

Methodologies Limiting or Avoiding Contamination by Organotin Residues in Organic Synthesis

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		1. INTRODUCTION	
		Organotin reagents are efficient and versatile chemicals in organic synthesis allowing chemo-, regio-, and stereoselective reactions under mild experimental conditions. ^{1–4} Their popularity is also due to their availability, and their high	

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stability against heating and oxidation, associated with their tunable reactivity thanks to the polarizability of the Sn–H, Sn–C, or Sn–O bonds.

Among all tin reagents, trialkyltin hydrides, especially tributyltin hydride, are privileged, as highlighted in a few review articles,^{1,5–11} as reagents for reductive radical reactions as well as for radical cyclizations. The organotin reagents are also widely used as coupling partners in palladium-catalyzed cross-coupling reactions, mainly for the construction of C_{sp}²–C_{sp}² bonds according to Stille–Migita cross-coupling.^{12–14} This reaction allows a good control of the stereochemistry in the resulting vinylic systems and a great functional group tolerance.^{15–20} Accordingly, some C–C bonds, not that easy to synthesize, as for instance those involving the cross-coupling of “umpolung” organotin reagents with acyl halide, can be obtained, providing for instance highly efficient syntheses of 1,2 or 1,4-dicarbonyl compounds^{21–23} with possible control of the stereochemistry.²³ Indeed, Stille cross-coupling reactions have found applications in disciplines ranging from natural products and macrolides synthesis^{24,25} to material sciences for the design of molecules having physical properties.²⁶

The allylation of aldehydes by γ -substituted allyltins has also been extensively studied and used for stereoselective syntheses. This reaction constitutes a versatile synthetic method for the preparation of homoallylic alcohols,^{27–32} the selectivity of which can be controlled by using appropriate experimental conditions^{33,34} to afford building blocks for the synthesis of many natural products and pharmaceuticals.^{32,35}

The regioselective esterification^{36–38} and alkylation of polyols such as carbohydrates^{39–41} using organotin alkoxides and dialkoxides as well as the cycloaddition involving alkynes and organotin azides toward tetrazoles^{42,43} are also key reactions of the organotin portfolio.

Despite the versatility of organotin reagents and their possible use in asymmetric synthesis,⁴⁴ their applications have been strongly hampered by the difficulty to remove organotin residues from final products combined with the high toxicity of some of them.^{45–51} Thus, Me₃SnX or Et₃SnX are highly toxic for animals and humans as underlined by the disaster encountered with the pharmaceutical preparation “Stalinon”,⁵² while most of them, like tributyltin derivatives, are moderately toxic (LD₅₀ generally over 150 mg/kg) despite their impact on environment as algaecides or molluscicides.^{53–58} Some others such as dioctyltindithioglycolates or other dioctyltin esters are nearly nontoxic compounds (in terms of acute toxicity) and have been used in food or pharmaceuticals wrapping materials.⁵⁹ As a general trend, the toxicity decreases upon size increase of the alkyl groups (Me₃SnX ~ Et₃SnX ≫ Bu₃SnX ≫ Octyl₃SnX) and upon decrease of the number of alkyl groups (R₄Sn ~ R₃SnX > R₂SnX₂ > RSnX₃).⁵¹ Taking into account the acuteness of organotin compounds, repeated doses studies, carcinogenicity, genotoxicity, immunotoxicity, reproductive and development toxicity, neurotoxicity, metabolism, and excretion, the European Food Safety Authority recommended a tolerable daily intake of 25 $\mu\text{g}/\text{kg}$ of organotin contaminants in food (mainly fish and shell-fish) for tributyltin, dibutyltin, triphenyltin, and dioctyltin contaminants. It corresponds to the dose with no adverse effect in terms of immunotoxicity impacted by a safety factor of 100.⁶⁰

While it is generally easy to reduce pollution to levels acceptable for purity criteria in microanalysis, it is necessary to remove tin residues down to part per million levels for health-care applications. These unbiased and also more subjective

considerations have nearly ruled out such reagents for the production of pharmaceutical drugs or for materials. This context associated with the irreplaceable nature of Bu₃SnH and other organotin reagents has induced several articles with highly expressive titles like “a race against tin”,⁶¹ “the tyranny of tin”,⁶² “tin hydrides substitutes”,⁹ or over 1000 articles and patents claiming “tin free” methods, a poorly scientific vocabulary as recently underlined by Curran.⁶³ Moreover, while acute and long-term toxicities (in the laboratory and in the environment) including degradation pathways^{64–66} are known for organotin reagents with speciation and quantification methods sometimes at the ppb level,^{55,67} the long-term toxicity and the degradation of organotin substitutes are often poorly known.

