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Palladium-Catalyzed Stille Cross-Coupling Reaction of Aryl Chlorides using a Pre-Milled Palladium Acetate and XPhos Catalyst System

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This paper is dedicated to our good friend Andreas Pfaltz on the occasion of his 60th birthday and in recognition of his numerous seminal contributions to the field of organic chemistry.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

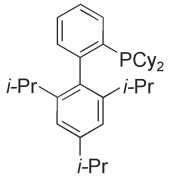
Abstract: A highly active catalyst system based upon a biaryl monophosphine ligand, XPhos, for the palladium-catalyzed Stille reaction has been developed. This method allows for the coupling of aryl chlorides with a range of tributylarylstannanes to produce the corresponding biaryl compounds in good to excellent yields (61–98%) in short reaction times (4 h). Palladium(II) acetate [$Pd(OAc)_2$] and XPhos in a 1:1.1 ratio were milled into a fine powder that was used as pre-catalyst for these reactions.

Keywords: aryl chlorides; biaryls; C–C coupling; palladium; phosphine ligands; Stille reaction

The Stille cross-coupling reaction has proven to be a powerful method for combining aryl halides and arylstannanes to give a ready access to biaryl motifs,[1] which are found in numerous biologically active compounds including both natural products and pharmaceutically interesting molecules.[2] Recent advances in the general area of cross-coupling have led to the development of highly active catalyst systems that were capable of transforming aryl chlorides, which are less expensive and more readily available than aryl iodides and bromides.[1f] While considerable research has been devoted to the Suzuki–Miyaura reaction,[1f,3] there have been fewer reports of catalytic methods for the reaction of aryl chlorides with organostannanes.[4] Although the tin by-products generated in the Stille reaction tend to have relatively high molecular weights and are toxic, the air- and moisture-stability of organostannanes combined with the broad functional group tolerance of the Stille reaction ensures its continued relevance, particularly as a tool for discovery chemists[5] and in natural product synthesis.[6] Herein, we describe a highly active catalyst system for the coupling of aryl chlorides with arylstannanes.

A family of air-stable biaryl monophosphine ligands has been developed in our laboratories and have proven useful as components of highly active catalyst systems for C–C and C–N bond-forming reactions.[3b,c,7] Based on previous work in our group and initial screening results, XPhos (Figure 1) was chosen as a supporting ligand and was combined with $Pd(OAc)_2$ to generate a highly active catalyst system that was used for further optimization.

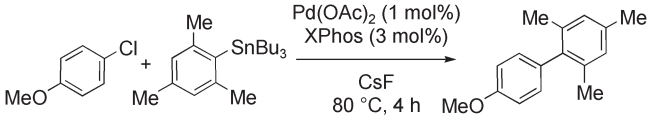
Recent work has shown that the addition of a fluoride source increases the reactivity of arylstannanes and results in a significant rate enhancement.[4a–c,f–h] While the use of TBAF and KF provided moderate results, CsF provided the greatest enhancement in the reaction rate (Table 1, entries 1–4). A further optimization showed that reactions in ethereal solvents or *tert*-butanol provided the desired biaryl in a greater yield. Dimethoxyethane (DME) was chosen over *tert*-butanol as the solvent for further studies due to the high melting point of *tert*-butanol. We found that very similar results were obtained with ligand:Pd ratios of 1:1, 2:1 and 3:1, thus reactions were conduct-



XPhos

Figure 1.

Table 1. Screen of solvents for the palladium-catalyzed cross-coupling of 4-chloroanisole and mesitylstannane.[a]



Entry	Solvent	CsF [equiv.]	Conv. [%]	Yield [%][b]
1	toluene	0.0	13	0
2	toluene	1.0	47	33
3	toluene	2.0	76	67
4	toluene	2.2	80	70
5	DCE	2.2	53	38
6	NMP	2.2	89	73
7	*n*-butanol	2.2	100	33
8	*t*-butanol	2.2	100	100
9	DEM	2.2	100	91
10	1,4-dioxane	2.2	100	92
11	DME	2.2	100	100

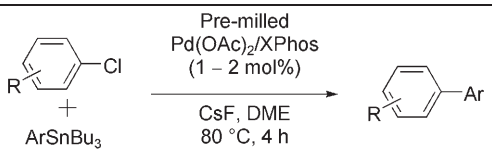
[a] *Reaction conditions:* 1.0 equiv of Ar-Cl, 1.1 equiv of (*n*-Bu)$_3$Sn-Ar, 1.0 mol% of Pd(OAc)$_2$, 3.0 mol% of XPhos, 1.0 mL of solvent/mmol of Ar-Cl, DCE = 1,2-dichloroethane, NMP = *N*-methylpyrrolidine, DME = dimethoxyethane, DEM = diethoxymethane.

