

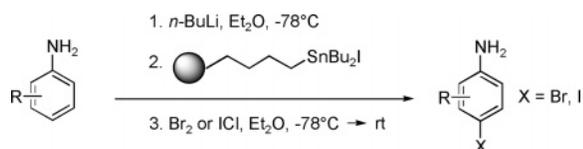
Polymer-Supported Organotin Reagents for Regioselective Halogenation of Aromatic Amines

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Polymer-supported triorganotin halides were used in the halogenation reaction of aromatic amines. Treatment of aromatic amines with *n*-butyllithium and polymer-supported organotin halides gave the corresponding polymer-bound *N*-triorganostannylamines, which by treatment with bromine or iodine monochloride gave the *para*-halogenated aromatic amines with high yields and high selectivities. The polymer-supported organotin halides reagents regenerated during the course of the halogenation reaction can be reused without loss of efficiency. The presence of tin residues in halogenated aromatic amines was also investigated and evaluated at under 20 ppm after three runs.

Functional aromatic halides such as bromo- and iodoanilines are key intermediates in organic chemistry because of their usefulness for creation of carbon-carbon bonds via cross-coupling reactions¹ or for preparation of organometallic reagents.² In addition, numerous biologically active molecules contain halogenated aromatic units in their structure. The direct halogenation of activated aromatic systems using either Br₂ or I₂ generates hydro-

halic acids (HBr or HI) able to cause protolytic cleavage of Ar-X with concomitant decrease of the yields.³ To overcome these problems, various bromination and iodination reagents have been developed, including NBS,⁴ NBS-HZSM-5,⁵ NBS-amberlyst,⁶ NIS,⁷ and NIS-CF₃SO₃H.⁸ Bromination or iodination reactions using halogens associated with quaternary ammonium salts such as (R₄N⁺Br⁻, Br₂), (R₄N⁺I⁻, Cl₂), (R₄N⁺I⁻, 2Cl₂), or (R₄N⁺I⁻, Br₂) species in both free⁹ and polymer-supported form¹⁰ have also been reported. Despite these improvements, some of these methods suffer from a lack of regioselectivity accompanied by a low control over polyhalogenation reactions. Recently, an interesting method for the selective bromination of aromatic amines using the corresponding *N*-trimethylstannylamine intermediates has been reported,¹¹ but in this case, the toxicity of the trimethyltin reagents and the difficulty of completely removing organotin residues from final products constitute two limitations for this methodology. To circumvent this problem, another recent method using boron instead of tin has been reported.¹² High *para* selectivities were obtained, but this way possibly creates another problem for removing the boron impurities.

Taking into account the above-mentioned remarks, our involvement in the development of polymer-supported organometallic reagents led us to an alternative route to obtain *para*-halogenated aromatic amines using polymer-supported *N*-triorganostannylamines as key intermediates. This strategy should therefore combine the advantages of the previously described method¹¹ with those expected from polymer-supported tin reagents in terms of handling, purification, and low pollution by tin residues in the final products. Herein, we wish to report our results concerning this study focusing both on the efficiency and the regioselectivity of the halogenation reaction of aromatic amines and on the negligible presence of tin in the isolated halogenated amines.

Several examples of polymer-supported organotin hydrides¹³ and chlorides,¹⁴ as well as polymer-supported vinyltins,¹⁵ have been reported. The investigations have

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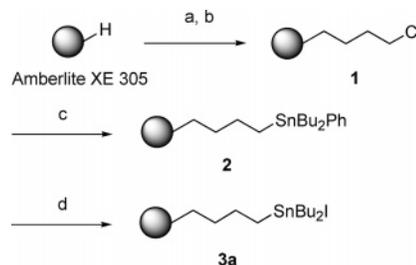
been mainly devoted to tin hydride mediated radical reactions,¹⁶ but examples involving Stille cross-coupling reactions¹⁷ or allylation reactions^{13f,14a,18} have also been reported.

In our case, we chose the polymer-supported triorganotin iodide **3a**, which has been previously described and characterized.¹⁹ The tetramethylene spacer aims at ensuring sufficient mobility and accessibility to the functionality as pointed out previously.^{13d,16d,19} Furthermore, the problem of tin releasing, which usually occurs when tin is located on the β -position relative to the aromatic ring of the polystyrene support, is avoided.^{13d,16d} Accordingly and because of its ease of formation and good loading (1.1–1.3 mmol.g⁻¹), resin **3a** appeared to be among the more suitable ones for our solid-phase application.