Therefore, over the past two decades, different approaches that facilitate the separation of tin residues from the desired adducts have been developed and recently reviewed for general use in organic synthesis,⁶⁸ or specifically for Stille cross-coupling reaction.¹⁴ Nevertheless, there is no general principle for achieving this goal. The purification problems can be reduced although not eliminated by using catalytic procedures, but when stoichiometric quantities of tin reagents are involved, special workup procedures or modified tin reagents are required to ensure the removal of tin residues from the reaction mixtures. This Review aims to cover the literature in this field up to the end of 2014 and provide an overview of the methods designed to limit or avoid the presence of organotin byproducts in reaction products. After an introduction, section 2 of this Review summarizes workup procedures that have been developed to facilitate the separation of organotin byproducts from the reaction mixtures as, for example, conversion of tin byproducts to insoluble polymeric tin fluorides. Section 3 deals with methodologies involving a catalytic amount of an organotin reagent with in situ recycling by means of a metal hydride reagent, to reduce tin waste. Section 4 is devoted to reactions carried out in media usually called “green solvents” like ionic liquids and polar solvents, which have been considered to facilitate the removal of tin side-products from the crude product. Finally, the synthesis and applications of modified organotin reagents including organotins bearing either polar groups or a fluororous tag and solid-immobilized organotins, which have all been designed to assist purification, with a special emphasis on polymer-supported organotin reagents are described in sections 5 and 6.

2. PROCEDURES BASED ON PARTITION METHODS

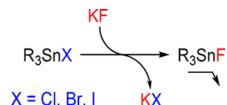
Most of the procedures for the removal of organotin residues by partition methods have been considered for reactions using the most popular reagent: tributyltin hydride. The aim is either to obtain the precipitation of tributyltin halides and related species as tributyltin fluoride or to remove nonpolar tetrabutyltin in alkane type solvents, when target compounds are polar, to have an immediate preliminary rough separation of desired and undesired species. Obviously the procedures can be extended to other insoluble organotin fluorides and to nonpolar tetraorganotin compounds. These procedures and their extensions are presented and discussed below.

2.1. Triorganotin Fluoride Precipitation

For reactions concerning reductions of organic halides by tributyltin hydride, tributyltin halides obtained as byproducts can be removed from the crude product by conversion into tributyltin fluoride through a halogen exchange reaction.

Contrary to the other tributyltin halides, tributyltin fluoride has a low solubility both in organic solvents and in water. Considering this property, Stille et al.¹⁵ and later Jacobus et al.⁶⁹ have developed a purification method consisting of the conversion of tributyltin halides into insoluble tributyltin fluoride through treatment of the reaction mixture by an aqueous alcoholic or acetonnic solution of potassium fluoride at the end of the reaction. This method allows the removal of most of the organotin residues by converting them into insoluble tributyltin fluoride species both in organic and in aqueous phase, which therefore can be readily separated by filtration (Scheme 1).

Scheme 1. Precipitation of Triorganotin Halides as Triorganotin Fluorides



This simple experimental procedure, which can also be used to remove trimethyltin^{70–74} or triphenyltin halides, is of interest in preparative organic chemistry for a primary elimination of organotin halides (about 99%), but by its nature it cannot afford nearly “tin-free” compounds with $[\text{Sn}] < 10$ ppm. Furthermore, it has the drawback to be sometimes incompatible with products containing an ester group (transesterification) or a silylated protective group (deprotection).

