Copper(I)-Promoted Palladium-Catalyzed Cross-Coupling of Unsaturated Tri-*n*-butylstannane with Heteroaromatic Thioether

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ABSTRACT



Palladium-catalyzed cross-coupling of vinyl- and arylstannanes with π -electron-deficient heteroaromatics was performed in good yields. This Stille-type reaction was carried out with a methylthioether function as an electrophile in the presence of a copper(I) bromide-dimethyl sulfide complex.

The discovery of new, efficient methods for the construction of carbon–carbon bonds represents an ongoing, central theme of research in the area of organic synthesis. In this context, the palladium-catalyzed cross-coupling of organometallic reagents with aryl or vinyl halides and triflates has become an attractive method.¹ Unfortunately, halides or triflates might be of limited availability and/or stability, especially in the heteroaromatic series. Consequently, recent reports have dealt with the discovery of new electrophiles for this type of reaction:² Liebeskind and Srogl have developed a palladium-catalyzed boronic acid–thioether cross-coupling protocol mediated by copper(I) carboxylate.³ Extension of this method has been reported for heteroaromatic derivatives.⁴

Considering the advantages of using trialkylorganotin species [for example, they are readily available (especially alkenyl and heteroaromatic stannanes)],⁵ we investigated a

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new type of electrophile for the Stille reaction. In this communication, we present our first results of a palladiumcatalyzed coupling reaction between stannanes and electronpoor heteroaromatic derivatives bearing a thiomethyl ether function as a leaving group.

Initially, we examined the cross-coupling of 3-methylthiotriazine $1a^6$ with the commercially available 2-tributylstannylfuran 2a. A series of experiments was performed to evaluate the feasibility of the carbon–carbon bond formation and to identify the best coupling agents. The results are shown in Table 1. By analogy with the cross-coupling

Table 1.	Influence of (Copper Cofactor	and	Palladium	Catalyst
on the Cro	ss-Coupling F	Reaction			

N N 1a	$\frac{1}{SMe} + \frac{0}{2a}$	"Pd" cofac -SnBu ₃ cofac	cat., ctor N 3a	Ď	
		Pd catalyst	reaction time	yield	
entry	cofactor/equiv	(5 %)	(h)	(%)	
1	CuMeSal/2.2	Pd(PPh ₃) ₄	24	60	
2	CuI/2.2	Pd(PPh ₃) ₄	48	50	
3	CuBr·Me ₂ S/2.2	Pd(PPh ₃) ₄	16	90	
4	CuBr·Me ₂ S/0.2	Pd(PPh ₃) ₄	48	15	
5	CuBr/2.2	Pd(PPh ₃) ₄	9	60	
6	CuBr/2.2		48	0 ^{<i>a</i>}	
7		Pd(PPh ₃) ₄	48	0 ^a	
8	CuBr·Me ₂ S/2.2	PdCl ₂ (PPh ₃) ₂	48	74	
^a Only starting material was recovered.					

reaction between thioether and boronic acids,⁴ we first used copper(I) methylsalicylate as a cofactor in the presence of Pd(PPh₃)₄ in boiling THF. Thus, we isolated the coupled product in 60% yield. In the mechanism proposed by Liebeskind and Srogl, the carboxylate counterion of the copper is clearly important in facilitating transmetalation from boron, possibly through direct coordination to trivalent boron.3b In the Stille mechanism, it is not essential (even if it can be helpful)^{1e,7} to go through a pentacoordinate tin intermediate for the transmetalation step.8 Indeed, in the presence of 2.2 equiv of CuBr·Me₂S (or CuBr, entry 3 or 5), compound 3a was obtained in 90% (or 60%) yield. Using CuI made the cross-coupling less effective. Compound 3a was isolated in only 50% yield, and starting triazine 1a was recovered in 10% yield (entry 2). Palladium catalyst and a stoichiometric amount of copper(I) are essential for the success of the reaction (entries 4, 6, and 7). Another source of palladium catalyst [PdCl₂(PPh₃)₂] was used, but the reaction was slightly slower (entry 8).

