Journal Name

ARTICLE

Polyphosphazenes for the Stille reaction: A new type of recyclable stannyl reagents.

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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The random phosphazene copolymer {[N=P((CH$_2$)$_7$-Br)Ph]$_{0,5}$[N=PMePh]$_{0,5}$}$_n$ (**2**) and the block copolyphosphazene {[N=P((CH$_2$)$_7$-Br)Ph]$_{25}$[N=PMePh]$_{20}$}-*b*-[N=P(O$_2$C$_{12}$H$_8$)]$_{55}$ (**5**), having a branch with two randomly distributed units, have been synthesized and used as precursors for the stannyl derivatives {[N=P((CH$_2$)$_7$-SnBu$_2$An)Ph]$_{0,5}$[N=PMePh]$_{0,5}$}$_n$ (**3**) and {[N=P((CH$_2$)$_7$-SnBu$_2$An)Ph]$_{25}$[N=PMePh]$_{20}$}-*b*-[N=P(O$_2$C$_{12}$H$_8$)]$_{55}$ (**6**, An = *p*-MeOC$_6$H$_4$). Polymers **3** and **6** were tested as recyclable tin reagents in the Stille cross-coupling reaction with C$_6$H$_5$I, using various Pd catalysts and different experimental conditions. Polymer **6** can be recycled without significant release of tin, but its efficiency decreased after three consecutive cycles. This effect was explained by studying the self-assembly of the polymer under the same conditions used for the catalytic experiments, which evidenced the progressive coalescence of the polymeric vesicles (polymersomes) leading to stable and bigger core-shell aggregates by the attraction of the [N=P(O$_2$C$_{12}$H$_8$)] rich membranes, thus decreasing the accessibility of the tin active centers.

Introduction

Polyphosphazenes, [N=PR$_2$]$_n$ PP, are probably the most recognizable and chemical versatile class of inorganic polymers. Beside the characteristic properties conferred by their N=P chain, such as inherent flexibility, and radiative thermal and chemical stabilities, most of the physical and chemical properties of PP´s, e.g., solubility, glass transition temperature, crystallinity, and chirality, can be tuned by simply changing the R substituents.[1] Because of those features, they can be transformed into very useful materials for many practical applications, including already commercial high-performance elastomers and fire-resistant foams. They also have potential for biomedical and optical applications.[2] The synthesis of high molecular weight polyphosphazenes[1c] can be achieved following two general methodologies: (1) The ring-opening polymerization (ROP) of hexachlorocyclotriphosphazene [N$_3$P$_3$Cl$_6$] to the linear uncross-linked polydichlorophosphazene, [N=PCl$_2$]$_n$,[3] followed by macromolecular substitution of the chlorine atoms by oxygen or nitrogen donor nucleophiles[1c] (Eq. 1 in chart 1); and (2) the polycondensation of phosphoranimines[4] (Eq. 2 in chart 1).

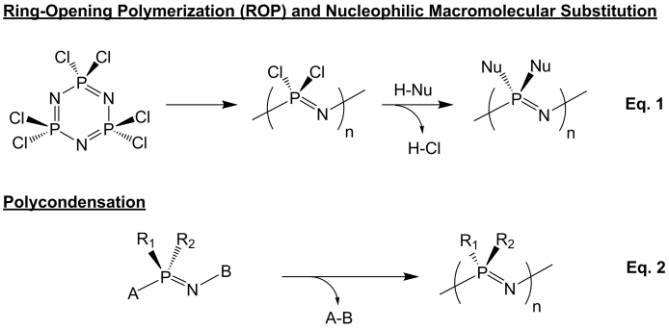

Chart 1. General synthetic routes to polyphosphazenes.

The first methodology (Eq 1 in chart 1) is a general route to polyphosphazenes carrying useful chemical functionalities, which are incorporated in the structure of the nucleophile (H-Nu).[1c,3] Polyphosphazenes carrying transition metal complexes have been used as supported catalysts including enzimes.[5] For instance, polyphosphazene random copolymers supporting ruthenium complexes, for hydrogen transfer reactions,[6] gold complexes as active catalysts in the hydration of alkynes,[7] and cobalt derivatives for the hydroformylation of alkenes.[8] Some of these supported catalysts could be recycled several times before losing their catalytic activity by metal leaching from the polymer-bound phosphine ligand rather than polymeric main-chain degradation.[6] In a different approach, gold and silver nanoparticles stabilized on the surface of hollow nanostructures (spheres and tubes) based on polymeric cyclotriphosphazene shells,[9] were used as recyclable catalysts in the oxidation of alcohols,[9a,b] aryl coupling reactions,[9c] and reduction of nitrophenol.[9d,e] Pt or

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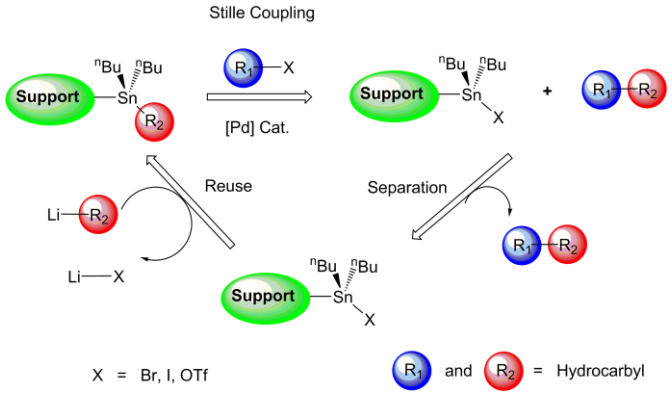
† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Pt-Co catalysts supported on polyphosphazene-coated carbon nanotubes have been applied to the electrocatalytic oxidation of methanol,[10] and finally, Co and Cu(II) moieties supported on polyphosphazenes having pyridine ligands were used in the catalytic oxidation of alkenes.[11]

The polycondensation of phosphoranimines shown in chart 1 (Eq. 2),[4] is a route to poly(alkyl/aryl)phosphazenes, $[N=PR_1R_2]_n$,[4d,12] (isoelectronic with the silicones) with pendant organic groups attached to the main chain through P-C bonds. Those substituents may be easily functionalized by deprotonation and electrophilic substitution strategies.[13] Moreover, it opens a very convenient route to polyphosphazene block copolymers[14] and it has been proven that an appropriate combination of polycondensation and macromolecular substitutions can gave rise to a variety of functionalized block-copolymers,[1,15] widening the opportunities for designing new types of supported catalysts or polymeric substrates for solid-phase synthesis.[16] A Pd-catalyzed cross coupling process that benefits from the use of a polymeric reagent is the well-known Stille reaction. It exhibits a high chemoselectivity and has proved very useful in the synthesis of macrocycles and natural products of pharmaceutical interest, where the purity of the coupling derivative is of paramount importance.[17] This method uses organotin derivatives which are moderately toxic and, therefore, the separation of the target product from the tin byproducts is a crucial step. On the other hand, the recovery and reuse of the tin-containing byproducts would make the whole process environmentally friendly. A suitable reagent for the Stille reaction needs an inert Sn-support bond not undergoing transmetalation to palladium, so the link to the polymer is preserved and the reactivity is centered on the chosen R to be coupled. Generally, R is an aryl, heteroaryl, alkenyl or alkynyl group and Sn-alkyl groups are used as non-reactive auxiliaries, as in $SnBu_3R$. Therefore, a convenient Stille synthesis would be that shown in scheme 1, where the tin species involved are strongly bonded to a polymeric support.