A modified protocol (with similar conditions) has been proposed by Corey et al. and consists of a treatment of the reaction mixture by CsF/CsOH and silica gel.⁷⁵ They described the preparation of the CsF/CsOH (2:1) fused salt and reported that the reaction crude has to be stirred during 25–30 min with a mixture of this salt and silica gel (ca. 1.5:1) to precipitate tin residues as organotin fluorides prior to purification by chromatography on silica gel. It is noteworthy that the addition of CsF^{76–78} or Bu_4NF ⁷³ in the Stille cross-coupling to fasten the reaction enables as well the precipitation of organotin residues as tin fluorides.

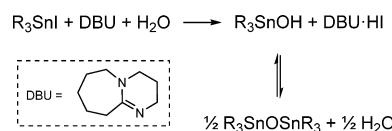
2.2. Selective Extraction by Hexane/Acetonitrile Partition

The partition method between nonmiscible solvents such as hexane and acetonitrile has also been used to purify the products when the latter are polar. This method developed by Roberts et al. takes advantage of the fact that tributyltin compounds and higher triorganotin analogues have a very good solubility in nonpolar solvents like hexane or pentane.⁷⁹ Thus, treatment of the reaction mixture containing polar chemicals by a biphasic mixture of hexane/acetonitrile enables the separation of organotin byproducts from organic molecules, which have a better affinity for acetonitrile.⁷⁹ However, it is worth noting that the efficiency of this method, in relation to the relative partition constants of organotin residues and reaction products between hexane and acetonitrile, is limited. The greater is the difference in the polarity of the organotin byproducts (e.g., nonpolar tetralkyltin) and the synthesized product (e.g., highly polar aminoalcohols or amino acids), the better is the partition of the residues, which can lead to tin contamination levels <10 ppm in favorable cases.^{80,81}

2.3. Treatments of Crude Mixture by Miscellaneous Reagents

2.3.1. Treatment with 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU). Curran and Chang have developed a procedure based on the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which has been applied to both triorganotin and hexaorganoditin derivatives. The tin species present in the reaction mixture are first converted into trialkyltin iodides by addition of a solution of iodine in diethyl ether to the reaction mixture and, subsequently, in tin hydroxides by addition of 1 equiv of DBU and 1 equiv of water.⁸² DBU is assisting the hydrolysis of tin halides into tin hydroxides (in equilibrium with the corresponding distannoxanes) with concomitant formation of DBU hydrohalide. The high affinity of hydroxystannanes and distannoxanes for Si–OH bonds of silica allows the removal of organotin residues by a filtration of the mixture through a short column of silica gel using diethyl ether as eluent. The solid DBU hydrohalide is also retained at the head of the column (Scheme 2). Following this procedure, more than 90% of the

Scheme 2. Conversion of Triorganotin Halides into Tin Hydroxides and Distannoxanes by Hydrolysis in the Presence of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)



organotin contamination in the products can be removed as evidenced by ^1H NMR, allowing an easier flash chromatography to purify the products. Accordingly, the method appears efficient to achieve a primary elimination of organotin byproducts, facilitating further workup.

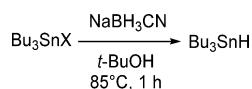
Obviously, this method is unable to afford a product containing just a few ppm of triorganotin residues and is limited by the strong basicity of DBU and by the high reactivity of iodine.

2.3.2. Treatment with Sodium Cyanoborohydride. The triorganotin halides or pseudohalides (R_3SnX) obtained as byproducts in a reductive dehalogenation reaction, the Stille cross-coupling or the Barton–McCombie reaction, strongly interact with silica gel during the liquid chromatography making the purification tedious. To overcome this issue, triorganotin halides can be converted into the corresponding tin hydrides by using a reducing agent like a borohydride. Indeed, tin hydrides that are nearly nonpolar compounds (with a low Lewis acidity at the tin center) can be separated more easily from the reaction products by chromatography on silica gel using a nonpolar eluting solvent.

Accordingly, Crich et al. proposed this method for the removal of organotin residues using NaBH_3CN as a reducing reagent.⁸³ The obtained organotin hydride was smoothly separated from the products of the reaction by liquid chromatography on silica gel using hexane as an eluent and can be, in this way, recovered and potentially recycled (Scheme 3).

