Use of polymer-supported phenyltin for the creation of aryl–aryl or aryl–heteroaryl bonds via Stille cross-coupling reactions

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ABSTRACT

An insoluble polymer-supported phenyltin reagent was successfully used in Stille cross-coupling reactions with aryl- and heteroaryl-halides. Cross-coupling products were isolated in good to high yields with very low contamination by tin and palladium residues after removal of the residual supported organotin halide. The regeneration and recyclability of the supported phenyltin reagent were also examined and proved to be possible, but required palladium cleaning of the grafted polymer to be efficient along 4 cycles when Pd(PPh$_3$)$_4$ was used as catalyst.

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1. Introduction

The development of efficient methods for the construction of carbon–carbon bonds represents an ongoing and central theme of research in organic synthesis. Transition-metal-catalyzed cross-coupling of organometallic reagents with halides or triflates constitutes today one of the most powerful methods to generate carbon–carbon bonds [1]. In particular, the Stille cross-coupling reaction [2–4], has emerged as one of the most popular methods for the synthesis of biaryls or heterobiaryls [5,6]. In addition, numerous total syntheses of highly functionalized compounds have implied a Stille cross-coupling reaction in the final steps [7–9]. This is mainly due to the air- and moisture-stability of organotin substrates, to the compatibility of the reaction with virtually any functional group [2–10], to the availability [10–12] and to the easy characterization of organostannanes [13–16].

However, the toxicity and difficulty of removing organotin residues from final products detract its synthetic appeal when pharmaceuticals and radiopharmaceuticals are targeted. During the course of the industrial preparation of active pharmaceutical ingredients (APIs), a serious problem is often encountered to remove

residual heavy metal at an acceptable trace level in the final product. Therefore, the development of clean or "green" processes to overcome these difficulties is currently being an active research area in organic syntheses involving organotin reagents [17].

In this context, various methodologies concerning the Stille cross-coupling reaction including the elimination of tributyltin halides as tributyltin fluoride [18,19], the use of monoorganotin reagents [20–22], a catalytic amount of organotin reagent [23–25], a biphasic system like a fluorous phase [26–28] or ionic liquids [29–31], have been reported. In addition, the concept of tin reagent grafted on a matrix has also been developed. This matrix can also be an imidazolium ionic liquid [32,33], a triarylphosphonium salt [34], a soluble polymer (which can be removed by precipitation) [35,36] or an insoluble macroporous polymer which can be separated by a simple filtration [37–40]. This last methodology is particularly well-suited for parallel and high-throughput syntheses which are widely developed for drug design in medicinal chemistry.

We recently reported on the synthesis of solid-supported organotin reagents grafted on an insoluble polystyrene matrix in order to get a facile workup and to avoid the presence of organotin residues in the products. We considered the halogenation reaction of aromatic amines [41], the allylation reaction of aldehydes [42–44], and the Stille cross-coupling reaction of vinyltins with arylhalides [45]. The efficiency of the immobilized reagents was illustrated by a similar reactivity when compared to their soluble

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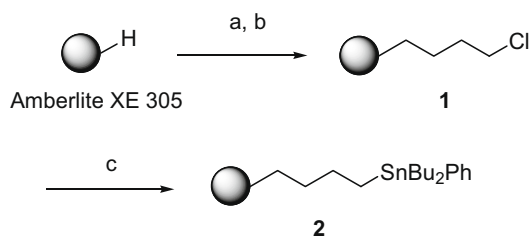
Scheme 1. Reagents and conditions: (a) n-BuLi/TMEDA, cyclohexane, 65 °C, (b) Br–(CH$_2$)$_4$–Cl, THF, 0 °C to rt and (c) Bu$_2$SnPhLi (1.3 equiv.), THF, rt.

analogs and by a low level of organotin residues in the corresponding synthesized products. However, in the case of the Stille cross-coupling reaction we observed a limited recyclability of the polymer-supported vinyltin reagents.

In the present contribution, we present an extension of our previous communication [45] and report on the preparation of an immobilized phenyltin reagent and its utilization for the synthesis of biaryl and aryl–heteroaryl units via Stille cross-coupling reaction. After examining the scope of the reaction, we have considered the recycling of the supported phenyltin reagent and have measured the residual tin and palladium amount in the cross-coupling products.

2. Results and discussion

2.1. Preparation of the polymer-supported phenyltin reagent

We first prepared the polymer-supported di-n-butylphenyltin reagent **2**. For this purpose, the macroporous polymer Amberlite XE-305 was treated by n-BuLi in cyclohexane in the presence of TMEDA. The obtained lithiated species were reacted with 1-bromo-4-chlorobutane to afford polymer **1** which upon stannylation with Bu$_2$SnPhLi afforded the polymer-supported reagent **2** according to literature (Scheme 1) [41,46,47]. The polymer-supported reagent **2** was characterized by FT-IR spectroscopy ($\bar{\nu}_{(Sn–Csp2)}$ = 726 cm^{-1}) and by ^{119}Sn MAS-NMR analysis which revealed a signal at δ_{Sn} = −43 ppm (Fig. 2) indicative of the formation of the expected supported phenyltin reagent **2** since a δ_{Sn} = −42 to −45 ppm is observed for Bu$_3$SnPh as neat liquid [48]. In addition, analysis of **2** by inductively coupled plasma atomic emission spectrometry (ICP-AES) indicated a tin loading of 1.0 mmol g^{-1} while the absence of chlorine was confirmed by potentiometry of silver salts.