The use of a polymeric stannane of the type Pol-$SnBu_2R$ where the polymer backbone is aliphatic or it has a pendant aliphatic chain has proved valid before. For instance, polymeric -$SnBu_2X$ reagents for this strategy have been developed using polystyrene,[18] polyfluorene,[19] and polynorbornene supports.[20] In the latter case, we developed a batch process with an immobilized stannyl polymer which allows to run the Stille coupling multiple times, with minimum work-up and very low tin contamination of the coupling products.[20a]

Because of the characteristics mentioned above, the polyphosphazenes could be easily transformed into robust and versatile supports; however, to our knowledge, no examples of such reagents supported on polyphosphazenes have been reported. Herein we describe the synthesis of polyphosphazenes containing -$SnBu_2R$ groups as reagents for the Stille coupling by a designed combination of a polycondensation of phosphoranimines followed by macromolecular substitution and or chemical modification. The efficiency and recyclability in the Stille synthesis of the stannyl functionalized polyphosphazenes derived from the poly(methylphenyl)phosphazene homopolymer ($[N=PMePh]_m$, **1**),[4g,12,13] and the block copolymer (BCP) $[N=P(O_2C_{12}H_8)]_n$-*b*-$[N=PMePh]_m$ (**4**, n = 55 and m = 45),[14c] having the poly(2,2´-dioxy-1,1´-biphenyl)phosphazene block ($[N=P(O_2C_{12}H_8)]$), were confirmed and, in the case of the later BCP supported reagent, fully explained, on the basis of their self-assembly.



Scheme 1. General strategy for the supported Stille coupling reaction and the separation and recycling of the tin byproducts.

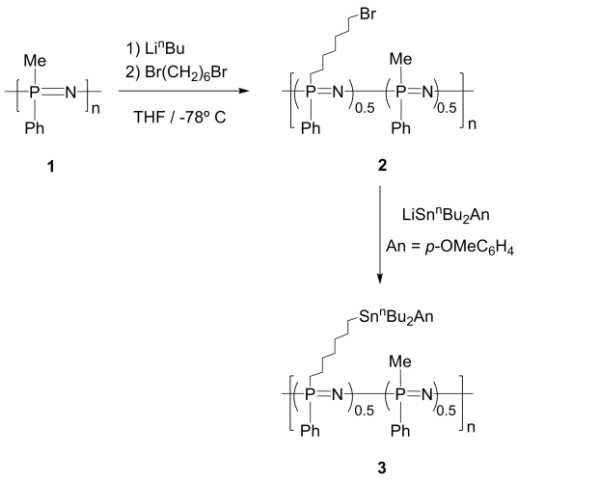
Results and Discussion

Synthesis of the stannylated polyphosphazenes 3 and 6.

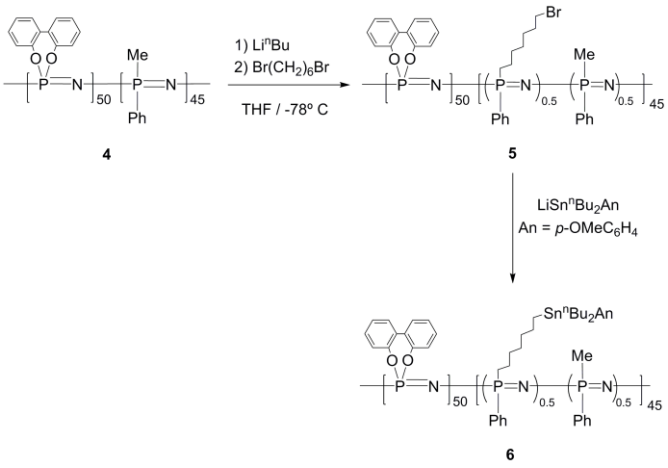
Very successful routes to polyphosphazenes carrying $-(CH_2)_n$-Br substituent and their stannylated derivatives were developed starting from the homopolymer **1** and the block copolymer **4** (see Schemes 2 and 3 respectively). The first route (polymers **2** and **3** in scheme 3), consisted on the functionalization of the methyl group in the flexible (T_g = 35 ˚C) and very soluble in polar organic solvents homopolymer $[N=PMePh]_m$ (**1**). The second route (polymers **5** and **6** in scheme 4), starting from the known block copolymer BCP $[N=P(O_2C_{12}H_8)]_n$-*b*-$[N=PCl_2]_m$,[14c] included a macromolecular chlorine substitution step to produce $[N=P(O_2C_{12}H_8)]_n$-*b*-$[N=PMePh]_m$ (**4**) containing rigid (T_g = 160 ˚C) and much less soluble $[N=P(O_2C_{12}H_8)]_n$ segments, which might allow an easier and more efficient recovery of the stannylated reagents **6** (see below).

The polyphosphazene **1** was prepared in 88 % yield as a yellowish sticky solid, following reported procedures by the polycondensation of the phosphoranimine $ClMePhP=NSiMe_3$ initiated by PCl_5 (see Experimental part for a detailed description of the procedures and characterization details). The average molecular weight determined by size exclusion chromatography was M_n = 18,500 and the polydispersity index (PDI) was very low (PDI = 1.2). The reaction of polymer **1** with Li^{n}Bu (1.2 equivalents per $-CH_3$ group) in THF at -78 ˚C gave, after 1.5 hours, a solution of the orange organolithium derivative $[N=PPhCH_2Li]_n$ (**1**-Li).[12,13] This latter reacted with an excess (*ca.* 50 %) of 1,6-dibromohexane to give the polyphosphazene **2** with ω-bromoalkyl pendant groups, that was isolated as a yellowish gummy solid in 85 % yield (see Scheme 2). The ^{31}P-NMR spectrum of **2** showed two broad peaks centered at 1.0 (50 % by integration) and 6.2 ppm (50 %

by integration) corresponding to the {N=P[$(CH_2)_7$-Br]Ph} and [N=PMePh] units respectively.



