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# Evaluation of polymer-supported vinyltin reagents in the Stille cross-coupling reaction

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**Abstract**—The synthesis of two new vinyltin reagents grafted on an insoluble macroporous polymer is reported. These reagents were used in the palladium-catalyzed Stille cross-coupling reaction with aryl halides. In all reactions, the conversion of the starting aryl halide is high and the amount of organotin by-product is particularly low (at the end of the catalytic run, the amount of Sn is up to 16 ppm in the crude reaction mixture removed of the insoluble polymer, and it is less than 1 ppm in the product purified by chromatography on silica gel).

The Stille cross-coupling of vinyltin reagents with a variety of organic electrophiles is a very useful method for the formation of carbon–carbon bonds in organic synthesis.[1–5] Due to its versatility and functional group compatibility, this reaction constitutes an invaluable method for the formation of a $\sigma$ bond between two sp$^2$ carbon centers especially in the total syntheses of complex natural molecules,[6,7] but also for versatile syntheses of molecules of interest for material chemistry as exemplified by previous work in our group.[8,9] However, the Stille reaction, which requires a stoichiometric amount of tin, suffers from the difficulty of obtaining products uncontaminated by organotin residues. In order to minimize this problem, several improvements have been suggested: (i) The use of monoorganotin reagents which lead to non-toxic tin by-products at the end of the Stille reaction.[10–13] (ii) The use of a catalytic amount of organotin reagent through a reduction/addition/cross coupling sequence.[14,15] In this case, low tin contamination can be obtained using a resin-supported organotin halide.[16] (iii) The grafting of the reactive electrophile on a solid support allowing the separation of soluble organotin by-products from solid-supported products of the reaction.[17] (iv) The use of solid-supported organotin reagents which can be removed at the end of a reaction by simple filtration, regenerated and reused. However, to our knowledge, a limited number of applications of this type have been reported for the Stille cross-coupling reaction.[18–20]

In our effort to develop polymer-supported organotin reagents, we recently reported on their use both in the halogenation reaction of aromatic amines[21] and in the allylation reaction of aldehydes.[22] The efficiency of these reagents was illustrated by the low level of organotin residues in the corresponding synthesized products. Herein, we wish to report our first results concerning the Stille reaction involving polymer-supported vinyltin reagents. In this work, we have chosen polymer-supported organotin reagents, bearing a vinyl or a 3,3-diethoxyprop-1-en-1-yl substituent, as target compounds and we describe their synthesis and their use in the palladium-catalyzed Stille cross-coupling reaction

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*Keywords*: Polymer-supported vinyltins; Stille cross-coupling reaction; Green chemistry; β-Formylvinylanion.

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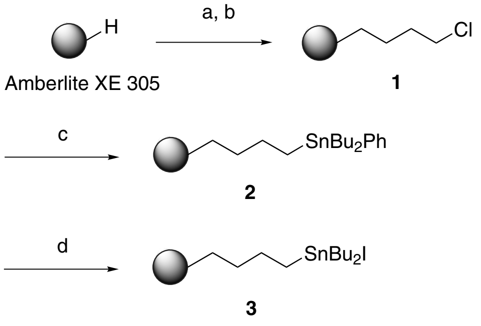
in order to evaluate the potential of these compounds and to identify the possible limitations of their application.

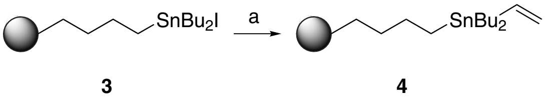
For this purpose, macroporous polymer-supported triorganotin iodide was first prepared in three steps according to the literature (Scheme 1).[21,23–25] Treatment of the lithiated Amberlite XE 305 with 1-bromo-4-chlorobutane gave resin **1**, which was stannylated with $Bu_2SnPhLi$ to afford stannylated polymer **2**. Iododearylation of **2** with a solution of iodine in ethanol led to the corresponding supported triorganotin iodide **3**.

To highlight the case of unfunctionalized supported vinyltin reagents, the vinylation procedure used in liquid phase[26] was subsequently applied to the polymer-supported triorganotin iodide **3** using two equivalents of vinyl-magnesium chloride in THF for 16 h at 45 °C before workup and filtration (Scheme 2).