2.2. Determination of the catalytic conditions

The Stille cross-coupling reaction was then considered and we focused our study on the evaluation of reagent **2** in the Stille cross-coupling reaction and the possibility to regenerate and re-use it along several cycles. The tetrakis(triphenylphosphine) palladium complex was chosen as catalyst although its poor thermal

stability [49]. This catalyst is commercially available or easily prepared [50], and has found a widespread use in this cross-coupling reaction.

Preliminary work was performed on 1-iodobenzene **3a** by reaction in refluxing toluene with a 1.1-fold excess of the supported phenyltin reagent **2** in the presence of Pd(PPh$_3$)$_4$ (5 mol%). Using these experimental conditions, a complete conversion in biphenyl **4a** was observed within 18 h (Scheme 2). By considering the less reactive p-iodoanisole **3b**, we found that 82% of conversion (56% of isolated yield) could be obtained within 48 h (Scheme 2). Then, we decided to perform further experiments in 48 h although such a reaction time could afford a higher decomposition of the catalyst and difficulties regarding recycling of **2**.

2.3. Scope and limitations of the reaction

Thereafter, various aryl and heteroaryl halides were considered in order to evaluate the scope of the reaction (Table 1). The electron-rich p-iodoanisole **3b** afforded 56% isolated yield in **4b** (entry 2) while the electron-poor 1-iodo-4-nitrobenzene **3c** furnished a higher yield of the desired Stille coupling product **4c** (82%, entry 3). No significant difference was obtained by using 1-bromo-4-nitrobenzene **3d** (84%, entry 4), although arylbromides are generally less reactive than aryliodides. The scope of the Stille cross-coupling reaction using **2** was further extended to reactions with halopyridines. The reaction was shown to be possible for the three regioisomers of bromopyridine (**3e**–**3g**, entries 5–7) with a lower reactivity of the 2-halopyridine **3e** as already observed by Buchwald in the chloropyridines series [51]. Subsequently, these cross-coupling reactions were extended to several functionalised 2-bromopyridines (**3h**–**3k**), affording the expected products in yields comparable with those obtained in solution (values in brackets in Table 1, entries 8–11). As expected, 2-chloropyridine **3l** afforded the product **4k** with a lower yield and a longer reaction time (120 h; entry 12, 53%) than **3k** (48 h; entry 11, 63%). Further extensions were performed on other heteroaromatic bromides with similar results. For instance, 5-bromopyrimidine **3m** (entry 13) was proved to react efficiently with **2** to afford the cross-coupling product **4m** in 79% isolated yield after 48 h heating. With both 2-bromo-thiophene **3n** and 5-bromo-thiophene-2-carbaldehyde **3o**, the desired products were obtained in good yields (entries 14 and 15), while a 55% yield was obtained by considering 3-bromothiophene **3p** in agreement with its lower reactivity in this type of reactions [52].

It is worth noting that in order to compare the results obtained with soluble phenyltributyltin to those observed with the supported organotin reagent **2**, parallel experiments were conducted using the same conditions (Pd(PPh$_3$)$_4$ 5 mol%, toluene, 110 °C, 48 h, see Table 1, values in brackets). Both set of experiments exhibit similar yields suggesting that the aryltin reagent is not affected by its linkage on the insoluble matrix (the linker seems to be long enough to allow similar accessibility to the tin center). In addition, whatever the tin reagent used (soluble or supported) biphenyl was observed as side product in every case with an amount increasing
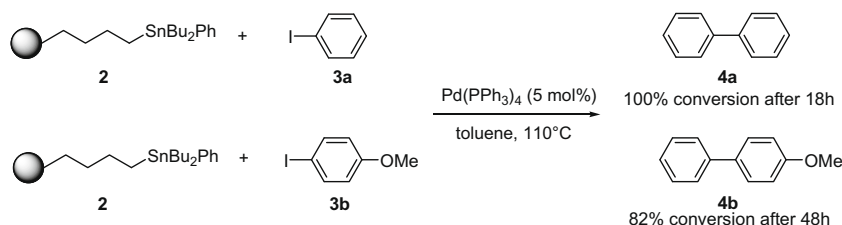
Scheme 2.