Scheme 2. Synthesis of stannylated random copolymer **3**.



Scheme 3. Synthesis of stannylated block copolymer **6**.

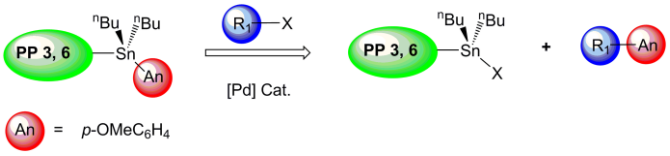
Since the lithiation of **1** under the experimental conditions used goes to completion,[12,13] (also checked by treating the [N=PPhCH$_2$Li] with Cl-SiMe$_3$ to give [N=PPhCH$_2$-SiMe$_3$] with no [N=PMePh] units), the presence of [N=PMePh] units in polymer **2** must be due to the reaction of **1**-Li with 1,6-dibromohexane, which could not be completed even using high excess of 1,6-dibromohexane (100 and 200 %), increasing the temperature (THF reflux) or the reaction times (48 h). The ^{1}H-NMR spectrum and the quantitative analysis of bromide were consistent with the molecular structure proposed for **2** (see Experimental). Interestingly, the M_n (16,500) and PDI (1.2) of **2** were almost identical to those of its precursor **1**, indicating that no chain degradation occurred during the lithiation and quenching with 1,6-dibrohexane. Note that, because of the statistical distribution of the units, polymer **2** is a random copolymer.

A similar experimental procedure led to the synthesis of the white BCP **5** in 89 % yield (see Scheme 4). The starting BCP **4**, was prepared following our previously described three steps synthesis using mono-end capped initiators of type [Ph$_3$P=N=PCl$_3$][PCl$_6$] to avoid bidirectional chain growth originating three-block copolymers.[14c] Treating BCP **4** in THF at -78 ˚C first with Li^{n}Bu and subsequently with 1,6-dibromohexane, gave BCP **5.** Again, only half of the [N=PMePh] units were converted into the ω-bromoalkyl substituted {N=P[$(CH_2)_7$-Br]Ph} units and, therefore, **5** is a peculiar block copolymer having a random copolymeric segment (see Scheme 3). Polymer **5** is soluble in THF and chlorinated solvents but not in hexane or alcohols. Its structure was confirmed by ^{31}P- and ^{1}H-NMR (experimental part) and the analysis of the SEC traces showed the absence of degradation of polymeric chains during the functionalization.

The reactions of the precursors **2** and **5** with LiSn^{n}Bu$_2$An (An = p-MeOC$_6$H$_4$) in THF at -78 ˚C gave respectively the stannylated polymers **3** and **6** (Schemes 2 and 3). In both cases, the substitution of –SnBu$_2$An for Br was complete, as demonstrated by the quantitative determination of bromide and the disappearance of the characteristic signals of the –CH$_2$Br group (3.3 ppm) in the ^{1}H-NMR spectra (see Experimental part). The stannyl group resonances are present in the ^{1}H and ^{13}C{^{1}H}-NMR spectra as well as in the ^{119}Sn{^{1}H}-NMR spectra where the observed signal at -41 ppm is characteristic of the SnR$_4$ organotin moiety. As expected, due to the large distance between the stannyl group and the phosphorous main chain, no significant variation was observed in the ^{31}P{^{1}H}-NMR of **3** and **6**.

Use of stannylated polyphosphazenes 3 and 6 in the Stille reaction.

Polymers **3** and **6,** having very different physical properties and solubilities were used in the Stille reaction (scheme 4) to prove their efficiency and ease of recovery.



Scheme 4. General scheme of Stille reaction.

We first evaluated the Stille reaction between the polymer **3** and C$_6$H$_5$I by using different palladium catalysts (always in 5% mol) and reaction conditions. The best results were obtained using [Pd(PPh$_3$)$_4$] as catalyst and dimethylacetamide (DMA) as solvent at 90 °C as shown in entry 1, Table 1 (for details of the results obtained under other reaction conditions, see ESI). We then extended the reaction to other organic electrophiles (Table 1, entries 1-6). In general, the aryl-aryl coupling requires higher reaction temperatures to ensure a fast oxidative addition step of the aryl halide and these reaction were carried out in DMA at 90 °C (entries 1-5, Table 1). More reactive organic halides, such as allyl chloride, work well at lower temperatures (50 °C in THF, entry 6 Table 1). Besides [Pd(PPh$_3$)$_4$] other catalyst were also used in some of the reactions, as specified in Table 1.

As can be seen in Table 1 (last column), and already observed in other Stille aryl couplings, the reaction is not selective and

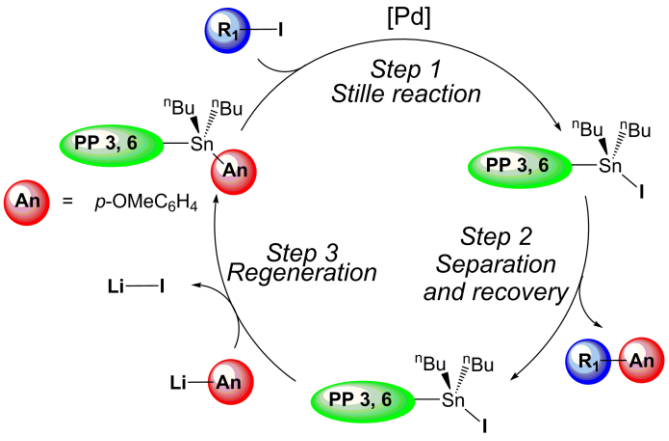
homocoupling derivatives, mostly diphenyl and some bis(4,4'-dimethoxydiphenyl), along with some dehalogenation products (benzene) were found in the reaction mixture. Also as expected,[18-20] the reaction times using stannyl supported polymers are longer than those observed using analogous but monomeric tin reagents.