The polymer-supported vinyltin reagent **4** was successively washed with THF and absolute ethanol, before being dried under vacuum. The FT-IR spectrum of polymer **4** exhibits a well defined band around $1650\ cm^{-1}$, indicative of the C=C double bond of the vinylic moiety. Chemical information on the tin environment was also obtained through solid-state $^{119}Sn$ MAS-NMR analysis allowing us to ascertain the level of conversion of resin **3** to resin **4**.[27,28] Indeed, the complete disappearance of the broad signal due to polymer **3** ($\delta_{Sn} = +81$ ppm) and the presence of a unique sharp signal ($\delta_{Sn} = -51$ ppm) typical of a Sn–Vinyl moiety was considered as a proof of an almost quantitative conversion (Fig. 1). Elemental analysis of resin **4** confirmed the absence of iodine and allowed us to estimate a tin loading of $1.4\ mmol\ g^{-1}$.



**Scheme 1.** Reagents and conditions: (a) *n*-BuLi/TMEDA, cyclohexane, 65 °C; (b) Br–$(CH_2)_4$–Cl, THF, 0 °C–rt; (c) $Bu_2SnPhLi$, THF, rt and (d) $I_2$, EtOH, 60 °C.



**Scheme 2.** Reagents and conditions: (a) VinylMgBr (2 equiv), THF, 45 °C.

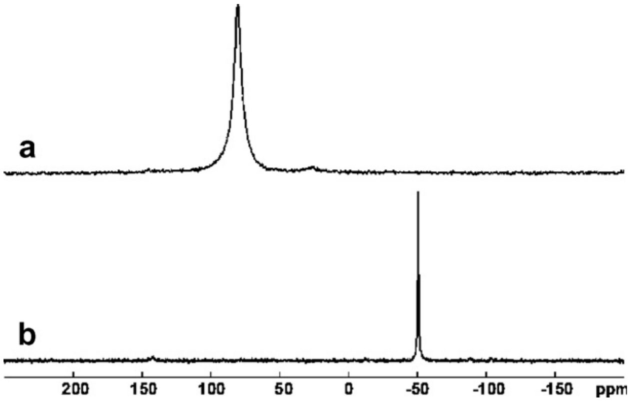


**Figure 1.** $^{119}Sn$ MAS-NMR spectra: (a) resin **3**: $\delta_{Sn} = +81$ ppm and (b) resin **4**: $\delta_{Sn} = -51$ ppm.

As the aforementioned synthesis is restricted to non-functionalized vinyltin reagents, we then explored the hydrostannation of alkynes as a possible route to polymer-supported functionalized vinyltins reagents. Resin **3** was first reduced quantitatively in polymer-supported tin hydride **5** with $LiAlH_4$ (5 equiv) in dry THF for 150 min at 40 °C. According to the literature,[29] the solid-state $^{119}Sn$ MAS-NMR spectrum exhibits a single signal indicative of the Sn–H function ($\delta_{Sn} = -91$ ppm, Fig. 2) but no signal attributable to **3** or for bis-stannylated species when the reaction was carefully performed in the dark and in the absence of dioxygen. In a second step, the supported tin hydride was reacted with 3,3-diethoxyprop-1-yne, in dry toluene at 110 °C, with a catalytic amount of AIBN (Scheme 3).

The complete conversion of **5**–**6** was established by $^{119}Sn$ MAS-NMR spectroscopy. Thus, the spectrum clearly highlights the disappearance of **5** and the formation of polymer-supported vinyltin reagent **6** as a mixture of two regioisomers α-**6** and β-**6** (Fig. 2). On the basis of $^{119}Sn$ NMR data in solution,[30] the larger signal at −47 ppm was assigned to α-**6** and (*E*)-β-**6** and the minor signal near −61 ppm to (*Z*)-β-**6**. Accordingly, the isomeric ratio of α-**6**, (*E*)-β-**6**, and (*Z*)-β-**6** given in Scheme 3 was determined indirectly by $^1H$ NMR analysis of the corresponding iododestannylation products (known to occur with retention of configuration[31]). It is to be noted

