

The effect of diethylamine on Stille alkylations with tetraalkylstannanes†

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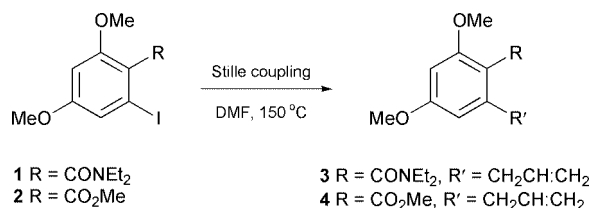
The addition of diethylamine to Stille alkylation reactions using stannanes improves yields by reducing β -hydride elimination and reduction reactions, it also serves as a substitute for other additives such as Cu(I).

The Stille reaction is a member of a large family of palladium-catalysed cross-coupling reactions. However, its generality and high degree of success have made it popular among synthetic chemists. One obvious reason for such popularity is the reaction's versatility.¹ It is frequently used in the total syntheses of large polyfunctional molecules for the coupling of complex subunits.^{2,3} However, it is sometimes found that it is not universally applicable and that many substrates require specific reaction conditions for cross-coupling to be successful.^{1–5}

There are relatively few examples of the successful introduction of alkyl groups employing Stille cross-coupling reactions described in the literature,⁶ and for α -iodocyclohexenones the reported yields are only moderate. This is probably due to failure resulting from competing β -hydride elimination when employing stannanes with alkyl groups bearing β -hydrogens and to the low reactivity of the system. A further problem often encountered is the competing reduction of vinylic or aromatic halides to the corresponding hydrocarbon. This can be a serious problem where the halide is unreactive.

Several reports have appeared relating to the importance of intramolecular participation by amino groups in Stille cross-coupling reactions. For example, it has been reported that alkyl derivatives of 1-aza-5-stannabicyclo[3.3.3]undecane were reactive in Stille couplings with aryl and alkenyl halides,^{7,8} without β -hydride elimination. It was suggested that intramolecular tin–nitrogen coordination could be the reason.

A difficult case for Stille coupling is represented in Scheme 1 (Table 1) where the highly substituted aryl iodide **1** having an



Scheme 1 Stille coupling at a polysubstituted aromatic compound.

Table 1 Stille coupling at polysubstituted aromatic compounds **1** and **2**^a

Cpd	Pd cat	Ligand	LiCl	Et ₂ NH	Prod.	Time	Yield
1	Pd(PPh ₃) ₂ Cl ₂	PPh ₃	Yes	No	3	2 h	95%
2	Pd(PPh ₃) ₂ Cl ₂	PPh ₃	Yes	No	4	1 h	36%
2	Pd(PPh ₃) ₂ Cl ₂	PPh ₃	Yes	Yes	4	1 h	87%

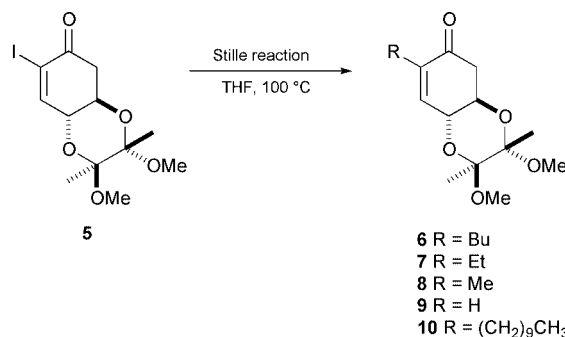
^a The solvent employed was DMF.

† Electronic Supplementary Information (ESI) available: Tables—Stille coupling of α -iodoenone **5** with Et₄Sn and Me₄Sn, and general procedure. See <http://www.rsc.org/suppdata/cc/b1/b103072h/>

amido group reacted readily with allyl triphenylstannane in the presence of Pd to form the expected product **3** in good yield (95%). The ester **2** under a wide range of normally successful conditions afforded a maximum of 36% of **4**.