Table 1. Stille reactions using polymers **3** or **6** as reagents.[a]

Entry	R^1X	**PP** (**PP**:R^1X)[b]	Time (h)	R^1-An Conv. (Yield %)[c]
1	PhI	**3** (1.25:1)	18	95(68)
2	*p*-$CHOC_6H_4I$	**3** (1.25:1)	18	100(87)
3[d,e]	C_6F_5I	**3** (1.25:1)	5	40(40)
4[d]	*p*-$F_3CC_6H_4I$	**3** (1.25:1)	5	87(75)
5[d]	*p*-$MeOC_6H_4I$	**3** (1.25:1)	5	86(86)
6[f]	CH_2=$CHCH_2Cl$	**3** (1.1:1)	5	100(100)
7	PhI	**6** (2:1)	48	90(74)
8	*p*-$F_3CC_6H_4I$	**6** (2:1)	44	100(94)
9[f]	CH_2=$CHCH_2Cl$	**6** (2:1)	5	100(100)

a) The reactions were carried out in DMA at 90 ˚C, using $[Pd(PPh_3)_4]$ as catalyst (5% mol Pd) unless otherwise noted. b) Molar ratio. c) Conversions and crude yields were determined by integration of ^1H or ^{19}F NMR signals. d) $[PdBrPf(AsPh_3)_2]$ was used as catalyst. e) Dioxane as solvent and 100 ˚C. The yield did not improve upon increasing the reaction time. f) The reaction was carried out in THF at 50 ˚C, using $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ as catalyst (1% mol Pd) and benzoquinone (1% mol).

The recyclability of polymer **3** was tested by the three step procedure shown in Scheme 5. After the Stille reaction (Step 1) the solvent was eliminated from the reaction mixture and MeOH was added to the residue. The polymeric by-product derived from **3**, i.e., PP-$SnBu_2I$, precipitated as a gum-like dark solid that was recovered by filtration (Step 2), and reacted with a LiAn to regenerate **3** for further use (Step 3).



Scheme 5. General procedure for recycling the tin polymeric reagent in the Stille reaction.

Table 2 shows the results obtained reusing polymer **3** nine times consecutively. It was noticed that **3** becomes slightly less soluble upon reuse which explains the gradual increase of the recovered polymer yields and the overall lowering of the tin contamination in the products (note that in cycle 4, higher **3**:PhI ratio was used). Although still lower than the contamination found with monomeric tin reagents and conventional separation methods (around 4-5%), the tin content in Table 2 is high when compared to other polymeric reagents (e.g. 50-15 ppm for the immobilized stannylated polynorbornenes).[20a] Low tin contamination in the products of Stille reactions have also been found for some stannylated polystyrenes (between 5-60 ppm).[18a-c]

The dark color of the recovered polymer is an indication of absorbed Pd black released at the end of the Stille reaction. In fact, we checked that it could be reused without added catalyst (Cycle 7 in Table 2) giving a better yield than those for other cycles. However, although the polymer is still dark, the yield decreased in a second experiment with no catalyst (cycle 8, Table 2). This showed that only a fraction of the deposited palladium is transformed into active catalytic species, most probably by release to the solution. As shown by cycle 9 in Table 2, 0.5% mol of Pd is enough to maintain the yields.

In order to improve the performance of the stannylated reagents for the Stille coupling, the much less soluble polymer **6** was tested. As seen in Table 1 (entries 7-9), polymer **6** is as efficient as polymer **3** in terms of conversions and yields, although, in general, it requires longer reaction times. Again, the synthesis of the diaryls shows a moderate selectivity explaining the lower yields observed for reactions with almost quantitative conversions. However, in contrast with **3**, and due to the presence of the rigid $[N=P(O_2C_{12}H_8)]$ segment, the PP-$SnBu_2X$ (X = I or Cl) tin byproducts could be recovered very easily as dark powders by precipitation in MeOH.

Table 2. Recycling experiments for the Stille coupling of C_6H_5I and polymer **3**.[a]

Cycle	R^1-R^2 Conv. (Yield, %)[b]	Recovered PP-$SnBu_2X$ (yield %)	Sn in R^1-R^2 (weight %)[c]
1	76(64)	71	2.721
2	64(40)	74	3.115
3	66(45)	82	1.181
4[d]	81(55)	87	3.281
5	100(50)	91	0.511
6	100(66)	92	0.135
7[e]	84(79)	91	0.957
8[e]	64(47)	90	2.140
9[f]	70(54)	98	1.101

a) The reactions were carried out in DMA at 90 ˚C for 24 h using $[Pd(PPh_3)_4]$ as catalyst. The molar ratio of reagents used was **3**:C_6H_5I:[Pd]=25:20:1. b) Conversions and crude yields were determined by integration of ^1H NMR signals.. c) Determined by ICP-MS on samples of the coupling product obtained by evaporation of the solvents and filtration through silica (see Experimental part). d) The molar ratio of reagents was changed to **3**:C_6H_5I:[Pd]=40:20:1. e) No catalyst added. f) The amount of catalyst used is 0.5% mol.

Thus, the synthesis of 4-trifluoromethyl, 4'-methoxy diphenyl (Eq. 1, R^1X = *p*-$CF_3C_6H_4I$) was repeated several times following the general recycling procedure shown in Scheme 6 (Table 3).

Polymer **6** can be reused three times with good yields. Importantly, the tin contamination of the coupling product is remarkably low (2-6 ppm), which is one of the lowest values reported so far for a Stille coupling using a very simple reaction workup. Moreover, as the reagent can be reused, the process is a truly clean Stille reaction. Polymer **6** shows, however, a loss of efficiency after the third cycle (entries 3 and 4, Table 3). Although the loss of activity is accompanied by an increase in the tin contamination of the coupling product by a factor of ten (entries 5 and 6, Table 3) or higher (entry 7, Table 3), the loss of tin is still very low when compared to the tin content of **6** (used in excess), thus not accounting for the drop of the yield. Therefore, an additional polymer deactivation mechanism must operate. In fact, as shown below, it is the direct consequence of the self-assembly behavior of **6**.

Table 3. Recycling experiments for the Stille coupling of p-$CF_3C_6H_4I$ and polymer **6**.[a]

Cycle	R^1-R^2 Conversion (Yield %)[b]		Recovered PP-$SnBu_2X$ (Yield %)	Sn in R^1-R^2 % weight[c]
	24 h	≥ 48 h		
1	100(81)	-	78	0.0002
2	100(82)	-	82	0.00061
3	100(77)	-	94	0.00024
4	77.2(57.9)	80.1(59.9)	92	0.00067
5	32.3(16.9)	48.5(21.5)[d]	89	0.0089
6	30(24.5)	64.4(39.6)[e]	88	0.0066
7	35(18)	63(19)[e]	85.6	0.0219

a) The reactions were carried out in DMA at 90 ˚C using $[Pd(PPh_3)_4]$ as catalyst. The molar ratio of reagents used was **6**:p-$CF_3C_6H_4I$:[Pd]=40:20:1. b) Conversions and crude yields were determined by integration of ^{19}F NMR signals. c) Determined by ICP-MS on samples of the coupling product obtained by evaporation of the solvents and filtration through silica (see Experimental part). d) Reaction time 4 days. e) Reaction time 3 days.