Polymer-supported triorganotin halides were prepared according to the literature^{13d,16d,19} in three steps (Scheme 1). Treatment of the lithiated Amberlite XE 305^{20,21} with 1-bromo-4-chlorobutane gave resin **1**, which was stannylated with Bu₂SnPhLi to afford stannylated polymer **2**. Halodearylation of **2** with a solution of iodine in ethanol led to the corresponding supported triorganotin iodide **3a**.

The loading of the solid support was evaluated to be 1.30 mmol.g⁻¹ from halogen and tin elemental analyses. The formation of the polymer-supported triorganotin halide **3a** was first established on the basis of the IR

SCHEME 1. Synthesis of the Polymer-supported Triorganotin Iodide **3a**^a



^a Reagents and conditions: (a) *n*-BuLi/TMEDA, cyclohexane, 65 °C. (b) Br-(CH₂)₄-Cl, THF, 0 °C to rt. (c) Bu₂SnPhLi, THF, rt. (d) I₂, EtOH, 60 °C.

spectrum, which showed total disappearance of the well-defined absorption band at 726 cm⁻¹ indicative of the Sn–Ph bond. Solid-state ¹¹⁹Sn MAS NMR of the polymer-supported triorganotin iodide **3a** revealed a single signal at 104 ppm (reference Ph₄Sn, $\delta_{\text{Sn}} = -97.35$ ppm). A comparison with the ¹¹⁹Sn MAS NMR spectra of the stannylated polymer **2** ($\delta = -20$ ppm) was indicative of its complete conversion into trialkyltin iodide **3a** in the limits of the NMR measurement.²²

We then studied the efficiency of the polymer-supported triorganotin halide **3a** on the selective bromination of aromatic amines for comparison with the liquid-phase synthesis using soluble trimethyltin chloride. A variety of aromatic amines were selected and submitted to the bromination reaction after conversion to *N*-triorganostannylamines (Table 1). In a typical procedure, a solution of the *N*-lithio aromatic amine **5** (ArNH-Li), formed by treating the corresponding amine **4** with *n*-BuLi in diethyl ether, was added at -78 °C under argon to a stirred mixture of solid-supported triorganotin reagent **3a** in diethyl ether. The temperature of -78 °C was chosen in order to avoid side reactions when other reactive groups are contained in the molecule, as for instance with **4i**. The resulting intermediate **6** was reacted in situ with bromine (without further characterization of the supported *N*-stannylated amine²³) and the reaction mixture was stirred for 2 h before filtration (Scheme 2).

After the usual treatments and concentration of the filtrate, the crude bromoanilines were submitted to analyses in order to establish the selectivity of the reaction, both for regioselectivity and for ratio monosubstitution products/polysubstitution products (Table 1).

When compared to the liquid-phase synthesis using Bu₃SnCl (Table 1, entry 1a) or Me₃SnCl (Table 1, entry 1b), the use of polymer-supported *N*-stannylated reagents **6a–i** (obtained in situ from triorganotin halide **3a** and aromatic amines **4a–i** through their *N*-lithioderivatives **5a–i**) allows an improved selectivity with a higher preference for the monosubstitution, which occurs mainly on the *para* position relative to the amino group to afford

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(20) Macroporous resin available from Rohm & Haas as 700 μm beads with permanent pores of 90 nm (manufacturer specifications). These values have been reexamined by the Bordeaux group and measured as 550–600 μm for the beads diameter and 200 nm as an average pores size.²¹

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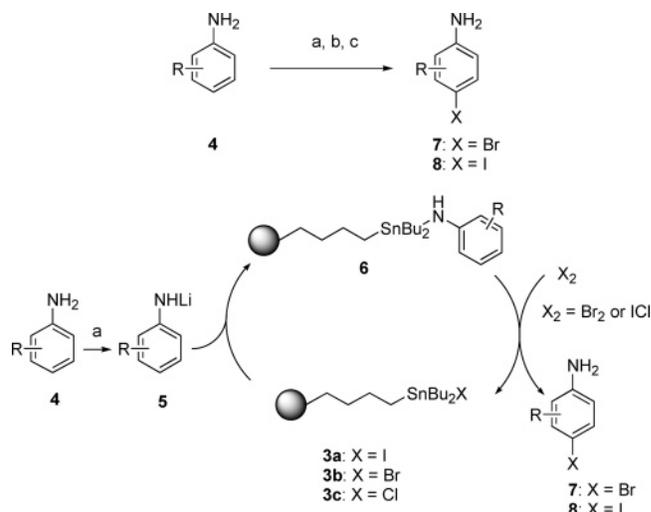
TABLE 1. Regioselective Bromination of Aromatic Amines via Polymer-Supported *N*-Triorganostannylamines Obtained from **3a or in Liquid Phase (entries 1a–1b and **2** for comparison)**