Assuming that the nitrogen atom of the amide was facilitating the aryl transfer process for **1** by intramolecular chelation,⁹ we added diethylamine to the reaction mixture, containing ester **2**, to ascertain if the corresponding intermolecular process was possible. This resulted in a 87% isolated yield of the expected allyl compound **4**. No amination¹⁰ or amidification products were isolated. We next applied these findings to other cases.

Alkylation of the iodoenone **5** under 'normal' Stille conditions with tetrabutylstannane gave none of the expected butylated compound **6** but high yields of the reduced product **9** (Scheme 2). The addition of diethylamine to this reaction



Scheme 2 Stille coupling at a substituted α -iodoenone.

Table 2 Stille coupling of α -iodoenone **5** with Bu₄Sn under several conditions^a

Pd catalyst	Ligand	CuI	Et ₂ NH	Prod.	Time	Yield
Pd ₂ (dba) ₃ ·CHCl ₃	AsPh ₃	Yes	No	9	24 h	99%
Pd ₂ (dba) ₃ ·CHCl ₃	AsPh ₃	Yes	Yes	6	48 h	96%
Pd ₂ (dba) ₃ ·CHCl ₃	AsPh ₃	No	No	9	24 h	98%
Pd ₂ (dba) ₃ ·CHCl ₃	AsPh ₃	No	Yes	6	48 h	97%
Pd ₂ (dba) ₃ ·CHCl ₃	PPh ₃	Yes	No	9	48 h	60%
Pd ₂ (dba) ₃ ·CHCl ₃	PPh ₃	Yes	Yes	9	48 h	63%
Pd ₂ (dba) ₃ ·CHCl ₃	PPh ₃	No	No	9	48 h	54%
Pd ₂ (dba) ₃ ·CHCl ₃	PPh ₃	No	Yes	9	48 h	61%
Pd(P(<i>o</i> -tol) ₃) ₂ Cl ₂	P(<i>o</i> -tol) ₃	No	Yes	6	48 h	99%
Pd(P(<i>o</i> -tol) ₃) ₂ Cl ₂	P(<i>o</i> -tol) ₃	No	No	9	24 h	96%

^a The solvent employed was THF.

Table 3 Effect of adding diethylamine to the Stille coupling of α -iodoenone **5** with [CH₃(CH₂)₉]₄Sn^a

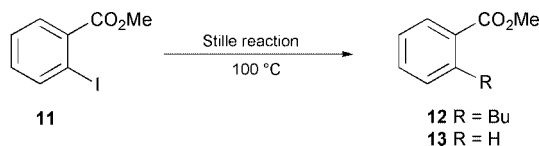
Pd catalyst	Ligand	CuI	Et ₂ NH	Prod.	Time	Yield
Pd ₂ (dba) ₃ ·CHCl ₃	AsPh ₃	Yes	No	9	24 h	99%
Pd ₂ (dba) ₃ ·CHCl ₃	AsPh ₃	Yes	Yes	10	48 h	86%

^a The solvent employed was THF.

Table 4 Stille coupling of methyl 2-iodobenzoate **11** with Bu₄Sn under several conditions

Pd Catalyst	Ligand	Solvent	LiCl	Et ₂ NH	Prod	Time	Yield
Pd(P(<i>o</i> -tol) ₃) ₂ Cl ₂	P(<i>o</i> -tol) ₃	THF	No	No	11	24 h	70%
Pd(P(<i>o</i> -tol) ₃) ₂ Cl ₂	P(<i>o</i> -tol) ₃	THF	No	Yes	11	24 h	99%
Pd(P(<i>o</i> -tol) ₃) ₂ Cl ₂	P(<i>o</i> -tol) ₃	DMF	No	No	12	24 h	68%
Pd(P(<i>o</i> -tol) ₃) ₂ Cl ₂	P(<i>o</i> -tol) ₃	DMF	Yes	Yes	11	48 h	96%
Pd(P(<i>o</i> -tol) ₃) ₂ Cl ₂	P(<i>o</i> -tol) ₃	DMF	No	Yes	12 + 11 ^a	48 h	96%
Pd(PPh ₃) ₂ Cl ₂	PPh ₃	DMF	Yes	No	12 + 13 ^b	48 h	97%
Pd(PPh ₃) ₂ Cl ₂	PPh ₃	DMF	Yes	Yes	12 + 11 ^c	48 h	99%
Pd(PPh ₃) ₂ Cl ₂	PPh ₃	DMF	No	Yes	12 + 11 ^d	48 h	98%

