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The effect of some additives on the Stille Pd⁰-catalyzed cross-coupling reaction

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Abstract

It has been found that the addition of cupric oxide to the cross-coupling reaction (Stille reaction) of 2-tributylstannylpyridine with various halobenzenes and heterocyclic halides leads to a much faster reaction and higher yields. This is also the case for the formation of thieno[3,2-*h*]-1,6-naphthyridine from 2-(2-trimethylstannyl-3-pyridyl)-1,3-dioxolane and *t*-butyl-*N*-(2-bromo-3-thienyl)carbamate.

1. Introduction

The Pd⁰-catalyzed cross-coupling reaction with organostannanes [1] has been extensively used for the synthesis of tricyclic heterocyclic systems [2,3] as well as that of 5-substituted uracils [4] and 5-substituted cytosines [5,6]. However, in many cases, long reaction times had to be used and low yields of products were often obtained. In order to promote the coupling reactions with organostannanes, lithium chloride [7] and copper(I) iodide [8] have been used. In the analogous Pd⁰-catalyzed couplings of boronic acids under basic conditions (Suzuki reaction), silver(I) oxide [9] and thallium(I) hydroxide or carbonate [10] have been used to increase the rate of coupling and to obtain higher yields. Recently, we found that the addition of equimolar amounts of silver(I) oxide greatly increased the rate and yields in the Pd⁰-catalyzed coupling of 2-bromo-3-acetamido- and 2-bromo-3-aminopyridine with 2-tributylstannyl-3-thiophene-aldehyde [2]. On the other hand, in the coupling of 4-amino- and 4-acetamido-3-bromopyridine with 2-tributylstannyl-3-thiophenealdehyde, the yields of the desired products were much lower owing to the formation of 3,3'-diformyl-2,2'-bithienyl through homocoupling of the tin derivative. The addition of thallium(I) carbonate also had a detrimental effect on yields when either tin derivatives or

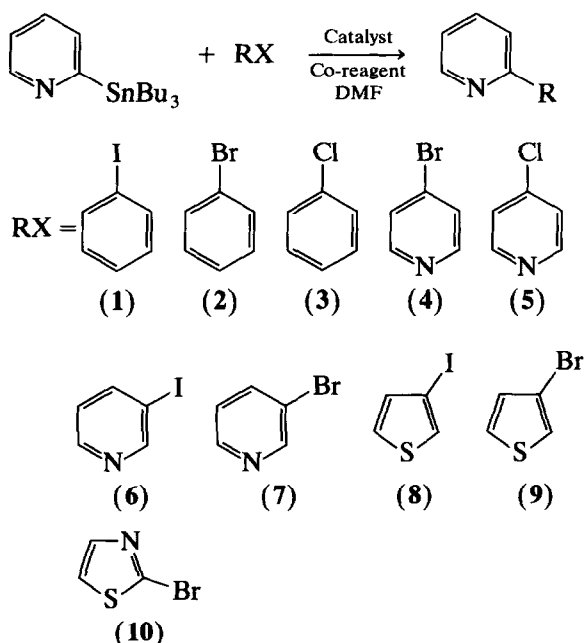
boronic acids were used as coupling partners [2]. We also found that the use of silver(I) oxide as an additive was helpful in the synthesis of bi- and terheterocyclic compounds, as well as of thieno[*h*]-1,6-naphthyridines, by the Stille reaction [3]. The presence of silver(I) oxide also appeared to increase the rate of the Suzuki coupling of boronic acids. However, owing to by-product formation, the yields were so low that the method was not preparatively satisfactory.

We have now undertaken a more detailed study of the effect of silver(I) oxide and cupric oxide as additives (co-reagents) and of various Pd⁰ catalysts on the Stille reaction of 2-tributylstannylpyridine with three halobenzenes, 4-bromo- and 4-chloropyridine, 3-iodo- and 3-bromopyridine, 3-iodo- and 3-bromothiophene and 2-bromothiazole. The reactions were monitored by GLC analysis and the reaction was considered to be complete when no aryl halide was left.