Table 1
Cross-coupling of arylhalides or heteroaryl halides.
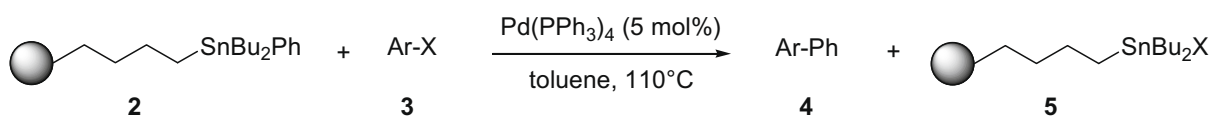
Entry	Aryl or heteroaryl halide		Product		Time (h)	Yield (%)[a]	Biphenyl (%)[b]
1		3a		4a	18	80 (81)	–
2		3b		4b	48	56 (59)	30 (28)
3		3c		4c	48	82 (77)	7 (5)
4		3d		4c	48	84 (76)	9 (8)
5		3e		4e	72	79 (65)	17 (27)
6		3f		4f	48	72 (75)	11 (16)
7		3g		4g	48	73 (73)	12 (12)
8		3h		4h	48	75 (76)	14 (7)
9		3i		4i	48	84 (90)	11 (3)
10		3j		4j	48	57 (59)	17 (21)
11		3k		4k	48	63 (63)	12 (18)
12		3l		4k	120	53 (48)	41 (38)
13		3m		4m	48	79 (78)	16 (17)
14		3n		4n	48	72 (67)	20 (10)
15		3o		4o	48	81 (80)	13 (11)
16		3p		4p	48	55 (58)	14 (13)

[a] Yield of isolated product after flash chromatography. The flash chromatographies were performed in order to separate the cross-coupling product from the palladium catalyst, the decoordinated PPh$_3$, its oxide (P(O)Ph$_3$) and the homocoupling product. Values in brackets are yields obtained in liquid phase using Bu$_3$SnPh as reagent.

[b] Homocoupling product observed on the crude by GC. Values in brackets correspond to percentage obtained in liquid phase using Bu$_3$SnPh as reagent.
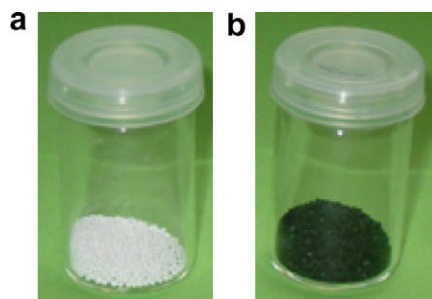
Fig. 1. Polymer-supported phenyltin reagent (a) before and (b) after Stille cross-coupling using Pd(PPh₃)₄ as catalyst.

when less activated substrates **3b**, **3j** and **3l** were involved. Its formation can be alternatively explained through a homocoupling product of reagent **2** or Bu₃SnPh in the presence of the palladium catalyst [53] or as a phenyl exchange from the triphenylphosphine [54–56].

2.4. Recycling experiments

At this stage, we decided to consider the recycling of the polymer-supported reagent **2**. 1-Bromo-4-nitrobenzene **3d** was chosen as the test substrate for these experiments in the coupling with polymer **2**. After the first cross-coupling, a simple filtration lead to the separation of the soluble product **4c** from the polymer-supported tin bromide **5** which appeared as a dark material (Fig. 1).

After being washed with THF, absolute ethanol and dried, the darkness was not removed, however regeneration of **2** was attempted using 2 equiv. of phenylmagnesium bromide. Then, the reactivity of the regenerated polymer-supported reagent **2** toward **3d** was evaluated using the same reaction conditions (48 h, 110 °C in toluene and with an additional amount of 5 mol% of Pd(PPh₃)₄). We observed a slight decrease of the conversion (80%) and obtained a lower yield in **4c** (66%, Table 2). This regeneration/recycling procedure was repeated a second and a third time in order to perform a third and a fourth cross-coupling reaction (Table 2). A dramatic decrease in the yield of the cross-coupling product was observed along the cycles (60% and 39% yield, respectively) with a concomitant increase of the yield of homocoupling product (biphenyl) and an increase of the darkening of the polymer.

A careful monitoring of the regeneration of **2** by ¹¹⁹Sn MAS-NMR indicated only a partial conversion of the supported Sn–Br moiety into Sn–Ph, explaining the lower conversion (Fig. 2). Similar results were observed by using an excess (5 equiv.) of phenylmagnesium bromide. A possible explanation of this result might be the presence of a palladium deposit in the macroporous polymer limiting the access to the polymer reactive sites. Accordingly, we decided to conduct experiments able to remove the palladium deposit from polymer **2**.