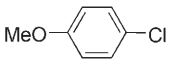
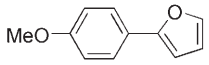
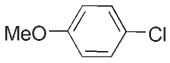
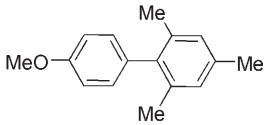
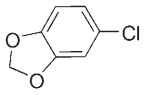
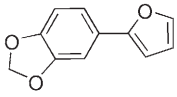
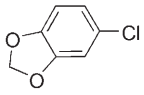
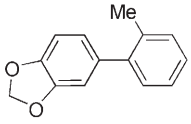
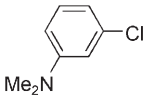
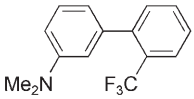
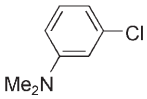
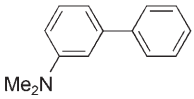
[b] GC Yield.

ed with only a slight excess of ligand (1.1:1, L:Pd). A mixture of palladium acetate and XPhos, in the aforementioned ratio, was milled with a mortar and pestle to give a fine, beige powder that was used in subsequent reactions. The milling process allowed for excellent control of the palladium to ligand ratio and facilitated precision when weighing samples for reactions. The results of reaction run with the powder were identical to those performed with separate Pd(OAc)$_2$ and XPhos (Table 2, entries 4 and 5) and the powder could be stored in a benchtop dessicator with no loss of activity over a six-month period.

Encouraged by these results, we sought to examine the scope of this process. The results are shown in Table 2. These conditions constitute the lowest temperature reactions and shortest reaction times reported for the coupling of unactivated aryl chlorides with arylstannanes reported to date. Chloroanilines, as a class of compounds, have not previously been used to generate biaryl compounds *via* the Stille reaction.[8] One example of this class of compounds, *N,N*-dimethyl-3-chloroaniline, using our conditions, was successfully coupled with a both aryl- and heteroarylstannanes (Table 2, entries 5 and 6). Similarly, while 4-chloroanisole has been combined with arylstannanes, the best reported conditions required that the reactions be conducted at 100 °C for 48 h.[4a,c] Employing our catalyst system this substrate, in combination with both a hindered arylstannane and a heteroarylstannane, provided excellent yields of product in 4 h at 80 °C (Table 2, entries 1 and 2). Additionally, 5-

Table 2. Stille cross-coupling reactions of unactivated aryl chlorides and deactivated chlorides.[a]



Entry	Aryl Chloride	Product	Yield [%][b]
1			97[c]
2			96
3			97
4			94
5			95[d]
6			89[c]
7			90[c]

[a] *Reactions conditions:* 1.0 equiv of Ar-Cl, 1.1 equiv of (*n*-Bu)$_3$Sn-Ar, 2.2 equiv of CsF, 1.0 mol% of pre-milled Pd(OAc)$_2$:XPhos (1:1.1), 1.0 mL of DME/mmol of Ar-Cl.

[b] Isolated yields (average of two runs).

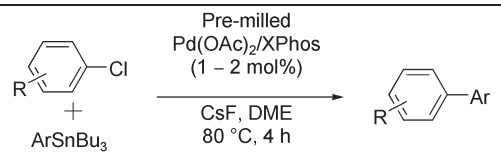
[c] 2.0 mol% of pre-milled Pd(OAc)$_2$:XPhos (1:1.1)

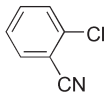
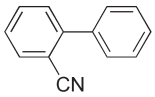
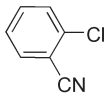
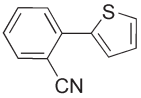
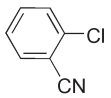
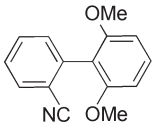
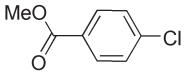
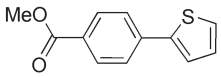
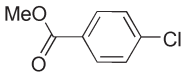
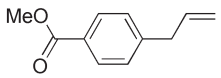
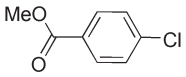
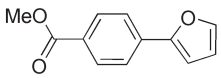
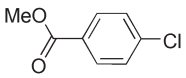
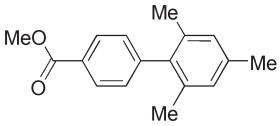
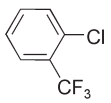
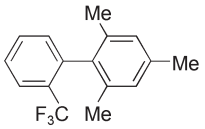
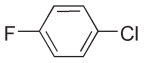
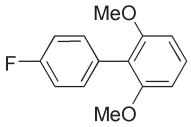
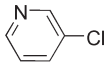
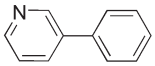
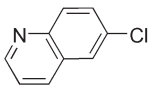
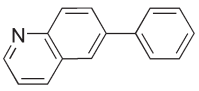
[d] 1.0 mol% Pd(OAc)$_2$ and 1.1 mol% XPhos added as separate solids.

chlorobenzo[*d*][1,3]dioxole (Table 2, entries 3 and 4), could be coupled in excellent yields with both aryl- and heteroarylstannanes. Previously, this substrate has been used in the Stille reaction to form a biaryl in only one other instance in which longer reaction times and higher temperatures (45 h and 110 °C) were required.[4h]