2. Results and discussion

The results are given in Table 1. The addition of cupric oxide had no effect on the coupling of chlorobenzene, and only traces of product were obtained, whereas the more reactive 4-chloropyridine gave a 44% yield in 220 min in the presence of cupric oxide, with Pd(dppb)Cl₂ as catalyst. It is noteworthy that bromo-derivatives gave better yields than the corresponding iodo-derivatives, probably owing to less by-

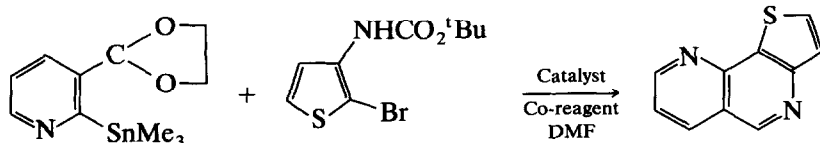
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Scheme 1.

product formation. It is also evident from our results that in most cases, $Pd(dppb)Cl_2$ is a better catalyst than $Pd(PPh_3)_4$. It is also clear that cupric oxide as additive gave higher yields than silver(I) oxide. In a few cases (3-bromopyridine, 3-bromothiophene), higher yields were obtained when no additives were used, but the reaction was then much slower.

As our main aim is to use the Stille coupling for the preparation of various heterocyclic fused naphthyridines, we studied the effect of the above-mentioned additives and various others on the coupling of 2-(2-trimethylstannyl-3-pyridyl)-1,3-dioxolane with *t*-butyl-*N*-(2-bromo-3-thienyl)carbamate, which gives thieno[3,2-*h*]-1,6-naphthyridine (Scheme 2). It can be seen (Table 2) that in the absence of any additive, the reaction is very slow and the yield is negligible. Addition of silver(I) oxide increased the reaction rate but the yield was still not satisfactory. The use of cupric oxide, however, led to a reaction time of 160–180 min and an isolated yield of 57%. Use of another Pd



Scheme 2.

TABLE 1. Coupling of 2-tributylstannylpyridine with different halogen compounds under various reaction conditions (Scheme 1)

Halogen compound	Catalyst	Co-reagent	Yield ^a (%)	Reaction time
1	$Pd(dppb)Cl_2$	CuO	64	70–80 min
1	$Pd(dppb)Cl_2$	None	40	20 h
2	$Pd(dppb)Cl_2$	CuO	82	80–90 min
2	$Pd(PPh_3)_4$	CuO	68	40–50 min
2	$Pd(dppb)Cl_2$	Ag_2O	48	70–80 min
2	$Pd(dppb)Cl_2$	None	47	4 h
3	$Pd(dppb)Cl_2$	CuO	trace	24 h
3	$Pd(dppb)Cl_2$	None	trace	72 h
4	$Pd(dppb)Cl_2$	CuO	75	70–80 min
4	$Pd(dppb)Cl_2$	Ag_2O	73	25–30 min
4	$Pd(PPh_3)_4$	Ag_2O	70	70–80 min
4	$Pd(dppb)Cl_2$	None	47	4 h
5	$Pd(dppb)Cl_2$	CuO	44	200–220 min
5	$Pd(dppb)Cl_2$	None	13	24 h
6	$Pd(dppb)Cl_2$	CuO	62	180–200 min
6	$Pd(dppb)Cl_2$	None	39	24 h
7	$Pd(dppb)Cl_2$	CuO	64	220–240 min
7	$Pd(dppb)Cl_2$	None	99	24 h
8	$Pd(dppb)Cl_2$	CuO	63	80–90 min
8	$Pd(PPh_3)_4$	Ag_2O	29	120–140 min
8	$Pd(dppb)Cl_2$	None	31	24 h
9	$Pd(dppb)Cl_2$	CuO	69	70–80 min
9	$Pd(PPh_3)_4$	CuO	70	70–80 min
9	$Pd(dppb)Cl_2$	Ag_2O	55	80–90 min
9	$Pd(PPh_3)_4$	Ag_2O	43	80–90 min
9	$Pd(dppb)Cl_2$	None	74	24 h
10	$Pd(dppb)Cl_2$	CuO	81	25–30 min
10	$Pd(PPh_3)_4$	CuO	46	15–20 min
10	$Pd(dppb)Cl_2$	Ag_2O	77	30–40 min
10	$Pd(dppb)Cl_2$	None	52	19 h

^a Yields are GLC yields.

catalyst did not affect the yields in this case and other types of additives had minor effects or destroyed the Pd catalyst. The isolated compound had analytical and spectral (1H NMR, MS) data consistent with the assigned structure.