Numerous approaches have been developed for removing residual palladium from products [57]. Among them, we considered extraction methods using ligands able to give soluble complexes with palladium. Since polymer **2** is incompatible with aqueous washings (the Amberlyst XE-305 is a macroporous polystyrene/divinylbenzene and furthermore aqueous solutions can affect the resin), we first considered the use of TMEDA as a possible palladium ligand. For this purpose, the resin **5** recovered after the first cross-coupling reaction was poured in a THF solution of TMEDA (500 mg of **5** in 8 mL of THF containing 6.6 μmol of TMEDA), and stirred overnight before being washed with THF, absolute ethanol and dried. However when followed by reaction with phenylmagnesium bromide this procedure did not provide satisfactorily results. We then considered N,N-diethylphenylazothioformamide, previously used for palladium removal from API [58,59], to regenerate **2**. Washing polymer **5** with a THF solution of N,N-diethylphenylazothioformamide (L₁) during 18 h affords a clearer polymer. Thereafter, ¹¹⁹Sn MAS-NMR monitoring indicated a complete regeneration of **2** (in the limit of the detection method) after treatment with 2 equiv. of PhMgBr allowing its recycling according to Scheme 3. However, while a similar yield (71%) was obtained in the second cross-coupling with **3d**, a decrease was obtained for the further ones (Table 2). Indeed, ¹¹⁹Sn MAS-NMR experiments revealed that the regeneration of **2** was incomplete in cycles 3, 4 and 5 and presumably due to a partial removal of the palladium residues along the cycles. On the other hand, we were delighted to see that treatment of polymer **5** with a THF solution of 2,4,6-trimercapto-s-triazine (L₂) [60,61], followed by a reaction with 2 equiv. of PhMgBr allowed both the regeneration and recycling of polymer **2** at least 4 times (Fig. 2d). ICP-AES analyses indicated that the tin loading was maintained in the polymer with a good regeneration along 4 cycles, however, a significant decrease in the regeneration occurred for cycles 5–7 (Table 2). These results might be due to the repeated experimental conditions along the
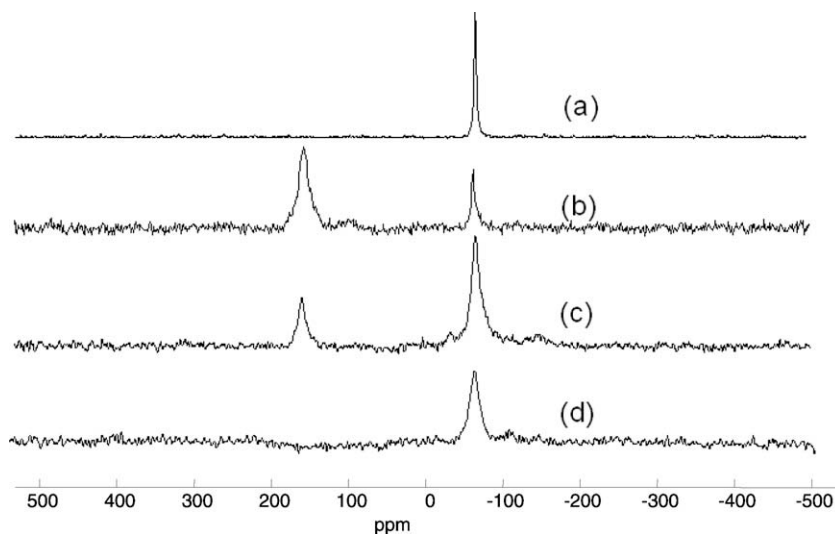
Table 2
Recycling and re-use of polymer-supported phenyltin reagent **2** in the Stille cross-coupling reaction.

Scavenger	No ligand			N,N-diethylphenylazothioformamide			2,4,6-trimercapto-s-triazine				
Cycle no.	Conv. (%)[a]	Yield (%)[b]	Homocoupling (%)[a]	Conv. (%)[a]	Yield (%)[b]	Homocoupling (%)[a]	Conv. (%)[a]	Yield (%)[b]	Homocoupling (%)[a]	Sn content in **4c** (ppm)[c]	Pd content in **4c** (ppm)[c]
1	>99	81	17	>99	82	10	>99	81	9	26	0.6
2	80	66	19	>99	71	16	>99	81	13	12.8	1.7
3	70	60	31	90	58	27	>99	78	17	9.3	0.3
4	51	39	41	75	49	26	97	76	19	1.35	<0.1
5	–	–	–	25	18	25	89	65	27	12.7	3.4
6	–	–	–	–	–	–	67	51	31	9.8	1
7	–	–	–	–	–	–	47	36	47	27.5[d]	–

[a] Determined by GC.
[b] Iolated yield obtained after flash chromatography.
[c] determined by ICP-MS.
[d] The high tin concentration measured is explained by a progressive abrasion of the polymer **2** inducing an important tin leaching.

Fig. 2. ^{119}Sn MAS-NMR spectra: (a) polymer **2** (δ = −43 ppm) obtained using **1** and Bu$_2$SnPhLi, (b) polymer recovered after Stille cross-coupling reaction (mixture of **2** and **5**), (c) polymer obtained after regeneration using 5 equiv. of PhMgBr (mixture of polymer **2** and polymer **5**) and (d) polymer obtained after treatment with 2,4,6-trimercapto-s-triazine, followed by regeneration using 2 equiv. of PhMgBr.

cycles which might induce some degradation of the macroporous polymer.

2.5. Tin contamination of the products

The residual amount of tin in product **4c** was measured by inductively coupled plasma atomic mass spectrometry (ICP-MS) at each cycle involving 2,4,6-trimercapto-s-triazine as a scavenger. The tin level was determined to be about 26 ppm in **4c** after the first cross-coupling reaction (Table 2). Thereafter, the residual amounts of tin measured were found to be around 10 ppm. It can be assumed that the higher value (26 ppm) is due to a slight leaching of non-linked tin moieties confined in the macroporous polymer **2** as its preparation involves soluble Bu$_2$SnPhLi. It appears that a tin content of 10 ppm is the average value in the subsequent reactions when the Stille cross-coupling reaction using **2** was conducted under our usual experimental conditions. The higher level of pollution (27.5 ppm) measured for cycle 7 can be explained by a significant alteration of the polymer support. These results point out the interest of this method when applied in appropriate experimental conditions (solvent, temperature and stirring mode) in order to control tin contamination around 10 ppm [62]. This result must be compared to the huge pollution obtained for the same product when the reaction was performed in solution with phenyltributyltin (about 60 000 ppm measured by ICP-AES). In addition, a low concentration of palladium in the products (measured around

1 ppm by ICP-MS) was found in spite of the use of a significant amount of a poorly stable palladium catalyst.