^a 2.3:1. ^b 1.5:1. ^c 1:4. ^d 3.6:1.

**Scheme 3**

resulted in the formation of the butylated compound **6** in good yield (Table 2). This was also the case for tetraethylstannane and for tetradecylstannane. The products **7** and **10** were obtained in good yield. Without added diethylamine, the reduced product **9** was formed exclusively.

Having shown that diethylamine did influence the outcome of these reactions we next proceeded to approach optimisation by studying several variables for this reaction (Tables 2, 3). Thus, the influence of using Pd(0) or Pd(II) as catalyst sources, the effect of the Pd ligands (PPh₃, P(*o*-Tol)₃ and AsPh₃), the presence of CuI as cocatalyst and the addition of LiCl for the aromatic substrates were analysed. We have concluded that both Pd(0) and Pd(II) were equally effective, as expected. The catalytic role of the Pd species was largely influenced by the ligand. AsPh₃ and P(*o*-Tol)₃ were found to be the best ligands tested while PPh₃ was considerably less effective. Remarkably, we have observed that for the Stille coupling of iodoenone **5** with tetramethyltin, CuI could effectively be replaced by diethylamine. When this reaction was carried out in the presence of diethylamine the workup was considerably simplified and the yields consequently higher. Analogous reactions reported in the literature used involatile NMP as the solvent.

Studies on the electron poor aromatic substrate **11** were also carried out. For this compound the reaction conditions as used for the iodoenone, had to be changed and DMF became the solvent of choice. The use of diethylamine again prevented reduction, as seen for the reaction of **11** with tetrabutyltin. The yield of the coupling product **12** was not improved over that of the same reaction without added amine but starting material was recovered when Et₂NH was present, whereas several other products were formed in its absence (Scheme 3 and Table 4). The addition of LiCl¹¹ alone simplified the product distribution but did not avoid reduction and the yield of coupling product was zero or low. When both LiCl and Et₂NH were included in the mixture the coupling product **12** was produced in low yield and starting halide **11** was recovered as the only other product.

The function of the amine is not yet clear but we suspect that it augments the activity of the phosphine ligand in maintaining the Pd(0) in solution. This complexation with the Pd atom of intermediates may also reduce the ability to undergo β-hydride elimination reactions, once it has bonded with the alkyl group by exchanging with the tin.

In conclusion, the addition of diethylamine clearly prevented β-hydride elimination/reduction in the Stille alkylation reactions tested when employing alkylstannanes with β-hydrogens, a problem frequently reported in the literature.¹ Its addition permits the use of more volatile less polar solvents in some cases and can reduce reaction times, as is well exemplified in the case of tetramethyltin.[†] In this case too the work up and purification of the reaction products was facilitated and the need to use cocatalytic CuI was eliminated. This method permits the efficient introduction of alkyl side chains into the synthetically useful α-iodoenones,¹² which are particularly difficult substrates for this kind of Stille cross-coupling¹³ reaction.

Recent reports¹⁴ highlighting the use of organozincs and organoboranes for the alkylation of α-iodoenones and vinyl halides have been described. Reduction and/or β-hydride elimination not a problem in these cases. The mechanism of Pd catalysed coupling reactions¹⁵ may change with the type of coupling reaction depending upon the metal or non-metal present.

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