Self-assembly studies of block copolymer 6.

Intrigued by this decrease of the activity of BCP **6** after three catalytic cycles, we studied the self-assembly processes of these materials by TEM and dynamic light scattering (DLS) under the same conditions used for the catalytic reaction, i.e. DMA as solvent, 40 mg/mL as concentration and 90 °C. Thus, when a 40 mg/mL solution of BCP **6** was analyzed by DLS at room temperature, we observed the presence of a single peak at $R_{h,App}$ = 400 nm which corresponds to the presence of aggregates (micelles) in solution (cycle 0 in Figure 1a). The nature of these aggregates was further studied by TEM. When a drop of the solution was directly casted on a carbon-coated copper grid and analyzed by TEM, we observed the presence of spherical micelles with diameters of 800-900 nm (Figure 2a), which is consistent with the size of the aggregates determined by DLS. A more in depth analysis of the aggregates revealed the core-shell nature of them by the observation of a capsule wall of *ca.* 45 nm thickness (the central region of the vesicles appears darker in DMA environment, see Figure 2b), multiple fusion processes between individual aggregates (white dashed circles in Figure 2a) and slightly collapsed structures, all of them typical of the presence of vesicles (see inset Figure 2a).

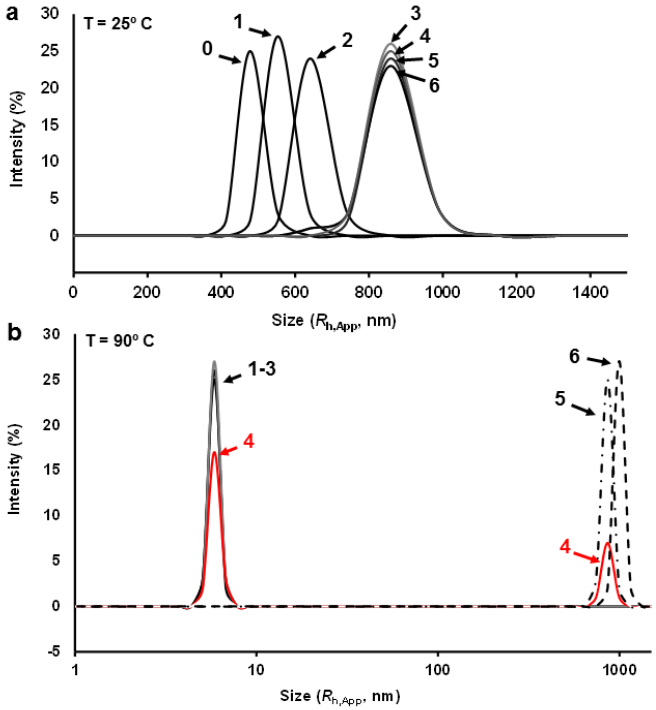


Figure 1. Dynamic light scattering traces of solutions of BCP **6** in DMA (40 mg / mL) at 25 ˚C (a) and 90 °C (b, logarithmic scale has been used for clarity). Numbers indicated the different cycle of heating-cooling. The samples were heated at 90 °C during 24 h each time. Number 0 in (a) denoted the DLS measure just after the solution of **6** in DMA.

A graphical representation of the structure of vesicles is depicted in Figure 2b, where the more insoluble [N=P($O_2C_{12}H_8$)] segment is located at the membrane, being the stannyl block at the corona (both at the outer and inner part of the vesicle). When the solution was heated at 90 °C, the DLS at this temperature showed the presence of a single peak at $R_{h,App}$ = 6 nm (cycle 1 in Figure 1b) which corresponds to solvated block copolymer chains, not observing the presence of aggregates. Thus, the vesicles were dissolved at the catalytic reaction temperature and only solvated chains having all the stannyl groups available to reaction were observed by DLS.

Indeed, when a drop of the solution at 90 °C was quickly casted on the TEM grid, the TEM revealed the presence of lamellar structures resulted from the thin film self-assembly of solvated chains of BCP **6** during the evaporation of the DMA (Figure 2c). When the solution was cooled down to room temperature after 24 hours of heating, DLS revealed the formation of slight larger aggregates $R_{h,App}$ = 550 nm (cycle 1 in Figure 1a). The TEM confirmed the presence of larger vesicles that, therefore, were reversibly formed during the cooling process. Similar behavior was observed (TEM and DLS) after a second a third heating (24 h / 90 °C) and cooling (room temperature) cycles, leading to increasingly bigger vesicles ($R_{h,App}$ = 670 and 800 nm respectively, see cycles 2 and 3 in Figure 1a and 1b). However, in the fourth cycle we detected

stable vesicles at 90 °C in both TEM and DLS (cycle 4, in red, in Figure 1b, and Figure 2).

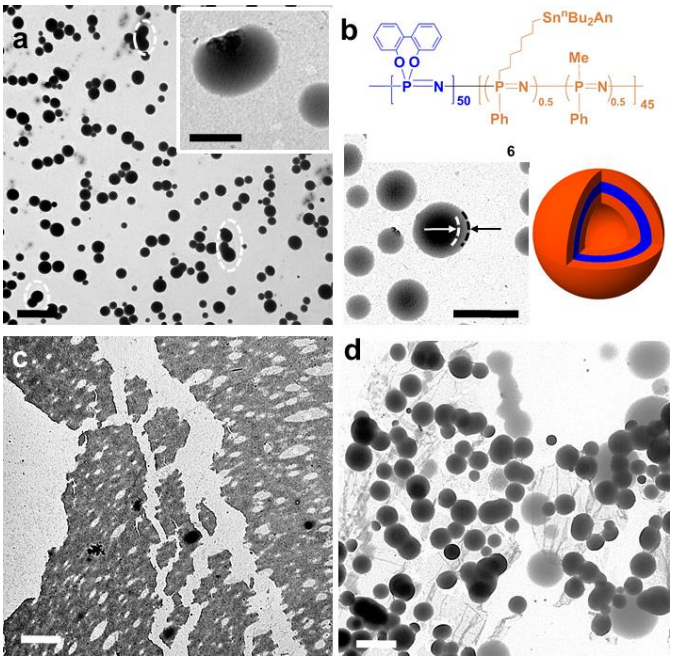


Figure 2. (a) Bright field TEM image of vesicles obtained by dissolving the BCP **6** in DMA (40 mg / mL) at 25 ˚C (inset scale bar corresponds to 2000 nm). Fusion of vesicles can be observed (dashed white circles). The inset TEM shows a collapsed vesicle structure (inset scale bar correspond to 500 nm). (b) Graphic representation of the vesicle structure and bright field TEM picture of a vesicle in which the capsule wall is observed (inset scale bar corresponds to 1000 nm). (c) Bright field TEM image of the lamellae structure obtained from drop-casting (at 90 ˚C) of the DMA solution of **6** after 24 h at 90 ˚C. (d) Bright field TEM image of the giant vesicles obtained after 3 consecutive heating (90 ˚C-24h)/cooling cycles. The sample was casted at 90 ˚C (inset scale bar corresponds to 2000 nm).