3. Conclusion

We have developed a clean and efficient method for the synthesis of biaryl and aryl–heteroaryl units that involves the use of a polymer-supported phenyltin reagent. The yields obtained by this methodology are similar to those obtained using its liquid analog (Bu$_3$SnPh) in liquid phase. The tin contamination of about 10 ppm in the cross-coupling products together with a palladium contamination of about 1 ppm place this methodology among the cleaner ones to achieve Stille cross-coupling reactions. In addition, after identification of the problems, the supported phenyltin reagent was regenerated using an appropriate procedure and re-used 4 times with preservation of good yields and without meaningful evolution of the tin pollution in the products. Current investigations are now in progress in order to consider the use of other polymer-supported organotin reagents either as more stable catalysts in order to generalize and simplify the described procedure.

4. Experimental

4.1. General

Starting materials were purchased from commercial suppliers and used without further purification. Di-n-butyltin dichloride and tributyltin chloride were obtained from Chemtura (Bergkamen). Dibutylphenyltin hydride [46] and 6-bromo-[1,3]-dioxolan-2-ylpyridine [63] were prepared according to the literature procedures. The polystyrene–divinylbenzene matrix (Amberlite XE-305 with diameter = 0.7 mm and pore = 90 nm) was purchased from Interchim.

NMR spectra were recorded on a Bruker Avance 300 spectrometer operating at 300.13 MHz for ^{1}H, 75.47 MHz for ^{13}C and 111.92 MHz for [119]Sn or on a Bruker ARX 400 spectrometer operating at 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C and 149.21 MHz for [119]Sn. NMR spectra were recorded in CDCl$_3$. Chemical shifts are given in ppm as δ values related to tetramethylsilane (^{1}H, ^{13}C) or tetramethylstannane ([119]Sn) and coupling constants are given in Hz. Solid-state MAS-NMR experiments were performed at room
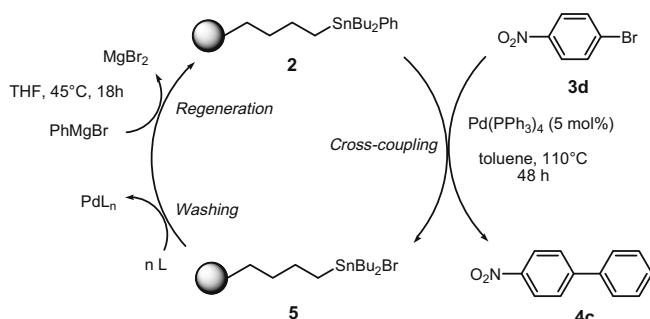
Scheme 3. Stille cross-coupling reaction of supported phenyltin reagent **2** and its regeneration procedure from the supported tin halide.

temperature with a Bruker Avance 500 spectrometer operating at 186.5 MHz for [119]Sn with a 4 mm double-bearing Bruker probehead. [119]Sn MAS spectra were acquired with ^{1}H TPPM decoupling during acquisition and a MAS frequency of 10 kHz. The repetition time was set to 20 s for quantitative purposes since [119]Sn T_1 were measured to be in the range of 3 s for the studied Sn cores contained in the present work. In a control experiment performed on a mixture of two different Sn species (Sn–X, Sn–C), with a repetition time of 300 s no change in the integration was observed when compared to spectra recorded with a repetition time of 20 s. Spectra were referenced to Me_4Sn with use of Ph_4Sn as a secondary reference ($\delta = -121.15$ ppm).

Mass spectra were obtained in EI mode (70 eV) using a quadrupolar analyser (HP apparatus, Engine 5989A) in direct introduction mode. IR spectra were recorded with a Bruker IFS Vector 22 apparatus. THF was distilled from sodium-benzophenone, toluene from sodium and cyclohexane from CaH_2 prior to use. TLC analyses were carried on silica-coated plates (Merck Kieselgel 60F254).

4.2. Synthesis of poly(4-chlorobutyl)styrene 1

To a suspension of Amberlite XE-305 (6.0 g) in dry cyclohexane (15 mL) were added successively, under argon, TMEDA (8.7 mL, 57.7 mmol) and a solution of n-butyllithium (2.5 M in hexanes, 27.7 mL, 69.2 mmol). The reaction mixture was heated at 65 °C for 4 h. The polymer was then washed under argon with dry cyclohexane (8 × 20 mL) and this procedure (TMEDA, n-butyllithium) was repeated once. The orange resulting lithiated polymer was then washed under argon with dry THF (12 × 20 mL). 1-Bromo-4-chlorobutane (7.9 mL, 68.6 mmol) was added, at 0 °C under argon, on the lithiated polymer suspension in dry THF (50 mL). The mixture was stirred at room temperature for 18 h then the resulting polymer was successively washed with a mixture of THF/H_2O (1:1 v/v, 40 mL), THF (6 × 40 mL), absolute ethanol (4 × 40 mL) and dried under vacuum (0.5 mbar) at 60 °C for 5 h. Polymer 1 was obtained as a white resin (7.8 g) and was found to contain 2.21 mmol of C–Cl/g: Elemental analysis found (%): C 82.59, H 7.72, Cl 7.86, Br 0.43; IR (KBr): $\bar{v}$ = 3082, 3059, 3025, 2921, 2850, 1942, 1870, 1802, 1719, 1601, 1586, 1493, 1452, 1028, 759, 698, 650, 539 cm^{-1}.