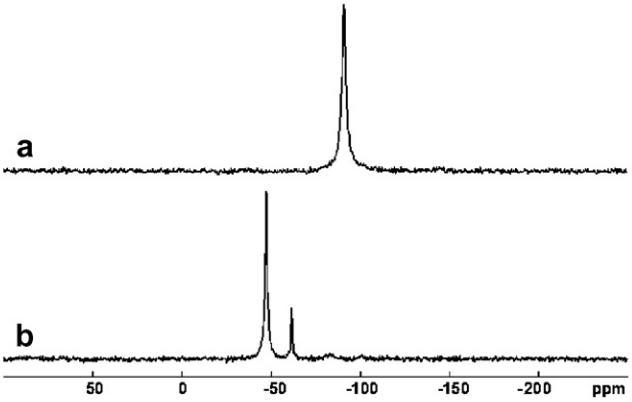
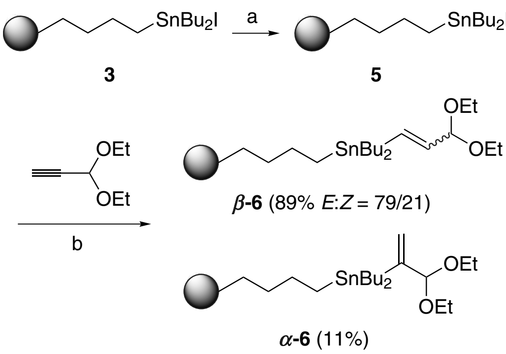


**Figure 2.** $^{119}Sn$ MAS-NMR spectra: (a) resin **5**: $\delta_{Sn} = -91$ ppm and (b) resin **6**: $\delta_{Sn} = -47$ ppm: (*E*) + α isomers; $\delta_{Sn} = -62$ ppm: (*Z*) isomer.

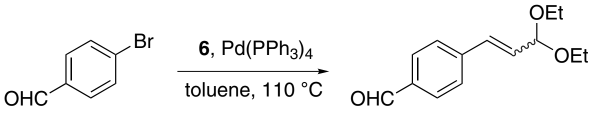


**Scheme 3.** Reagents and conditions: (a) $LiAlH_4$, THF, 40 °C and (b) AIBN, toluene, 110 °C.

that the presence of the regioisomer α-**6** is not prejudicial to a primary exploration of the reactivity of these vinyltins since the regioisomer α-**6** is known to be less reactive than (*E*)-*β*-**6** and (*Z*)-*β*-**6**.[30] Elemental analysis indicated a tin loading of 1.14 mmol $g^{-1}$ on this sample.

Having established the grafting degree and the nature of the substituents around tin in supported vinyltins **4** and **6**, we tested their reactivity in the palladium-catalyzed Stille cross-coupling reaction with various aryl iodides and bromides. In order to determine the appropriate experimental conditions, the coupling of reagent **6** with 4-bromobenzaldehyde **7a** was first examined in dry toluene at 110 °C and the amount of palladium catalyst ($Pd(PPh_3)_4$) as well as the reaction time were varied (Table 1). At this temperature, the higher conversions in **8a** were obtained with 5 mol % of palladium catalyst after 40 h of reaction.

**Table 1.**



**7a** **8a**

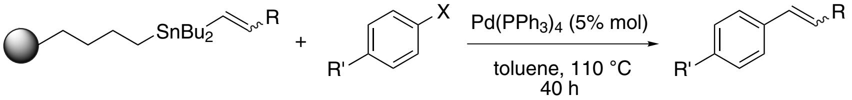
| Entry | $Pd(PPh_3)_4$ (mol %) | Reaction time (h) | Conversion[a] (%) |
|---|---|---|---|
| 1 | 2 | 18 | 77 |
| 2 | 2 | 40 | 79 |
| 3 | 5 | 18 | 83 |
| 4 | 5 | 40 | 100 |

[a] Conversion determined by GC analysis of the crude product.

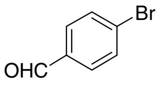
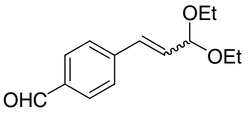
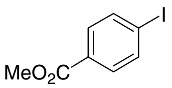
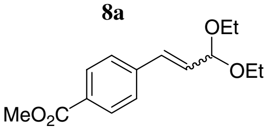
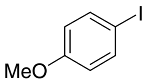
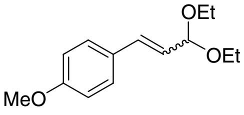
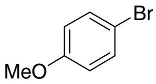
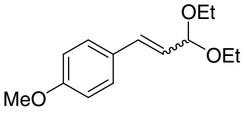
Using these experimental conditions,[32] further attempts were achieved in Schlenk tubes by heating resin **4** or **6** in toluene in the presence of the aryl iodide or bromide **7a**–**e** using an ellipsoidal stirring (Table 2). Good conversions were obtained from the resins **4** and **6**, regardless of the nature of the functional group on the aryl halide substrate.