The reactivity and the restricted selectivity of the reducing agent at 85 °C constitute limitations to the method, which is therefore incompatible with substrates and/or products bearing functionalities sensitive to reductive conditions such as aldehydes or α,β -unsaturated ketones. Moreover, the fact that

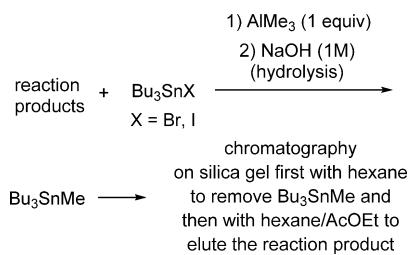
Scheme 3. Reduction of Triorganotin Halides by Sodium Cyanoborohydride



slightly polar products cannot be easily separated from the organotin hydride constitutes another limitation.

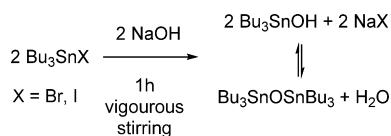
2.3.3. Treatment with Trimethylaluminum or Sodium Hydroxide. Renaud et al. have proposed two complementary procedures for the removal of organotin residues from a reaction mixture.⁸⁴ When synthesized organic compounds are polar, the treatment by trimethylaluminum after the reaction allows the transformation of the obtained Bu_3SnX into Bu_3SnMe , which is sufficiently nonpolar to be separated more easily from the products by chromatography on silica gel using hexane as eluent (**Scheme 4**).

Scheme 4. Alkylation of Triorganotin Halides by Trimethylaluminum



When the synthesized organic products are nonpolar, the reaction mixture is treated with a 1 M sodium hydroxide aqueous solution to transform the tri-*n*-butyltin halide into the corresponding tin hydroxide, in equilibrium with the corresponding distannoxane. Thus, due to the large affinity of this organotin hydroxide with the silanol sites of silica, after liquid chromatography, the products of the reaction can be isolated from organotin byproducts at the NMR detection level (**Scheme 5**).

Scheme 5. Conversion of Tributyltin Halide into Tributyltin Hydroxide and Hexabutyldistannoxane



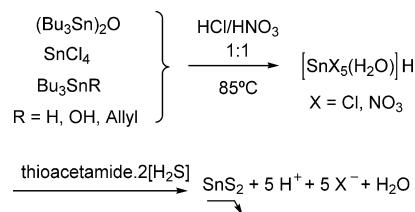
Once more, the versatility of this method is strongly limited by the possible reactivity of functions present in the substrate with trimethylaluminum or sodium hydroxide.

When tribenzyltin hydride was used, the more reactive benzyl substituents allowed an easier separation of the tribenzyltin halide on silica gel, and the treatment of the reaction mixture by hydrogen peroxide under basic conditions afforded benzyl alcohol, allowing an easy separation of the desired products from the unwanted residues.⁸⁵ This statement should be also valid for other organotin hydrides having labile Sn–C bonds.

2.3.4. Treatment with a HCl/HNO₃ Mixture Followed by Precipitation as a Tin Sulfide. Another procedure developed by Mascaretti involves the conversion of triorganotin

compounds into inorganic tin compounds of low toxicity.⁸⁶ This procedure involves two successive steps, including first the generation of a tin(IV) complex $[\text{SnX}_5(\text{H}_2\text{O})]\text{H}$ from different tin species such as Bu_3SnH , Bu_3SnOH , $(\text{Bu}_3\text{Sn})_2\text{O}$, $\text{Bu}_3\text{SnAllyl}$, or SnCl_4 through treatment by a concentrated HCl/HNO_3 mixture, followed by the formation of an insoluble salt SnS_2 by addition of thioacetamide·2[H₂S] to the reaction mixture. The obtained SnS_2 is separated from the product by filtration (**Scheme 6**).

Scheme 6. Precipitation of Organotin Residues as Tin Sulfide



In the case of byproducts such as Bu_3SnX ($\text{X} = \text{Cl, Br, I}$), the reaction mixture can be first treated with an aqueous solution of KF to precipitate tributyltin fluoride, but due to the harsh conditions used in this method, it can only be applied to poorly functionalized substrates and/or products.