Moreover, the TEM of a sample prepared at 90 ˚C revealed mostly the presence of fused and bigger vesicles (diameter *ca.* 2,000 nm, Figure 2d), evidencing a coalescence process between vesicles at 90 ˚C. Indeed the $R_{h,App}$ (at room temperature) of the vesicles after the third heating-cooling cycle is 800 nm (cycles 4 to 6 in Figure 1a), the double of the size of the vesicles formed by the first solution of BCP **6** in DMA at room temperature (cycle 0 in Figure 1a). As revealed (by DLS and TEM, see Figures 2 and 3), after three heating-cooling cycles the vesicles were stable at 90 ˚C, maintaining its size almost constant. These observations can explain the loss of activity of BCP **6** after 3 cycles, assuming that during the first 3 cycles the vesicles are reversibly dissolved at 90 ˚C, ensuring the availability of all the stannyl groups to the other reagents and catalyst. However, the reversibility is lost after the third cycle resulting in stable vesicles in which part of the stannyl groups are occluded in the inner part and therefore less available to other reagents.

Conclusions

A designed synthetic procedure has allowed the synthesis of the new phosphazene copolymer derivatives {[N=P((CH$_2$)$_7$-SnBu$_2$An)Ph]$_{0,5}$[N=PMePh]$_{0,5}$}$_n$ (**3**) and {[N=P((CH$_2$)$_7$-SnBu$_2$An)Ph]$_{25}$[N=PMePh]$_{20}$}-*b*-[N=P(O$_2$C$_{12}$H$_8$)]$_{55}$ (**6**, An = *p*-MeOC$_6$H$_4$), carrying -(CH$_2$)$_7$-SnBu$_2$An groups, that could be used as recyclable reagents in the Stille coupling in the presence of various Pd catalysts under different conditions.
Polymer **3** was efficient and recyclable up to nine times, but it released tin in higher proportion than other polymer supported stannyls. The less soluble polymer **6** was a robust and efficient reagent not releasing tin, but lossing efficiency after three cycles. This fact could be fully accounted for by studying its self-assembly under the same conditions used in the Stille reaction. It was found (DLS and TEM) that polymer **6** led to vesicles at room temperature. However, these core-shell aggregates were soluble at the Stille coupling temperature (90 °C), facilitating the accessibility of the stannyl moieties to the reagents and the Pd catalyst. After 3 heating-cooling cycles, however, the vesicles become stable and bigger at 90 ˚C (as a result of the attraction of the biphenoxy rich cores that promoted a progressive coalescence of the vesicles), impeding the availability of the Sn-centers occluded in the vesicles inner parts.

Experimental part

^{1}H, ^{13}C{^{1}H}, ^{19}F, ^{31}P{^{1}H}, and ^{119}Sn NMR spectra in solution were recorded using Bruker AV-400 and Agilent MR-500 instruments. Chemical shifts (δ) are reported in ppm and referenced to Me$_4$Si (^{1}H and ^{13}C), CFCl$_3$ (^{19}F), H$_3$PO$_4$ (^{31}P), or SnMe$_4$ (^{119}Sn). All the NMR spectra were recorded at 293 K. Some of the NMR spectra were recorded in protic solvents using an acetone-d$_6$ capillary. The tin content of the products was determined by ICP–MS, using Agilent 7500i equipment; the samples were dissolved in a mixture of HNO$_3$/H$_2$SO$_4$ = 7:3 using an ETHOS SEL Milestone microwave oven. The bromo content in the polymers was determined by oxygen-flask combustion of a sample and analysis of the residue by the mercurimetric titration of bromide.[21] Bright-field TEM micrographs were obtained on a JEOL-2000-EX-II microscope operating at 160 kV and equipped with a GATAN digital camera. For the statistical size analysis, between 150 and 300 nanostructures were traced manually using ImageJ software (http://rsb.info.nih.gov/ij/) to determine the diameter length. Each micrograph was analyzed completely in order to reduce subjectivity. Dynamic light scattering measurements were performed using a Malvern Zetasizer Nano Series running DTS (Dispersion Technology Software) software and operating a 4 mW He Ne laser at 633 nm. Analysis was performed at an angle of 173° and a constant temperature of 25 ˚C, using 1 cm glass cuvettes.
Solvents were dried using a solvent purification system SPS PS-MD-5 or distilled from appropriate drying agents under nitrogen, prior to use. The organic halides, ^{n}butyl- and methylithium, and NH(*i*-Pr)$_2$ were purchased from Aldrich or Acros. The compounds SnBu$_2$AnH,[19] [Pd$_2$(μ-Cl)$_2$(η^3-C$_3$H$_5$)$_2$],[22] [PdBrC$_6$F$_5$(AsPh$_3$)$_2$],[23] and [Pd(PPh$_3$)$_4$][24] were prepared according to the literature procedures. The polydichlorophosphazene and the substituted 2,2'-diphenoxy

polyphosphazene used in Scheme 3 were synthesized as described before.[14c]

The coupling products synthesized and collected in Tables 1-3 and the homocoupling products are known (*p*-$MeOC_6H_4$–C_6H_5,[25] *p*-$MeOC_6H_4$–C_6H_4-*p*-CF_3,[26] *p*-$MeOC_6H_4$–C_6H_4-*p*-COH,[27] *p*-$MeOC_6H_4$–C_6H_4-*p*-OMe,[28] *p*-$MeOC_6H_4$–$CH_2CH=CH_2$,[29] *p*-$CF_3C_6H_4$–C_6H_4-*p*-CF_3,[30] Ph-Ph[31]) and some are commercially available. They were characterized by NMR and the spectra compared with data in the literature or with spectra of authentic samples.