ICP-MS analyses performed on **8a**–**d** and **9a**–**d** exhibited very low amount of organotin residues in the products (under 16 ppm when the analysis is performed on the crude product and under 1 ppm when the analysis is realized on the purified product). This very low contamination by organotin by-products demonstrates the efficiency of these polymer-supported vinyltin reagents as non-polluting reagents. In this way, their use in the synthesis of biologically active molecules may be considered even in the late steps of the synthetic strategy. At this

**Table 2.** Stille cross-coupling reactions of aryl halides (**7a**–**e**) with polymer-supported organotin reagents **4** or **6**[33,34]

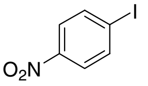
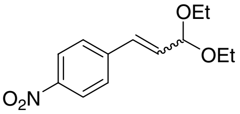
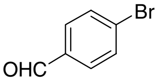
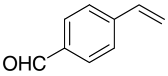
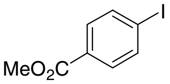
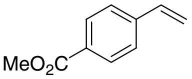
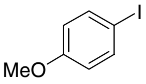
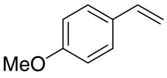
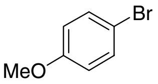
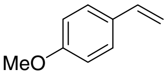
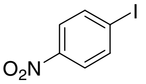
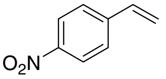


**4** or **6** **7a-e** **8a-9d**

| Entry | Resin[a] | Ar–X | Product | Conversion[b] (%) | Sn[c] (ppm) |
|---|---|---|---|---|---|
| 1 | **6**: R = $CH(OEt)_2$ |  <br>**7a** |  <br>**8a** | 100 | 7.2[d] |
| 2 | **6**: R = $CH(OEt)_2$ |  <br>**7b** |  <br>**8b**[33] | 96 (92) | < 0.5[e] |
| 3 | **6**: R = $CH(OEt)_2$ |  <br>**7c** |  <br>**8c** | 80 | —[f] |
| 4 | **6**: R = $CH(OEt)_2$ |  <br>**7d** |  <br>**8c** | 78 | —[f] |

(*continued on next page*)

**Table 2** (*continued*)

| Entry | Resin[a] | Ar–X | Product | Conversion[b] (%) | Sn[c] (ppm) |
|---|---|---|---|---|---|
| 5 | **6**: R = CH(OEt)$_2$ | <br>**7e** | <br>**8d**[34] | 100 (95) | <0.5[e] |
| 6 | **4**: R = H | <br>**7a** | <br>**9a** | 100 | 4.2[d] |
| 7 | **4**: R = H | <br>**7b** | <br>**9b** | 100 | 9.0[d] |
| 8 | **4**: R = H | <br>**7c** | <br>**9c** | 81 | 8.1[d] |
| 9 | **4**: R = H | <br>**7d** | <br>**9c** | 83 | 16.4[d] |
| 10 | **4**: R = H | <br>**7e** | <br>**9d** | 100 | 10.2[d] |

[a] Resin **6** was used as a mixture of α-**6** + (*E*/*Z*)-β-**6**. 1.12 equiv were used in order to take into account the presence of nearly unreactive α-**6**.
[b] Conversion determined by GC analysis of the crude product, the *E*/*Z* ratio is similar to those observed in β-**6**. For entries 2 and 5, isolated yields are in brackets. It has to be noted that no homo-coupling by-product has been observed.
[c] Quantification of tin residues in the products determined by ICP-MS.
[d] These quantities have been measured on the crude product without any purification.
[e] These quantities have been measured on the purified product after chromatography on silica gel (eluent: petroleum ether–AcOEt 80:20).
[f] Not determined.

stage, the complete validity of the method required the possibility of recycling polymer-supported tin reagents recovered at the end of the cross-coupling reaction. For this purpose, the resin recovered at the end of the Stille process was washed with THF, absolute ethanol, dried under vacuum and characterized by FT-IR and $^{119}$Sn MAS-NMR spectroscopy before being regenerated and reused. Thus, in the $^{119}$Sn MAS-NMR spectra of the recovered resins, the signals at +133 ppm or +81 ppm are characteristic of the regeneration of the polymer-supported tin halides Sn–Br or Sn–I. The resin recovered after reaction of resin **4** with aryl halide **7e** was successfully regenerated, utilizing the aforementioned procedure for its synthesis, and reacted again with **7e** with a similar efficiency as in the course of the first coupling. However, at the end of this cycle, a grey-black color is observed on the polymer, possibly due to a palladium deposit during the reaction.