Results for different stannanes and π -deficient heteroaromatics are depicted in Table 2. Methylthiotriazine **1a** reacted

Table 2.	Copper(I)-Promoted Palladium-Catalyzed
Cross-Cou	pling of Organostannanes with Heteroaromatic
Thioethers	a^{a}

	thiomethyl- ether	organo- stannanes	time (h)	product	yield (%)
1	N ^N N N SMe 1a	∑ _{SnBu₃} 2b	5	^N ^N N Sh	90
2	1a	O ₂ N SnBu ₃	24		80
3 ^ь	1a	SnBu ₃	48	3c	92
4 ^{b. c}	1a	MeO SnBu ₃	48	3d	80
5"	1 a	∠e NSnBu₃ 2f	48	3e	60
6 [°]	1a	29 ^d	9	3f	60
7°	Ib	-s 2a	48	3g	95
8 ^ь	1b	2c	48		62
9 ^ь	SMe SSMe ■	2a	3	$3i$ $s \rightarrow 0$ $3i$	81
10 ^b	1c	2g	6		70
11	1c	L_ _{SnBu₃} 2h	48	3k	36°

^{*a*} Thioether (0.78 mmol), organostannane (1.7 mmol), and CuBr•Me₂S (1.7 mmol) were dissolved in THF (6 mL). After the vessel was flushed with argon, Pd(PPh₃)₄ (5 mol %) was added and the reaction mixture was stirred at reflux. ^{*b*} Reaction was performed in boiling DME instead of THF. ^{*c*} Used 10 mol % Pd(PPh₃)₄. ^{*d*} Compound **2g** was prepared regio- and stereospecifically by reacting Bu₃Sn(Bu)CuCNLi₂ with phenylacetylene in THF at -78 °C. ^{*c*} Low yield was obtained because of the instability of compound **3l**.

rapidly with electron-poor arylstannanes **2b** and **2c** to give compounds **3b** and **3c**, respectively, in high yields (entries 1 and 2). With less reactive stannanes, reaction was completed within 48 h in boiling DME, and for the electronrich arylstannane **2e**, 10 mol % Pd(PPh₃)₄ was necessary (entry 4). This method was successfully applied to vinylstannane **2g** to produce **3g** in good yield with total retention of stereochemistry of the organostannane (entry 6). Extension of the reaction to methylthiopyrimidine **1b** and methylthiobenzothiazole **1c** was successful, and compounds **3h**–**j**

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(from arylstannanes, entries 7–9) as well as compounds **3k**,**l** (from vinylstannanes, entries 10 and 11) were obtained in good yields. From a mechanistic point of view, copper could take part at two stages as reported in Scheme 1.

First, we believe that the oxidative addition of heteroarylmethylthioether to palladium is enhanced in weaker Csp²–S bonds^{3c,4,2f} independent of the presence of copper(I) (**I**, Scheme 1). Indeed, when 5-furyl-3-methylthio-1,2,4-triazine was treated with *p*-methoxyphenylmagnesium bromide in THF with 5 mol % PdCl₂(dppf) for 24 h, we isolated 30% of 5-furyl-3-*p*-methoxyphenyl-1,2,4-triazine suggesting that copper was not essential for the oxidative addition of arylthioether to palladium.⁹ However, as suggested by Liebeskind^{3c} in the palladium-catalyzed cross-coupling reaction between boronic acids and sulfur-containing species, copper could polarize the Pd–S bond through Cu(I) coordination to S (**II**, Scheme 1) to ease the rate-determining transmetalation step.

Second, since 1990, the beneficial influence of cocatalytic Cu(I) on the cross-coupling reaction has been extensively used and mechanistic studies suggest the partial transmetalation from tin to copper.¹⁰ This transmetalation would also

be the cause of the intramolecular oxidative coupling of alkenyltrimethylstannane functions.¹¹

Surprisingly, in our case we never observed this rapid (less than 1 h) oxidative homocoupling reaction between stannanes. This observation was, a priori, in contrast with the transmetalation of tin to copper postulated by Piers.¹¹ In fact, when treating 2-tributylstannylthiophene **2b** with 2.5 equiv of CuBr•Me₂S in DMF for 5 h (Piers' conditions), we have observed the formation of the homocoupled product in 62% yield. When performing the same reaction with CuBr•Me₂S in DME, no homocoupled product was detected after 18 h, showing that DME does not contribute to the oxidative coupling of heteroarylstannanes. However, at this stage we were unable to recover the starting 2-stannylthiophene and mainly observed by GC analyses the protiodestannylated compound suggesting the transmetalation from tin to copper had really occurred (**III**, Scheme 1).

In summary, we have shown that π -electron-deficient heteroaromatics bearing a methylthio group were coupled with vinyl- and arylstannanes in the presence of copper(I) and a catalytic amount of Pd(PPh₃)₄. Copper is not essential for the oxidative addition of arylthioether to palladium but plays a role at two stages: transmetalation from tin to copper and probably activation of the Pd–S bond to ease the transmetalation step in the palladium catalytic coupling cycle.

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Supporting Information Available: Experimental procedures and characterization data for 2g and 3a-l. This material is available free of charge via the Internet at http://pubs.acs.org.

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