2.4. Separations by Liquid Chromatography

2.4.1. Reversed-Phase Flash Chromatography. The purification by reversed-phase flash chromatography on a silica made hydrophobic by capping the silanol sites, with for instance octadecyldimethylsilyl groups, and with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ 4:6⁸⁷ or $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ ⁸⁸ as eluents, allows the elimination of nonpolar organotin byproducts, which have a good affinity for the octadecyl chains grafted onto the silica and therefore have very long retention time. This method is only applicable when the synthesized products are more polar than the organotin byproducts.

2.4.2. Chromatography with KF–Silica or K_2CO_3 –Silica Mixtures as Stationary Phase. On the basis of the first tin removal method developed by Stille and Jacobus,^{15,69} Harrowven et al. proposed an inexpensive purification method by chromatography using a mixture of KF/silica (1:9 ratio) as the stationary phase.^{89,90} During the chromatography, organotin byproducts are converted into organotin fluorides, which are nearly insoluble in the eluting solvent. This method applied for a range of reduction and radical cyclization reactions mediated by tri-*n*-butyltin hydride provided a level of tin residues in the products lower than 30 ppm. This straightforward procedure was widely used. However, the fact that the stationary phase cannot be stored for a long time because of the hygroscopicity of KF is harmful, because wet KF induces a poor separation due to a lower adsorption. In addition, the chromatography has to be performed carefully because of the trend of KF to plug the column chromatography inducing a back pressure.

Later, Harrowven et al. improved their method by using a stationary phase composed of 10% powdered anhydrous K_2CO_3 and silica.⁹¹ This mixture allows very effective purifications and reduces to about 15 ppm the amount of organotin impurities contained in the products. In addition to the efficiency of the purification, the K_2CO_3 /silica stationary phase is cheap and stable over several months. More recently, Pivnitsky et al. reported the use of a mixture of fluorous salts

(KF/CaF_2 , 20 wt % of KF) to easily remove tributyltin derivatives by filtration on a plug of silica after conversion into Bu_3SnF .⁹²

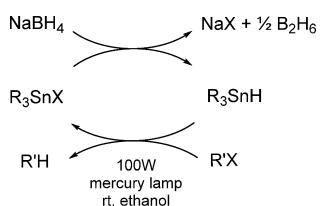
3. USE OF ORGANOTIN REAGENTS IN A CATALYTIC AMOUNT

The use of an organotin precursor in a catalytic amount in the presence of an appropriate reagent (often hydride) contributes logically to decrease the pollution by organotin impurities in synthesized products and facilitates further treatments and purifications. Thus, several methods using different reducing agents have been developed for reactions involving tin hydrides.

3.1. Reactions Involving Triorganotin Halides with Aluminohydrides or Borohydrides

The first attempts in this field were achieved using LiAlH_4 in the presence of a catalytic amount of tri-*n*-butyltin halide,^{93–95} prior to the development of milder reducing agents. Thus, Corey et al. have elaborated a dehalogenation method of alkyl and aryl halides in the presence of 0.1–0.3 equiv of trialkyltin halide and an excess of NaBH_4 in ethanol,⁹⁶ to obtain an easier purification of the products due to the lower amount of tin reagent in the starting materials (Scheme 7).

Scheme 7. Use of a Catalytic Amount of Triorganotin Halide in the Presence of Sodium Borohydride



This method was modified later by Bergbreiter et al. using 5–10% of Bu_3SnCl with an excess of NaBH_4 in toluene in the presence of benzo-15-crown-5 as a phase-transfer catalyst.⁹⁷ In the case of organic substrates that are sensitive to the reductive conditions brought by NaBH_4 , Stork et al.⁹⁸ and Curran et al.⁹⁹ have used NaBH_3CN , which is a milder reductant to achieve dehalogenating reductions and radical dehalogenation-cyclization reactions.

