The effect of diethylamine on Stille alkylations with tetraalkylstannanes†

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† Electronic Supplementary Information (ESI) available: See http://www.rsc.org/suppdata/cc/b1/b103072h/

The addition of diethylamine to Stille alkylations 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. It is frequently used in the total syntheses of large polyfunctional molecules for the coupling of complex derivatives of 1-aza-5-stannabicyclo[3.3.3]undecane were reactive in Stille couplings with aryl and alkenyl halides,7,8 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-couplings. For example, it has been reported that alkyl 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,5 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

\[
\text{Stille reaction} \quad \text{THF, 100°C}
\]

\[
\begin{array}{cccccc}
R & \text{Stille coupling} & \text{DMF, 100°C} & \text{OMe} & \text{MeO} \\
\text{Me} & \text{CONeq} & \text{R} & \text{MeO} & \text{MeO} \\
\text{1} R = \text{CONeq} & \text{2} R = \text{COOeq} & \text{3} R = \text{CONeq}, R' = \text{CH}_2\text{CH}_2\text{R} & \text{4} R = \text{COOeq}, R' = \text{CH}_2\text{CH}_2\text{R} & \text{Scheme 1 Stille coupling at a polysubstituted aromatic compound}.
\end{array}
\]

Table 1 Stille coupling at polysubstituted aromatic compounds 1 and 2

<table>
<thead>
<tr>
<th>Cpd</th>
<th>Pd cat</th>
<th>Ligand</th>
<th>LiCl</th>
<th>Et$_3$NH</th>
<th>Prod</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh$_3$)$_2$Cl$_2$</td>
<td>PPh$_3$</td>
<td>Yes</td>
<td>No</td>
<td>3</td>
<td>2 h</td>
<td>95%</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh$_3$)$_2$Cl$_2$</td>
<td>PPh$_3$</td>
<td>Yes</td>
<td>No</td>
<td>4</td>
<td>1 h</td>
<td>36%</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh$_3$)$_2$Cl$_2$</td>
<td>PPh$_3$</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
<td>1 h</td>
<td>87%</td>
</tr>
</tbody>
</table>

† The solvent employed was DMF.

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resulted in the formation of the butylated compound 6 in good yield (Table 2). This was also the case for tetraethylstannane and for tetradeckylstannane. 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, these reactions we next proceeded to approach optimisation by it augments the activity of the phosphine ligand in maintaining product.

The addition of LiCl\(^+\) alone simplified the product distribution was zero or low. When both LiCl and \(\text{Et}_2\text{NH}\) were included in the presence of CuI as cocatalyst and the addition of LiCl for the aromatic substrates were analysed. We have concluded that tetraethylstannane was produced in low yield, as seen for the reaction of \(\text{Bu}_3\text{Sn}\) with tetramethyltin, CuI could effectively be replaced by DMF became the solvent of choice. The use of diethylamine again prevented problems frequently reported in the literature used involatile NMP as the solvent.

Notes and references

11 LiCl is known to inhibit coupling reactions in some circumstances, E. Piers, R. W. Friesen and B. A. Keay, Tetrahedron, 1991, 47, 4555.