Synthesis of homopolymer 2. In a round-bottom flask under dry atmosphere of N_2(g), 3 g of [N=PMePh] (**1**, 22 mmol) were dissolved in 40 mL of dry THF. The solution was placed at -78 ˚C and 11 mL of a 2.5 M solution of Li^{n}Bu in *n*-hexane (27 mmol) was dropped slowly during *ca.* 30 min. The resulting orange solution was stirred 1.5 h at -78 ˚C and, at the same temperature, 20 mL of $Br(CH_2)_6Br$ (55 mmol) were quickly added. The solution was stirred at room temperature for 12 h, concentrated to 1/3 of the initial volume and poured onto 250 mL of hexanes (with magnetic stirring). The white solid obtained was filtered and purified by several precipitations from concentrated solutions of THF into water (x2) and hexanes (x2). The resulted white solid was dried under vacuum at room temperature (12 h) and at 50 ˚C (2 days). Yield 85 %

^{1}H NMR ($CDCl_3$, 400.13 MHz), δ (ppm): 7.8 (b, 2H, H_{Ph}), 7.1 (b, 3H, H_{Ph}), 3.3 (b, -CH_2-Br), 2-0.7 (b, CH_2, P-CH_3), ^{31}P{^{1}H} NMR ($CDCl_3$, 161.97 MHz), δ (ppm): 6.15 (b, N=PPh$(CH_2)_7$Br), 1.05 (b, N=PPhMe). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.613 MHz), δ (ppm): 131.5, 130.7, 129.4, 127.4 (b, C_{Ph}), 33.9, 32.7, 30.7, 30.3, 28.3, 28.0, 23.2, 21.9 (b, *C*H_2, P-*C*H_3). M_n = 16476 D; M_w/M_n = 1.2. The bromo content of the polymer is 194.9 mg Br / g.

Synthesis of block copolymer 5. In a round-bottom flask under dry atmosphere of N_2(g), 1.8 g of [N=P$(O_2C_{12}H_8)$]$_n$-*b*-[N=PMePh]$_m$ (**4**, 10 mmol; 4,5 mmol of –CH_3) were dissolved in 30 mL of dry THF. The solution was placed at -78 ˚C and 2.2 mL of a 2.5 M solution of Li^{n}Bu in *n*-hexane (5.4 mmol) was dropped slowly during *ca.* 30 mins. The resulting orange solution was stirred for 1.5 hours at -78 ˚C and, at the same temperature, 5 mL of $Br(CH_2)_6Br$ (14 mmol) were quickly added. The solution was stirred at room temperature for 12 h, concentrated to 1/3 of the initial volume and poured onto 250 mL of hexanes (with magnetic stirring). The white solid obtained was filtered and purified by several precipitations from concentrated solutions of THF into water (x2) and hexanes (x2). The resulted white solid was dried under vacuum at room temperature (12 h) and at 50 ˚C (2 days). Yield 89 %

^{1}H NMR ($CDCl_3$, 400.13 MHz),), δ (ppm): 7.8 (b, Ph), 7.5-6.5 (b, Ph; N=$PO_2C_{12}H_8$), 3.3 (b, -CH_2Br), 2.0-0.5 (b, CH_3, CH_2). ^{31}P{^{1}H} NMR ($CDCl_3$, 161.97 MHz),), δ (ppm): 5.90 (b, N=PPh$(CH_2)_7$Br), 1.06 (a, 1P; N=PPhMe), -6.37 (b, N=$PO_2C_{12}H_8$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.613 MHz),), δ (ppm):148.7, 132.3, 130.9, 129.2, 128.7, 125.0, 122.8 (b, C_{Ph}, $C_{12}H_8O_2$), 34.0, 33.8, 32,4, 31.6, 29.8, 27.8, 22.7, 14.4 (b, *C*H_2, P-*C*H_3). M_n = 63500; M_w/M_n = 1.13. The bromo content of the polymer is 98.2 mg Br / g.

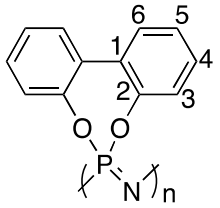
Synthesis of the stannylated polyphosphazenes. Synthesis of homopolymer 3. To a solution of NH*i*Pr_2 (2.3 g, 22.7 mmol) in dry THF (30 mL) at -78 ˚C is added dropwise a solution of Li^{n}Bu in *n*-hexane (14.7 mL, 1.6 M, 23.5 mmol). The mixture was stirred for one hour and then warmed up to –60 ˚C. $SnBu_2$AnH (7.7371 g, 22.7 mmol) was added dropwise to the former solution and the mixture stirred for an additional hour. The resulting solution containing $LiSnBu_2$An was added via cannula to a solution of **2** (3.3 g, 7.6 mmol) in dry THF (120 mL) at –60 ˚C. The mixture was stirred for 24 h and, during this time, the temperature slowly raised to room temperature. Then, the solution was poured onto MeOH (400 mL) and the gum like solid was stirred for 2 h. The MeOH was decanted and the solid was washed with water (300 mL) and then MeOH (200 mL). The sticky brownish solid, **3**, was dried in vacuo (4.6029 g, 87% yield).

3: ^{1}H NMR ($CDCl_3$, 400.13 MHz), δ (ppm): 7.8 (b, H_{Ph}), 7.4 (b, H_{ortho}, An), 7.1 (b, H_{Ph}), 6.8 (m, H_{meta}, An), 3.8 (b, OCH_3), 1.9-0.7 (b, CH_3; Bu; CH_2). ^{31}P{^{1}H} NMR ($CDCl_3$, 161.97 MHz),), δ (ppm): 6.44 (b, N=PPh$(CH_2)_7SnBu_2$An), 1.13 (b, N=PPhMe), ^{13}C{^{1}H} NMR ($CDCl_3$, 100.613 MHz),), δ (ppm): 159.7 (s, *C*-OCH_3), 137.4 (s, C_{ortho}, An), 131.8 (s, C_{An}-Sn), 131.6, 130.7, 129.3, 127.4 (b, C_{Ph}), 113.9 (s, C_{meta}, An), 54.9 (s, O*C*H_3), 34.5, 31.1, 28.9, 23.5, 22.7, 21.7, 21.1 (b, (*C*H_2)$_7$; P-*C*H_3), 29.1 (s, $^2J_{Sn\text{-}C}$ = 19.5 Hz, *C*H_2, Bu), 27.3 (s, $^3J_{Sn\text{-}C}$ = 55 Hz, *C*H_2-CH_3, Bu), 13.7 (s, *C*H_3, Bu), 9.9 (s, $^1J_{Sn\text{-}C}$ = 327.3 Hz, *C*H_2-Sn, (CH_2)$_7$), 9.6 (s, $^1J_{Sn\text{-}C}$ = 332.5 Hz, *C*H_2-Sn, Bu). ^{119}Sn {^{1}H} NMR ($CDCl_3$, 149.211 MHz), δ (ppm): -42.1 (b). The bromo content of the polymer is 0.0 mg Br / g.