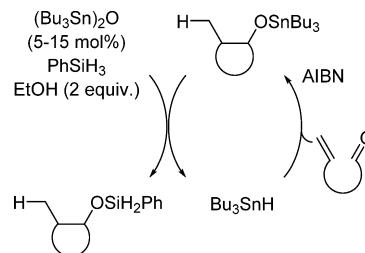
3.2. Reactions Involving Tin Oxides or Alkoxides with Hydrogenosilanes

The preparation of tri-*n*-butyltin hydride obtained by $\text{Sn}-\text{O}/\text{Si}-\text{H}$ exchange performed generally with bis(tributyltin) oxide and tetramethyltetrasiloxane was proposed five decades ago.^{100–102} Its reaction mechanism was studied in the case of the exchange reaction between hydrogenosilanes and alkoxytriorganotins.¹⁰³ From the early 1970s, the mixture $\text{Bu}_6\text{Sn}_2\text{O}/$ polymethylhydrosiloxane was employed to form in situ the tri-*n*-butyltin hydride to use it in various reduction reactions of halogenated,¹⁰⁴ carbonyl or nitro compounds.¹⁰⁵ However, as the driving force of the exchange is the oxophilicity of silicon, the reduction reaction works with a catalytic amount of tin precursor only when a $\text{Sn}-\text{O}$ bond is present in the tin byproducts.

A similar approach was subsequently applied by Fu and Maleczka when the use of the organotin reagent in a stoichiometric amount was considered as prohibitive. Fu et al. have developed a method of radical reductive cyclization of enals and enones using a catalytic amount of $(\text{Bu}_3\text{Sn})_2\text{O}$ (5–15

mol %) in the presence of PhSiH_3 and 2 equiv of ethanol, to generate in situ the tri-*n*-butyltin hydride (Scheme 8).^{106,107}

Scheme 8. In Situ Generation and Use of Tin Hydride in Reductive Cyclization Reactions



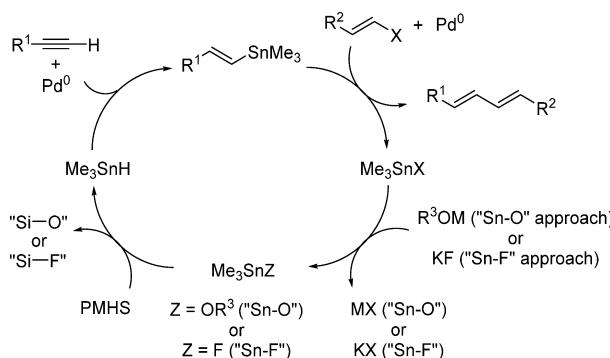
This strategy was subsequently extended to the reduction of α,β -unsaturated ketones¹⁰⁸ and nitroalkanes;¹⁰⁹ however, as already mentioned, it remains limited to reactions generating tin alkoxides as intermediates.

Fu et al. have also applied this strategy to the Barton–McCombie deoxygenation¹¹⁰ as well as to the reduction of imines¹¹¹ and azides,¹¹² using polymethylhydrosiloxane (PMHS) as a cheaper and nontoxic¹¹³ coreducing agent ($\text{LD}_{50} = 80\,000 \text{ mg kg}^{-1}$).

To improve the reduction of halogenated compounds, Maleczka et al. proposed a few modifications of this method, which consist of using 10–25% of Bu_3SnCl in the presence of PMHS and KF, the latter increasing the reductive properties of the system, due to longer and weaker apical bonds in the pentacoordinated silicon and tin species.^{114–116}

These authors have developed a one-pot tandem palladium-catalyzed hydrostannylation/Stille cross-coupling protocol using a catalytic amount of tin halide in the presence of PMHS according to two different methods. The first one, called the “ $\text{Sn}-\text{O}$ ” approach, uses Na_2CO_3 or NaOPh to transform in situ the tin halide obtained at the end of the Stille coupling into an organotin alkoxide, which can be exchanged by PMHS (Scheme 9).^{117–119} In this case, the best results were obtained

Scheme 9. Stille Cross-Coupling Reaction through in Situ Preparation of a Trimethylvinyltin



