 1 are probably Pd(0) catalyzed.

The third reaction investigated was the Suzuki coupling. When the highly activated 4-methoxyphenylboronic acid and 2-fluoro-nitrobenzene were subjected to the conditions of the amination reaction [Pd(PPh₃)₄, Cs₂CO₃, DMF, 65 °C], the expected Suzuki coupling product was detected by LC/MS, although the conversion was no more than 20%.⁵ Reasoning that electron-withdrawing groups would favor the desired process,^{3e,f} aryl fluorides that bear strong electron-withdrawing groups at both the ortho- and the para-positions (see Table 1) were subjected to Suzuki⁴ coupling reactions with phenyl boronic acid and 4-methoxy-phenylboronic acid. The results are summarized in Table 2. In the presence of Pd(PPh₃)₄, all four reactions (entries 1, 2, 6, 7 in Table 2) afforded the Suzuki coupling product, in 33–86% yield. In the control reactions (entries 3–5, 8–10), no Suzuki product was detected by HPLC. Because boronic acids are also capable of reducing Pd(II) to Pd(0), the presence of Pd(II) in these reactions is not likely. These results further suggest Pd(0) catalysis.

Scheme 1. S_NAr Mechanism of Oxidative Addition

In summary, when activated by strong electron-withdrawing group(s), aryl fluorides are capable of undergoing Pd(0)-catalyzed amination, Stille coupling, and Suzuki coupling. The mechanism of these reactions is not known with certainty; notwithstanding, the experimental data appeared to converge on the oxidative addition/reductive elimination pathway. Oxidative addition does not have to proceed via a concerted mechanism. In the cases of electron-deficient aryl fluorides, the Pd(0) species may act as a nucleophile and displace the fluoride in an S_NAr manner to form the carbon–palladium bond, as suggested by Amatore and others,^{2,7a,b} (Scheme 1). The fact that a second electron-withdrawing group is only required for Stille and Suzuki reactions (but not amination) implied that oxidative addition is perhaps not even rate determining for these processes (electron-withdrawing groups do accelerate reductive elimination^{3e,f}). The details of the mechanism and the full scope of these reactions, as well as other palladium-catalyzed coupling reactions, are under investigation in our laboratories, and the results will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all of the new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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