While the results in Table 3 do not represent the lowest temperature reaction conditions reported for Stille reactions with activated aryl chlorides,[9] they do represent a significant decrease over most of the reaction times reported and one of lowest operating temperatures of available Stille methods with these substrates. For instance, the coupling 2-chlorobenzonitrile has been previously reported at temperatures greater than 100 °C with reaction times longer than 24 h.[4h,10] By using our standard protocol, 2-chlorobenzonitrile was efficiently coupled with aryl, heteroaryl and electron-rich arylstannanes (Table 3, entries 1–3). En-

Table 3. Stille cross-coupling reactions of aryl chlorides and heteroaryl chlorides.[a]



Entry	Aryl Chloride	Product	Yield [%][b]
1			86
2			92
3			74
4			91
5			84
6			97
7			96
8			61[c]
9			93[c]
10			92[d]
11			98[d]

[a] *Reactions conditions:* 1.0 equiv of Ar-Cl, 1.1 equiv of (n-Bu)$_3$Sn-Ar, 2.2 equiv of CsF, 1.0 mol% of pre-milled Pd(OAc)$_2$:XPhos (1:1.1), 1.0 mL of DME/mmol of Ar-Cl.

[b] Isolated yields (average of two runs).

[c] 2.0 mol% of pre-milled Pd(OAc)$_2$:XPhos (1:1.1).

[d] Reactions run in dioxane at 100 °C, with 2.0 mol% pre-milled Pd(OAc)$_2$:XPhos (1:3).

tries 4–7 of Table 3 show coupling reactions with methyl 4-chlorobenzoate and a variety of stannanes including allyl, heteroaryl and sterically-demanding arylstannanes. While the importance of fluorinated aromatic rings in pharmaceutically active compounds as a means to alter a molecule′s pharmacokinetics is well known,[11] examples of Stille reactions of fluoride-containing aryl chlorides are relatively scarce. In the lone example of coupling an aryl chloride with an *ortho*-trifluoromethyl group, the process was carried out at for 48 h at 150 °C;[12] only one example was found for a Stille coupling of fluorinated aryl chlorides.[13] By using our conditions, both *o*-chlorobenzotrifluoride and *p*-fluorochlorobenzene could be efficiently coupled with arylstannanes (Table 3, entries 8 and 9). Additionally, we found that by increasing the reaction temperature to 100 °C and choosing 1,4-dioxane as a solvent to accommodate the increased temperature, it was possible to couple heteroaryl chlorides (Table 3, entries 10 and 11) with tributyl(phenyl)stannane.[14]

With regard to the arylstannane component: heteroaryl (Table 2, entries 1 and 3, Table 3, entries 2, 4 and 6), electron-rich aryl (Table 3, entries 3 and 9), electron-deficient aryl (Table 2, entry 6) and allylstannanes (Table 3, entry 5) were all coupled in high yields. It is noteworthy to mention that 2,6-dimethoxyphenyltributylstannane, which has not previously been used in Stille cross-coupling reactions,[15] was found to perform well under our conditions (Table 3, entries 3 and 9).

In conclusion, we have developed a highly active catalyst system for the reaction of a diverse range of aryl chlorides with a variety of arylstannanes. The use of CsF as an activator allows for a reduction of the temperatures commonly used in Stille reactions, and the use of ethereal solvents such as DME along with XPhos as a ligand allow for the reduction of the reaction times regularly used in these reactions.

Experimental Section

Catalyst System

Palladium acetate (225 mg, 1.00 mmol) and XPhos (524 mg, 1.10 mmol) were ground together using a mortar and pestle until a fine beige powder was formed. This powder (effective molecular weight: 749 g mol^{-1}) was stored in a benchtop dessicator for up to six months with no loss of activity and was used as the pre-catalyst for all reactions described in this paper.

N,N-Dimethyl-2′-(trifluoromethyl)biphenyl-3-amine (Table 2, entry 5)

Pre-milled palladium acetate and XPhos (15.0 mg, 2.0 mol%) and cesium fluoride (334 mg, 2.20 mmol) were added to an oven-dried test tube. The tube was fitted with a rubber

septum, sealed with electrical tape, and evacuated and backfilled with argon (this process was repeated a total of 3 times). Dimethoxyethane (DME, 1.0 mL), 3-chloro-*N,N*-dimethylaniline (137 μL, 1.00 mmol) and tributyl[2-(trifluoromethyl)phenyl]stannane (389 μL, 1.10 mmol) were added *via* syringe to the tube. The reaction was heated to 80 °C with stirring for 4 h. At this time the reaction vessel was removed from the oil bath, allowed to cool to room temperature, diluted with ethyl acetate (5 mL) and filtered through a pad of silica gel eluting with ethyl acetate (150 mL). The solvent was removed with the aid of a rotary evaporator, and the residue was taken up in dichloromethane (20 mL) and added to silica gel (~1 g). The solvent was concentrated under reduced pressure and the residue (adsorbed on silica) was loaded onto the top of a Biotage 25M column and purified by flash chromatography using a Biotage SP4 to provide the titled compound as pale yellow oil; yield: 229 mg (87%).

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