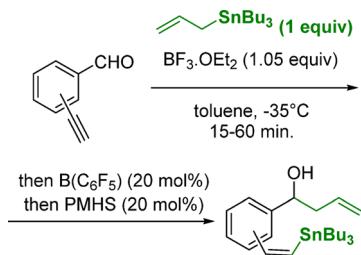
on enynols when 6% of Me_3SnCl was used as the triorganotin hydride precursor. Accordingly, up to 15 cycles have been realized without a noticeable decrease of the activity.¹¹⁸ The second method, called the “ $\text{Sn}-\text{F}$ ” approach, uses an aqueous KF solution and a catalytic amount of TBAF (1 M solution in THF) to form tin fluorides at the end of the cross-coupling reaction. This protocol displays the benefit to afford insoluble

trimethyltin fluorides, which allow the elimination of about 99.5% of tin residues from the synthesized compounds.^{120,121}

Despite their ability to minimize the contamination by organotin residues, these two last approaches suffer from major drawbacks, which strongly decrease their interest: (i) the toxicity of trimethyltin halide (Maleczka's approach) and (ii) the cost and the instability of PhSiH₃ (Fu's initial approach). It should be emphasized that Maleczka showed that substituting trimethyltin derivatives for tributyltin ones resulted in a significant efficiency drop.

Using a similar concept, the same group also achieved a one-pot allylation-hydrostannylation sequence with the recycling of the tin waste generated through the allylation to carry out the hydrostannylation. Concomitant use of allyltributyltin in the presence of BF₃·Et₂O at -35 °C and recycling of the tin fluoride species by B(C₆F₅)₃ and PMHS allows simultaneous allylstannation of an aldehyde and hydrostannylation of an alkyne bond when contained in the same molecule (Scheme 10).¹²²

Scheme 10. One-Pot Allylation and Hydrostannylation of Alkynals

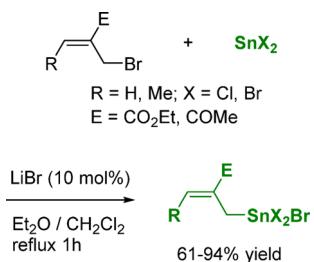


4. REACTIONS INVOLVING HIGHLY POLAR ORGANOTIN REAGENTS OR HIGHLY POLAR MEDIA

4.1. Reaction of Mono-organotin Trihalides and Related Species

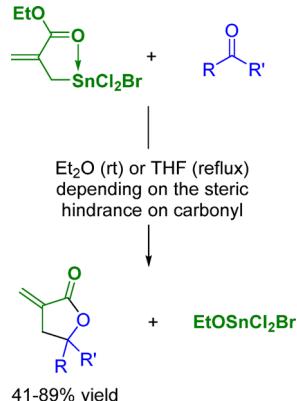
Mono-organotin reagents are very appealing reagents, because when used for an organic transformation, inorganic byproducts are generated at the reaction end. The latter are considered as nontoxic compounds, and the toxicity of their mono-organotin precursors is very low when compared to those of triorganotin analogues.⁵¹ The use of mono-organotins in organic synthesis has mainly been developed by Pereyre and Fouquet in terms of both preparation and evaluation as synthetic tools. They first prepared allyltin reagents by reaction of an allyl bromide with a stannous dihalide (SnCl₂ or SnBr₂) in the presence of a catalytic amount of lithium bromide. Accordingly, functionalized allyltin trihalides were obtained in yields ranging from 61% to 94% (Scheme 11).^{123,124}

Scheme 11. Preparation of Allyltin Trihalides



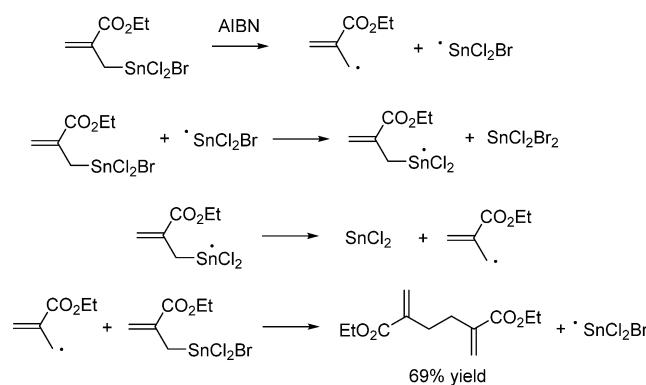
These reagents have been mainly used in allyl transfer reactions with aldehydes and ketones. Using 2-(ethoxycarbonyl)allyltin trihalides, α -methylene γ -lactones were efficiently synthesized and isolated after treatment of the reaction mixture with water because the eliminated ethoxytin trihalide was converted into water-soluble mixed tin hydroxide (Scheme 12).^{124,125}