4.3. Preparation of poly[4-(dibutylphenylstannyl)butyl]styrene 2

Supported phenyltin reagent 2 was obtained according to a previously described procedure by reacting supported butyl chloride 1 with $PhSnBu_2Li$ [41,46]. When regenerated from supported triorganotin halide 5, supported phenyltin reagent 2 was obtained by reacting with phenylmagnesium bromide (vide infra). For comparative experiments, phenyltributyltin was obtained by trapping of phenylmagnesium bromide with tributyltin chloride.

4.4. Typical procedure for the Stille cross-coupling reaction

In a Schlenk tube were successively added the polymer 2 (530 mg, 0.53 mmol), the aryl halide or the heteroaryl halide (0.47 mmol), $Pd(PPh_3)_4$ (27 mg, 0.024 mmol) and toluene (8 mL). The reaction mixture was heated at 110 °C for 48 h. The polymer was washed with THF (6 × 10 mL) and the filtrate was concentrated under vacuum. The resulting crude residue was analyzed by GC and purified by flash chromatography on silica gel using petroleum ether/ethyl acetate as eluent. On the other hand, the resulting polymer 5 was washed with absolute ethanol (4 × 10 mL) and dried under vacuum (0.5 mbar) at 60 °C for 5 h.

4.5. Typical procedure for the washing of polymer 5

To a suspension of polymer 5 (500 mg, 0.5 mmol) in THF (10 mL) was added N,N-diethylphenylazothioformamide (22 mg, 0.1 mmol) or 2,4,6-trimercapto-s-triazine (18 mg, 0.1 mmol). The reaction mixture was stirred at 60 °C for 18 h. The polymer was filtered and washed successively with THF (6 × 10 mL) and with absolute ethanol (6 × 10 mL) before dried under vacuum (0.5 mbar) at 60 °C for 5 h.

4.6. Typical procedure for the regeneration of polymer 2

To a suspension of polymer 5 (500 mg, 0.5 mmol) in dry THF (10 mL) was added phenylmagnesium bromide (1 mL, 1 M in Et_2O, 1 mmol). The reaction mixture was stirred and refluxed at 35 °C for 18 h. The polymer was filtered and washed with THF (6 × 10 mL), then with absolute ethanol (6 × 10 mL) and dried under vacuum (0.5 mbar) at 60 °C for 5 h.

4.7. Characterization of the cross-coupling products

4.7.1. Biphenyl (4a) [64] (CAS: 92-52-4)
Compound 4a was obtained from iodobenzene (0.5 mmol) and polymer 2 (0.56 mmol) as a white solid after purification by flash chromatography (petroleum ether/ethyl acetate 9:1, $R_f = 0.8$): 80%. ^{1}H NMR: δ 7.60 (m, 4H), 7.45 (m, 4H), 7.35 (m, 2H); ^{13}C NMR: δ 141.4 (2C), 128.9 (4C), 127.4 (2C), 127.3 (4C); MS (EI, 70 eV): m/z 154 (100, M$^{+\cdot}$), 76(13). mp 71 °C. (from EtOH, lit. [64], 71–72 °C).

4.7.2. 4-Methoxybiphenyl (4b) [64] (CAS 613-37-6)
Compound 4b was obtained from 4-bromoanisole as a white solid after purification by flash chromatography (petroleum ether, $R_f = 0.41$): 56%. ^{1}H NMR: δ 7.5–7.6 (m, 4H), 7.42 (m, 2H), 7.31 (m, 1H), 6.98 (d, 2H, [3]J 8.7), 3.86 (s, 3H). ^{13}C NMR: δ 159.3, 141.0, 133.9, 128.8 (2C), 128.3 (2C), 126.9 (2C), 126.8, 114.3 (2C), 55.4; MS (EI, 70 eV): m/z 184 (100, M$^{+\cdot}$), 169(56), 152(8), 141(64), 115(50) mp 89 °C. (from EtOH, lit. [64], 91 °C).

4.7.3. 4-Nitrobiphenyl (4c) [65] (CAS: 92-93-3)
Compound 4c was obtained from 1-iodo-4-nitrobenzene or 1-bromo-4-nitrobenzene as a light yellow solid after purification by flash chromatography (petroleum ether/ethyl acetate 98:2, $R_f = 0.53$): 81%. ^{1}H NMR: δ 8.31 (AA'BB'system, 2H, J 8.9), 7.75 (AA'BB'system, 2H, J 8.9), 7.63 (m, 2H), 7.43–7.54 (m, 3H); ^{13}C NMR: δ 147.7, 147.3, 138.9, 129.3 (2C), 129.1, 127.9 (2C), 127.5 (2C), 124.2 (2C); IR(KBr): 2929, 1575, 1559, 1514, 1345, 1286, 1105, 853, 740, 700, 693. MS (EI, 70 eV): m/z 199 (84, M$^{+\cdot}$), 169(44), 152(100), 141(43); mp 113 °C (from EtOH lit. [65], 115 °C).

