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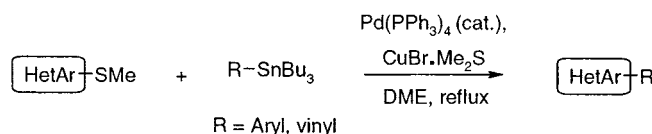
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ABSTRACT

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 organo-metallic 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 palladium-catalyzed coupling reaction between stannanes and electron-poor heteroaromatic derivatives bearing a thiomethyl ether function as a leaving group.

Initially, we examined the cross-coupling of 3-methyl-thiotriazine **1a**[6] with the commercially available 2-tributyl-stannylfuran **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

entry	cofactor/equiv	Pd catalyst (5 %)	reaction time (h)	yield (%)
1	CuMeSal/2.2	Pd(PPh₃)₄	24	60
2	CuI/2.2	Pd(PPh₃)₄	48	50
3	CuBr·Me₂S/2.2	Pd(PPh₃)₄	16	90
4	CuBr·Me₂S/0.2	Pd(PPh₃)₄	48	15
5	CuBr/2.2	Pd(PPh₃)₄	9	60
6	CuBr/2.2		48	0[a]
7		Pd(PPh₃)₄	48	0[a]
8	CuBr·Me₂S/2.2	PdCl₂(PPh₃)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

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	thiomethyl-ether	organo-stannanes	time (h)	product	yield (%)
1	**1a**	**2b**	5	**3b**	90
2	**1a**	**2c**	24	**3c**	80
3[b]	**1a**	**2d**	48	**3d**	92
4[b,c]	**1a**	**2e**	48	**3e**	80
5[b]	**1a**	**2f**	48	**3f**	60
6[b]	**1a**	**2g**[d]	9	**3g**	60
7[b]	**1b**	**2a**	48	**3h**	95
8[b]	**1b**	**2c**	48	**3i**	62
9[b]	**1c**	**2a**	3	**3j**	81
10[b]	**1c**	**2g**	6	**3k**	70
11[b]	**1c**	**2h**	48	**3l**	36[e]

[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. [e] 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 electron-rich arylstannane **2e**, 10 mol % Pd(PPh₃)₄ was necessary (entry 4). This method was successfully applied to vinyl-stannane **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 methyl-thiobenzothiazole **1c** was successful, and compounds **3h**−**j**

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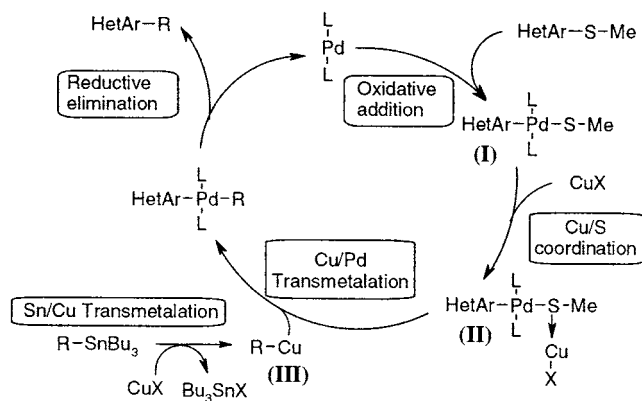
(from arylstannanes, entries 7−9) as well as compounds **3k,l** (from vinylstannanes, entries 10 and 11) were obtained in good yields. From a mechanistic point of view, copper could take part at two stages as reported in Scheme 1.

First, we believe that the oxidative addition of heteroaryl-methylthioether to palladium is enhanced in weaker Csp^2−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 % $PdCl_2$(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 $CuBr·Me_2S$ 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 $CuBr·Me_2S$ 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.

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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(9) Blank reaction performed without palladium catalyst gave no coupled compound, and starting material was mainly recovered, suggesting that palladium is essential in the coupling process.

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