entry	amine	major product	yield (%) ^a	selectivity (%) ^b		
				mono-(<i>p/o</i>) ^c	di- ^d	tri- ^e
1a ^f			nd ^g	67 (99/1)	31	2
1b ^h			nd ^g	66 (99/1)	32	2
<hr/>						
2			76	91 (99/1)	8.5	0.5
3			55	100 (100/0)	0	0
4			46	91 (99/1)	9	0
5			70	90 (87/13)	10	0
6			73	91 (100/0)	9	0
7			41	83 (94/6)	17	0
8			53	61 (ortho)	39 ⁱ	0
9			42	82 (100/0)	18	0
10			68	100 (100/0)	0	0

^a Isolated yield of 4-substituted derivative (**7a–i**) after column chromatography. ^b Selectivity determined by ¹H NMR spectroscopy or GC–MS analysis of the crude. ^c Monosubstitution: ratio between 4-substituted and 2-substituted compounds. ^d Disubstitution in positions 2,4. ^e Trisubstitution in positions 2,4,6. ^f Results obtained in liquid phase using Bu₃SnCl. ^g Yield not determined because of the presence of R₃SnBr in **7a**. ^h Results obtained in liquid phase using Me₃SnCl. ⁱ 2,6-Dibromo-4-methoxyaniline.

aromatic amines **7a–i** (Table 1). In the case of *p*-methoxyaniline **4g** where this *para* substitution is prohibited, it is worth noticing that the regioselectivity is governed by the amino group (obtaining **7g**). This governing effect of the amino group is also observed with *o*-methoxyaniline **4e** (obtaining **7e**). These results can be rationalized by the effect of the triorganotin substituent which strongly prohibits the *ortho* substitution since effective reactive species are *N*-stannylated amines. Furthermore, the polymer matrix seems also to be sterically involved in this selectivity at least for the limitation of polysubstitution products. Accordingly, the

SCHEME 2^a



first substitution is likely to occur on the *para* position, whereas the second substitution (obtaining the 2,4-disubstituted product) appears to be strongly disfavored as the steric requirements near the *ortho* position are increasing. In practice, because of the difficulty of having a perfect 1/1 stoichiometry between *N*-stannylated amines and bromine, most of the reactions have been achieved with a slight excess of bromine inducing the concomitant formation of polyhalogenated species. This point has been checked in an experiment starting from 0.8 equiv of bromine for 1 equiv of **4a**, and in this case a conversion rate of 57% in monosubstituted compound **7a** (*para/ortho* > 99/1) was obtained with a negligible amount of disubstituted species (less than 1%). Finally, it appears that the nature of the halogen in the tin halide precursor is of no importance as pointed out by further recycling experiments (vide infra).

Moreover, after chromatographic purification on silica gel of the crude products, the analysis by ICP–MS of isolated amine **7a** exhibited low or insignificant tin contamination (<35 ppm). In comparison, the reaction using soluble tributyltin chloride gave the product **7a** with a tin pollution of about 60 000 ppm (6%) after a single precipitation of the tin halide as tributyltin fluoride using a potassium fluoride solution in aqueous acetone and subsequent chromatography on silicagel.²⁴ The pollution by tin residues was reduced to about 9000 ppm (0.9%) after one recrystallization in petroleum ether, a method that can be improved by several successive recrystallizations, but we were unable to obtain a tin pollution under 1000 ppm (0.1%) in a reasonable delay. The recently proposed purification method using a KF/silica mixture²⁵ has not been attempted for our compounds because we considered it had poor chance to be competitive with a method involving a complete immobilization of the organotin reagent in terms of control of tin pollution of the final products, whatever their nature and their polarity.

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TABLE 2. Regeneration of Polymer-Supported Tin Reagent 3b

run	yield (%) ^a	% Sn ^b	N ^{Sn} (mmol·g ⁻¹) ^c	Sn pollution (ppm) ^d
1	76	15.5	1.3	32
2	78	15.2	1.3	24
3	74	15.1	1.3	26
4	75	15.1	1.3	19
5	77	15.4	1.3	6

^a Isolated yields in 4-bromoaniline (the *para* isomer **7a** was obtained with a purity above 99%). ^b Percentage of tin in the regenerated polymer **3b** determined by elemental analysis (these values in the range of 15.3 ± 0.3 can be considered as unmodified if the measure uncertainty for this type of analyses is taken into account). ^c Tin loading on the regenerated polymer **3b**. ^d Tin pollution in the final products **7a** determined by ICP-MS analysis.