4.7.4. 2-Phenylpyridine (4e) [66,67] (CAS: 1008-89-5)
Compound 4e was obtained from 2-bromopyridine as a colorless liquid after purification by flash chromatography (petroleum ether/ethyl acetate 9:1; $R_f = 0.26$): 79%. ^{1}H NMR: δ 8.70 (bd, 1H, [3]J 4.8), 7.98 (m, 2H), 7.71–7.90 (m, 2H), 7.38–7.51 (m, 3H), 7.19–7.26 (m, 1H); ^{13}C NMR: δ 156.2, 148.3, 138.1, 135.4, 127.6, 127.4 (2C), 125.6 (2C), 120.8, 119.2; MS (EI, 70 eV): m/z 155 (100, M$^{+\cdot}$), 154(65), 128(10), 127(12), 77(12).

4.7.5. 3-Phenylpyridine (4f) [66,67] (CAS: 1008-88-4)
Compound 3f was obtained from 3-bromopyridine as a colorless oil after purification by flash chromatography (petroleum ether/ethyl acetate 8:2, $R_f = 0.17$): 72% ^{1}H NMR: δ 8.86 (s, 1H), 8.61 (d, 1H, [3]J 4.0), 7.88 (bd, [3]J 8.0), 7.57–7.62 (m, 2H), 7.35–7.55 (m, 4H); ^{13}C NMR: δ 148.7, 148.6, 138.1, 136.9, 134.6, 129.3 (2C),

128.4, 127.4 (2C), 123.8; MS (EI, 70 eV): m/z 155 (100, M$^{+\cdot}$), 154(39), 127(12).

4.7.6. 4-Phenylpyridine (**4g**) [68] (CAS: 939-23-1)

Compound **3g** was prepared from 4-bromopyridine hydrochloride using diisopropylamine as a base. For this purpose 0.47 mmol of diisopropylamine was added to obtain 4-bromopyridine and the mixture was subsequently submitted to usual cross-coupling reaction conditions. The product **3g** was obtained as a white solid after purification by flash chromatography (petroleum ether/ethyl acetate 7:3, R_f = 0.47): 73%. ^{1}H NMR: δ 8.66 (d, 2H, ^3J 4.6,), 7.64 (m, 2H), 7.42–7.53 (m, 5H); ^{13}C NMR: δ 150.3 (2C), 148.4, 138.2, 129.2 (3C), 127.1 (2C), 121.7 (2C); MS (EI, 70 eV): m/z 155 (100, M$^{+\cdot}$), 154(44), 128(10), 127(12), 115(8), 102(8), 77(9); mp 73 °C (from hexane, lit. [67], 73–74 °C).

4.7.7. 6-Phenylpyridine-2-carbaldehyde (**4h**) [69] (CAS: 157402-44-3)

Compound **4h** was obtained from 6-bromopyridine-2-carbaldehyde as a yellow liquid after purification by flash chromatography (petroleum ether/ethyl acetate 9:1, R_f = 0.6): 75%. ^{1}H NMR: δ 10.2 (s, 1H), 8.10 (dd, 2H, ^3J 6.9, ^4J 1.7), 7.91–7.97 (m, 3H), 7.47–7.55 (m, 3H); ^{13}C NMR: δ 193.9, 157.9, 152.8, 138.1, 137.8, 129.7, 129.0 (2C), 127.0 (2C), 124.5, 119.8; IR(neat): 3063, 3036, 2830, 1707, 1587, 1451, 1301, 1217, 760, 693. MS(CI, NH$_3$): m/z 184 (100, M+H)$^+$.

4.7.8. 2-[1,3]-Dioxolan-2-yl-6-phenylpyridine (**4i**) [63] (CAS: 897943-06-5)

Compound **4i** was obtained from 6-bromo-[1,3]-dioxolan-2-ylpyridine as a colorless oil after purification by flash chromatography (petroleum ether/ethyl acetate 8:2, R_f = 0.6): 84%. ^{1}H NMR: δ 8.04 (m, 2H), 7.80 (t, ^3J 7.8), 7.72 (dd, ^3J 7.9, ^4J 1.1), 7.35–7.55 (m, 4H), 5.94 (s, 1H), 4.12–4.25 (m, 4H); ^{13}C NMR: δ 156.0, 138.0, 136.5, 128.4, 128.1, 127.9 (2C), 126.1 (2C), 119.7, 117.8; 103.1, 64.6 (2C); MS (EI, 70 eV): m/z 227 (4, M$^{+\cdot}$), 184(100), 154(27), 127(16), 73(70), 45(28).