In conclusion, these preliminary experiments support strongly the fact that polymer-supported vinyltin reagents can be used efficiently in the Stille cross-coupling reaction in order to limit organotin pollution at very low levels. However, the observed palladium deposit, which is not prejudicial to the first cycle, should be taken into account if regeneration and reuse of this reagent is desired. For discovery research, this regeneration is not imperative but, regio and stereoselective syntheses of functional polymer-supported vinyltin reagents have to be achieved (as it has been done in solution[35,36]) so as to transfer organic units with fixed configuration to organic substrates without the drawbacks of metallic pollution. Work is in progress in order to deliver various vinyltin reagents in a context of green chemistry, a concept which can be also applied to functional aryltin, heteroaryltin or allyltin reagents.

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32. *Typical procedure for the palladium-catalyzed Stille cross-coupling reaction with polymer-supported vinyltin reagents*: In an oven-dried Schlenk flask were successively added, under argon, the polymer **4** (0.3 mmol) or **6** (0.3 mmol), the aryl halide (0.3 mmol), $Pd(PPh_3)_4$ (0.015 mmol) and dry toluene (3 mL). Dodecane (0.3 mmol) was used as internal standard. The reaction mixture was then heated at 110 °C for 40 h. The polymer was removed by filtration, washed with THF ($6 \times 10$ mL) and the filtrate was concentrated under vacuum. The resulting crude residue was analyzed by GC and the identity of the products was confirmed by $^{1}$H NMR, $^{13}$C NMR and MS. On the other hand, the resulting polymer was washed with absolute ethanol ($4 \times 10$ mL) and dried under vacuum (0.5 mbar) at 60 °C for 5 h before reuse.
33. (*E*)-Methyl 4-(3,3-diethoxyprop-1-en-1-yl)benzoate (**8b**). $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta_H$ 1.20–1.44 (6H, m), 3.55–3.72 (4H, m), 3.94 (3H, s), 5.21 (1H, d, $^{3}J = 4.8$ Hz), 5.91 (1H, dd, $^{3}J = 4.8$ Hz, $^{3}J = 16.0$ Hz), 6.70 (1H, d, $^{3}J = 16.0$ Hz), 7.48 (2H, AA′BB′ system, $^{3}J = 8.3$ Hz), 8.04 (2H, AA′BB′ system, $^{3}J = 8.3$ Hz); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta_C$ 15.2 (2C), 52.1, 61.2 (2C), 101.1, 126.6 (2C), 129.4, 129.9 (2C), 131.9, 132.2, 140.7, 166.8; MS (EI, 70 eV): *m*/*z* (relative intensity) 264 ($M^{+\cdot}$, 8), 233 (7), 219 (100), 193 (40), 191 (30), 159 (57), 131 (58), 115 (41), 103 (30), 77 (25), 59 (28), 29 (34).
34. (*E*)-[3,3-Diethoxy-1-(4-nitrophenyl)]prop-1-ene (**8d**). $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta_H$ 1.26 (6H, t, $^{3}J = 6.9$ Hz), 3.52–3.80 (4H, m), 5.10 (1H, d, $^{3}J = 4.7$ Hz), 6.36 (1H, dd, $^{3}J = 4.7$ Hz, $^{3}J = 16.2$ Hz), 6.78 (1H, d, $^{3}J = 16.2$ Hz), 7.50 (2H, AA′BB′ system, $^{3}J = 8.9$ Hz), 8.18 (2H, AA′BB′ system, $^{3}J = 8.9$ Hz); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta_C$ 15.7 (2C), 61.8 (2C), 101.0, 123.9, 124.4 (2C), 127.7 (2C), 131.2, 132.0, 143.1; MS (EI, 70 eV): *m*/*z* (relative intensity) 251 ($M^{+\cdot}$, 10), 234 (9), 206 (100), 178 (59), 150 (17), 149 (26), 132 (45), 131 (27), 103 (28), 77 (21), 29 (38).
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