Block copolymer **6** was prepared in the same way, using the precursor block copolyphosphazene **5** as reagent. White solid, 95% yield.

6: ^{1}H NMR ($CDCl_3$, 400.13 MHz),), δ (ppm): 7.8 (b, H_{Ph}), 7.5-6.5 (b, H_{An}; H_{Ph}; (N=$PO_2C_{12}H_8$)), 3.8 (b, OCH_3), 1.9-0.7 (b, P-CH_3; Bu; (CH_2)$_7$). ^{31}P{^{1}H} NMR ($CDCl_3$, 161.97 MHz),), δ (ppm): 6.11 (b, N=PPh$(CH_2)_7SnBu_2$An), 1.17 (b, N=PPhMe), -6.52 (b, N=$PO_2C_{12}H_8$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100.613 MHz), δ (ppm): 159.6 (s, *C*-OCH_3), 148.7 (b, C^2), 137.4 (s, C_{ortho}, An), 131.8 (s, C_{An}-Sn), 129.2 (b, C^4; C^6; Ph), 128.7 (b, C^1), 131.6, 130.8, 127.3 (b, Ph), 124.9 (b, C^5), 122.8 (b, C^3), 113.9 (s, C_{meta}, An), 54.9 (s, O*C*H_3), 34.5, 31.0, 28.9, 23.5-21.1 (b, (*C*H_2)$_7$; P-*C*H_3), 29.1 (s, $^2J_{Sn\text{-}C}$ = 18.2 Hz, *C*H_2, Bu), 27.3 (s, $^3J_{Sn\text{-}C}$ = 51.5 Hz *C*H_2-CH_3, Bu), 13.7 (s, *C*H_3, Bu), 9.9 (s, *C*H_2-Sn, (*C*H_2)$_7$), 9.6 (s, $^1J_{Sn\text{-}C}$ = 337.9 Hz *C*H_2-Sn, Bu). ^{119}Sn {^{1}H} NMR ($CDCl_3$, 149.211 MHz), δ (ppm):-40.8 (b). The bromo content of the polymer is 0.0 mg Br / g.

The numbering scheme used for the 2, 2'-diphenoxy group is:



General procedure for the Stille reactions. Synthesis of *p*-$MeOC_6H_4$–C_6H_5 (entry 4, Table 1). Polymer **3** (0.0335 g, 0.048 mmol of –$SnBu_2$An), iodobenzene (0.0078 g, 0.038 mmol) and dry DMA (0.5 mL) were mixed under nitrogen in an NMR tube. [$Pd(PPh_3)_4$] was added (0.0022 g, 0.0019 mmol) and the

mixture was shaken and placed in heat bath at 90 ˚C. After the allotted reaction time the conversion and crude yield were determined by ^{1}H NMR using an internal acetone-d_6 capillary. The reactions collected in Table 1 were carried out in the same way, using the corresponding stannylated polyphosphazene and the reaction conditions specified in the table feet.

General procedure for the reuse of polymers 3 and 4 in the Stille reactions.

Stille reaction (step 1) and polymer recovery (step 2). Synthesis of *p*-MeOC$_6$H$_4$–C$_6$H$_5$ (cycle 3, Table 2). A mixture of polymer 3 (0.9808 g, 1.40 mmol of –SnBu2An), iodobenzene (0.23 g, 1.12 mmol) and dry DMA (20 mL) was placed in a Schlenk tube in a nitrogen atmosphere. [Pd(PPh$_3$)$_4$] was added (0.0649 g, 0.056 mmol) and the mixture was stirred at 90 ˚C for 24 h. After this time a sample was analyzed by ^{1}H NMR, using an internal acetone-d_6 capillary, to determine the conversion (66%) and crude yield (45%). The solvent was removed by distillation and MeOH (40 mL) was added to the residue. The resulting suspension was stirred for 15 min and the dark gum-like polymer was filtered, washed with MeOH (3x10 mL) and air-dried (0.841 g, 74% yield). The filtrate was evaporated to dryness and the residue was filtered through a silica column using Et$_2$O as eluent. After evaporation of the ethereal solution, the coupling product was obtained as a brownish solid (0.0606 g, 31% yield). It contained 1.181% weight of tin.

Polymer regeneration (step 3). A solution of Li^{n}Bu in n-hexane (1.61 mL, 1.6 M, 2.57 mmol) at 0 ˚C was diluted with THF (20 mL) and cooled to -90 ˚C. 4-Bromoanisole (0.44 g, 2.34 mmol) was slowly added and the mixture was stirred for 10 min and then, the temperature was increased to -50 ˚C. The polymer recovered after the Stille reaction, PP-SnBu$_2$I (0.841 g, 1.17 mmol) was added to the former solution and the mixture was stirred while the temperature was slowly raised to room temperature over a period of 24 h. Water (10 drops) was added to the reaction mixture and the solvent was evaporated. The residue was triturated and stirred with MeOH (30 mL). The supernatant solution was decanted and the resulting gum-like solid was again washed with MeOH (3x10 mL) and dried in vacuo. This polymer, **3**, can be used in a subsequent Stille reaction.

The experiments collected in Tables 2 and 3 were carried out in the same way. The conversions and crude yields collected in Table 3 were determined by ^{19}F NMR.

General procedure for self-assembly studies. The sample solutions of block copolymer **6** (40 mg / mL) were prepared using micro-filtered HPLC-grade DMA and dissolved using an ultrasonic cleaning bath operating at 35 kHz and 160 W.

Preparation of the samples by drop-casting: The samples were prepared by direct casting of one drop (*ca.* 10 μl) of BCPs **6** solution onto a carbon-coated copper grid which was placed on a piece of filter paper to remove excess solvent for TEM analysis.

Acknowledgements

The authors are grateful to FICYT (Projects SV-PA-13-ECOEMP-83 and GRUPIN14-106), Universidad de Oviedo (Project UNOV-13-EMERG-GIJON-08), the Spanish MINECO (DGI, grants CTQ2014-56345-P and CTQ2013-48406-P) and the Junta de Castilla y León (grant VA302U13) for funding. We are also grateful to the COST action Smart Inorganic Polymers (SIPs-CM1302 - http://www.sips-cost.org/home/index.html). APS would like to thank the MICINN for the Juan de la Cierva and MEC for the Ramón y Cajal programs. SSS is grateful to the MEC for the FPU grant.

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Graphical Abstract