4.7.9. 2-Methoxy-6-phenylpyridine (**4j**) [70] (CAS: 35070-08-7)

Compound **4j** was obtained from 2-bromo-6-methoxypyridine as a colorless oil after purification by flash chromatography (petroleum ether, R_f = 0.28): 57%. ^{1}H NMR: δ 8.09 (dd, 2H, ^3J 8.2, ^4J 1.5), 7.63 (dd, 1H, ^3J 7.6, ^3J 8.1), 7.38–7.53 (m, 3H), 7.36 (d, 1H, ^3J 7.6), 6.72 (d, 1H, ^3J 8.1), 4.05 (s, 3H);. ^{13}C NMR: δ 163.8, 154.7, 139.2, 139.1, 128.9, 128.7 (2C), 126.8 (2C), 112.8, 109.3, 53.2; IR (KBr): 3061, 2946, 2926, 2852, 1635, 1599, 1589, 1576, 1499, 1449, 1256, 1151, 763, 693. MS (EI, 70 eV): m/z 185 (76, M$^{+\cdot}$), 184(100), 155(39), 154(70), 127(15), 115(10), 77(22).

4.7.10. 3-Nitro-6-phenylpyridine (**4k**) [71] (CAS: 89076-64-2)

Compound **4k** was obtained from 2-chloro-5-nitropyridine or 2-bromo-5-nitropyridine as a light yellow solid after purification by flash chromatography (petroleum ether/ethyl acetate 9:1; R_f = 0.43). ^{1}H NMR: δ 9.5 (d, 1H, ^4J 2.4), 8.52 (dd, 1H, ^3J 8.8, ^4J 2.4), 8.06–8.11 (m, 2H), 7.91 (d, 1H, ^3J 8.8), 7.52–7.55 (m, 3H); ^{13}C NMR: δ 162.5, 145.3, 142.9, 137.1, 132.0, 130.9, 129.1 (2C), 127.7 (2C), 120.0; MS (EI, 70 eV): m/z 200 (100, M$^{+\cdot}$), 154(44), 127(98), 115(28), 77(62), 51(32). mp 118 °C. (from MeOH).

4.7.11. 5-Phenylpyrimidine (**4m**) [72] (CAS: 34771-45-4)

Compound **4m** was obtained from 5-bromopyrimidine as a colorless liquid after purification by flash chromatography (petroleum ether/ethyl acetate 7:3; R_f = 0.15): 79%. ^{1}H NMR: δ 9.19 (s, 1H), 8.94 (s, 2H), 7.42–7.58 (m, 5H). ^{13}C NMR: δ 157.6, 155.0 (2C), 134.4, 134.3, 129.5 (2C), 129.1, 127.1 (2C); MS (EI, 70 eV): m/z 156 (100, M$^{+\cdot}$), 155(22), 102(75), 76(13), 51(13).

4.7.12. 2-Phenylthiophene (**4n**) [64] (CAS: 825-55-8)

Compound **4n** was obtained from 2-bromothiophene as a white solid after purification by flash chromatography (petroleum ether/ethyl acetate 85:15; R_f = 0.75): 72%. ^{1}H NMR: δ 7.46–7.55 (m, 2H), 7.13–7.38 (m, 5H), 6.95–7.0 (m, 1H); ^{13}C NMR: δ 143.4, 133.3, 127.8, 127.7 (2C), 127.0, 126.2, (2C), 124.9, 123.7; MS (EI, 70 eV): m/z 160.0 (100, M$^{+\cdot}$), 115(27). mp 35 °C (from hexane, lit. [64], 35–36 °C)

4.7.13. 5-Phenylthiophene-2-carbaldehyde (**4o**) [73] (CAS: 19163-21-4)

Compound **4o** was obtained from 5-bromothiophene-2-carbaldehyde as a light green solid after purification by flash chromatography (petroleum ether/ethyl acetate 85:15; R_f = 0.72): 81%. ^{1}H NMR: δ 9.89 (s, 1H), 7.74 (d, 1H, ^3J 3.9), 7.67 (m, 2H), 7.38–7.47 (m, 4H); ^{13}C NMR: δ 183.0, 154.5, 142.6, 137.5, 133.2, 129.6, 129.4 (2C), 126.6 (2C), 124.2; IR (KBr): 3095, 3060, 1652, 1443, 1234, 1065, 819, 759, 752, 680. MS (EI, 70 eV): m/z 188 (80, M$^{+\cdot}$), 187(100), 115(86). mp 81 °C (from hexane, lit. [74], 80–81 °C).

4.7.14. 3-Phenylthiophene (**4p**) [64,75] (CAS: 2404-87-7)

Compound **4p** was obtained from 3-bromothiophene as a colorless solid after purification by flash chromatography (petroleum ether/ethyl acetate 85:15; R_f = 0.75): 55%. ^{1}H NMR: δ 7.62 (m, 2H), 7.3–7.53 (m, 6H). ^{13}C NMR: δ 141.4, 136.0, 128.9 (2C), 127.3, 126.6 (2C), 126.5, 126.3, 120.4; MS (EI, 70 eV): m/z 160 (100, M$^{+\cdot}$), 159(12), 134(10), 128(16), 115(43), 89(14). mp 89 °C. (from EtOH, lit. [64], 89–91 °C).

4.8. Evaluation of tin and palladium contamination

The quantification of tin and palladium was measured as total tin or total palladium contamination by ICP-AES or ICP-MS techniques in UT2A Laboratory (Pau, France) after careful mineralization of the samples according to a previously described procedure [76,77].

Acknowledgements

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