3. Experimental details

Tetrakis(triphenylphosphine)palladium(0) [11], dichloro(triphenylphosphinebutane)palladium(II) [12], copper(II) trifluoroacetate [13], 3-iodothiophene [14], 3-iodopyridine [15], 3-(2-pyridyl)thiophene [16], 2-(4-pyridyl)pyridine [3] and 2-(2-pyridyl)thiazole [3] were

TABLE 2. Results of the use of various reaction conditions for the coupling of 2-(2-trimethylstannyl-3-pyridyl)-1,3-dioxolane with *t*-butyl-*N*-(2-bromo-3-thienyl)carbamate (Scheme 2)

Catalyst	Co-reagent	Yield (%)	Reaction time
Pd(PPh ₃) ₄	None	9 ^a	72 h
Pd(PPh ₃) ₄	Ag ₂ O	24	60–80 min
Pd(PPh ₃) ₄	Ag ₂ O ^b	12	120–140 min
Pd(PPh ₃) ₄	Cr ₂ O ₃	10	120–180 min
Pd(PPh ₃) ₄	CuO	57	160–180 min
Pd(PPh ₃) ₄	MgO	8	180–240 min
Pd(PPh ₃) ₄	Cu ₂ O	14	140–180 min
Pd(PPh ₃) ₄	Al ₂ O ₃	10	17 h
Pd(PPh ₃) ₄	ZnO	0	21 h
Pd(PPh ₃) ₄	CuCl ₂	0	< 5 min ^c
Pd(PPh ₃) ₄	Cu(CO ₂ CF ₃) ₂	0	< 5 min ^c
Cl ₂ Pd(PPh ₃) ₂	CuO	0	20 h
PdCl ₂ (dppb) ^d	CuO	48	40–60 min
PdCl ₂ (dppf) ^e	CuO	16	40–60 min

^a GLC yield. ^b Half of the stoichiometric amount was used. ^c The palladium catalyst was rapidly destroyed under these reaction conditions. ^d Diphenylphosphine butane. ^e Diphenylphosphine ferrocene.

prepared by published procedures. Dimethylformamide was distilled over a molecular sieve prior to use. Quinoline was distilled at 107°C/15 mmHg prior to use. All other chemicals were purchased from commercial sources in analytical grade and used without further purification.

The ¹H NMR spectra were recorded on a Varian XL-300 spectrometer. The mass spectra was recorded on a Finnigan 4021 spectrometer. Gas chromatographic analyses were performed on a Varian 3700 gas chromatograph, equipped with a 20 m OV-1701 capillary column. Peak areas were determined electronically with a Varian 4270 integrator. Quinoline was used as internal standard for quantitative GLC analyses and known biaryls were used as references.

3.1. General procedure in the Pd-catalyzed synthesis of biaryls

A mixture of the appropriate halogeno compound (2.0 mmol), palladium catalyst (0.1 mmol) and co-reagent (2.0 mmol) in 8 ml of DMF was stirred at 100°C. After 5 min, a solution of 0.88 g (2.4 mmol) of 2-tributylstannylpyridine [17] dissolved in 2 ml of DMF was added in one portion. When the halogeno-compound had been consumed, the mixture was allowed to attain room temperature and the precipitate filtered off. Conditions and yields are given in Table 1.

3.2. Thieno[3,2-*h*]-1,6-naphthyridine

Thieno[3,2-*h*]-1,6-naphthyridine was prepared by the modified procedure described in ref. 3. A mixture of 0.63 g (2.0 mmol) of *t*-butyl-*N*-(2-bromo-3-thienyl)carbamate [18], palladium catalyst (0.1 mmol), and co-reagent (2.0 mmol) in 8 ml of DMF was stirred at 100°C. After 5 min, a solution of 0.94 g (3.0 mmol) of (2-trimethylstannyl-3-pyridyl)-1,3-dioxolane [3] in 2 ml of DMF was added in one portion. When the starting materials had been consumed, 6 ml of 2 N hydrochloric acid was added and the mixture was allowed to warm to room temperature, and then treated with 6 ml of 2 N aqueous sodium hydroxide. The precipitate was then filtered off and the filtrate evaporated to dryness. The residue was subjected to chromatography (silica) and HPLC using chloroform/isopropanol (99:1) as eluent. Conditions and yields are given in Table 2.

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