Obviously, the use of the polymer-supported organotin reagent constitutes a strong improvement in this type of synthesis because it allows an improved selectivity together with an easy workup to recover the products (in the filtrate) and the new polymer-supported triorganotin bromide **3b** (retained by filtration). The insignificant pollution of the products by tin residues is also confirmed.

At this stage, the complete validity of the method requires the possibility of recycling the polymer-supported triorganotin bromide **3b** recovered at the end of the reaction. For this purpose, **3b** was successively washed with THF and absolute ethanol, dried under vacuum, and characterized by elemental analysis, IR and ¹¹⁹Sn MAS NMR (single signal at 157 ppm)²² before reuse for a similar reaction.

Table 2 shows the functional group capacity values, as well as the yields of 4-bromoaniline **7a** obtained after one to five regeneration cycles. The recycled resin **3b** gave similar high selectivity and reactivity on subsequent reactions. We have additionally checked the presence of tin in the final products by ICP-MS and found low-level or insignificant tin contamination (32 ppm to 6 ppm). These results are in agreement with the constant tin loading in polymer **3b** showing that the loss of tin from the supported reagent **6a** is negligible after five runs (Table 2). The small decrease in tin pollution after the first runs can be explained by a leaching of nonlinked organotin reagents.

This methodology was finally extended to the iodination reaction of the same aromatic amines. In this case, we used the polymer-supported tin reagent **3a** and iodine monochloride as halogenation reagent. Thus, when a solution of iodine monochloride in diethyl ether was added at -78 °C to the solid-supported *N*-triorganostannylamine **6**, the iodination took place very smoothly (24 h at room temperature) to give the iodoanilines **8a–h** in 44–67% yield when the reactions were performed in the dark (iodoanilines are light-sensitive compounds) (Scheme 2, Table 3).

As shown in Table 3, when compared to the bromination reaction, as a result of the difference in the size of halogens, the iodinated aromatic amines were obtained with a higher *para* selectivity (if the less favorable case **4d** is considered) and minor amounts of polyhalogenated compounds. The polymer was completely regenerated as a polymer-supported triorganotin chloride **3c** (¹¹⁹Sn MAS NMR δ = 170 ppm)²² during the course of the reaction and easily recovered by filtration. In addition, in an

TABLE 3. Regioselective Iodination of Aromatic Amines via Polymer-Supported N-Triorganostannylamines Obtained from 3a

entry	amine	product	yield (%) ^a	selectivity (%) ^b		
				mono- (<i>p/o</i>) ^c	di- ^d	tri- ^e
1			61	100 (100/0)	0	0
2			63	100 (100/0)	0	0
3			67	99 (99/1)	1	0
4			44	88 (99/1)	12	0

^a Isolated yield after column chromatography. ^b Selectivity determined by ¹H NMR spectroscopy of the crude. ^c Monosubstitution: ratio between 4-substituted and 2-substituted compounds. ^d Disubstitution in positions 2,4. ^e Trisubstitution in positions 2,4,6.

experiment using **3c** as the organotin precursor to obtain **6a**, the subsequent bromination afforded **7a** in 71% yield and without modification of the products distribution.

From a mechanistic point of view, the nucleophilic counterion (Br⁻ or Cl⁻) expected from the reaction of *N*-triorganostannylamine **6** with Br₂ or ICl is involved for the in situ regeneration of the polymer-supported triorganotin halides **3b** and **3c**. Their recovery by simple filtration at the end of the reaction allows their reuse for many times without loss of activity and selectivity.

The use of polymer-supported triorganotin halides as activating reagents for halogenation of anilines and related compounds (when converted into *N*-triorganostannylamines) results in a strong improvement of the method when compared with those achieved in solution. The selectivity is improved especially in the case of 4-iodoanilines, and furthermore the nature of the activating reagent linked to the polymer allows a limitation of the pollution by organotin residues at a very low level when compared to the reaction achieved in solution. The efficiency of the polymer-supported activating reagents was unaffected after five runs, allowing their reuse for preparation of “tin-free” *p*-bromo or *p*-iodo aromatic amines, a class of compounds of high interest for the preparation of bioactive molecules.

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Supporting Information Available: Detailed experimental procedures for preparation of polymer-supported organotin reagents, general procedure for bromination and iodination of amines, compound characterization data, and analytical method for determination of tin pollution. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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