Scheme 12. 2-(Ethoxycarbonyl)allyltin Trihalides in the Synthesis of α -Methylene γ -Lactones



Fouquet and Pereyre have also considered the reactivity of these allyltin trihalides under radical conditions, but no allylic transfer was observed by reaction with primary or secondary alkyl halides. This result was explained by an halogen abstraction on the allyltin trihalide by the $\cdot\text{SnX}_3$ radical to give tin tetrahalide, tin dihalide, and an allylic radical whose addition on a second molecule of allyltin trihalide followed by a β -elimination affords the organic dimer (Scheme 13).^{124,126}

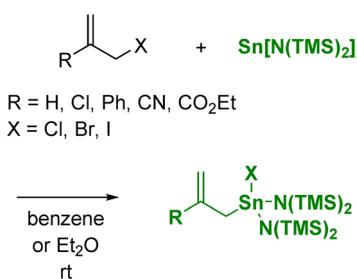
Scheme 13. Dimerization of the Allyl Unit of Allyltin Trihalides under Radical Conditions



To overcome this problem, the reactivity of the Sn–X bond can be used to convert the monoallyltin trihalide reagent into the corresponding allyltributyltin or allyltriphenyltin, which reacts conventionally (with a concomitant formation of Bu₃SnBr or Ph₃SnBr as byproducts).

In contrast, the monoallylstannanes obtained by insertion of the Lappert's stannylene^{127,128} into the C–X bond of allylic halides (Scheme 14) were found to be efficient reagents for allyl transfer both in free radical and in Stille cross-coupling conditions (Schemes 15 and 16).^{79,126,129,130}

Scheme 14. Insertion of a Lappert's Stannylenes into an Allylic C–X Bond



In the free radical allylation, the concentration of tin residues (poorly toxic) in the products was found to be around 100 ppm starting from ethyl bromomethyl acrylate.¹²⁶

In the case of the Stille cross-coupling, due to the tin pentacoordination taking place at tin in the mono-organotin generated *in situ* from the alkyl-bis-[*N,N*-bis-(trimethylsilyl)-amino]tinhalide in the presence of Bu₄NF, the lengthening of the Sn–C bond allows an easier transfer of the organic group (R¹). This transfer is possible in allyl, aryl, and vinyl series but also in alkyl series because pentacoordination increases the kinetics of the organic group transfer but does not modify significantly the kinetic of the β -elimination (Scheme 16).^{130–134} This reaction seems to be general and efficient, allowing the preparation of products that can be theoretically contaminated only by nontoxic inorganic tin byproducts.

This methodology that allows short reaction times and workups was applied to the synthesis of selectively labeled [¹¹C]methyl quinolines, which are potential tracers for positron emission tomography (PET), using the Lappert-type ¹¹C-monomethylstannate^{135,136} (Scheme 17).

Taking into account the possible enhancement of their reactivity in Stille cross-coupling reactions (*vide supra*), mono-organotin reagents offer promising prospects, especially for reactions in highly polar solvents, as for instance in allylstannation of carbonyl compounds in water, which will be discussed in section 4.2 (*vide infra*).

Wang et al. did not use mono-organotin trihalides but tetraphenyldtin and tetrabutyltin in a Stille cross-coupling reaction to generate the formation of an inorganic tin byproduct.¹³⁷ This procedure, carried out in polyethylene glycol as solvent, might be attractive because aryl bromide can be reacted with 0.25 equiv of tetraorganotin reagent only. However, the scope is limited by the poor availability of functionalized tetraaryltins and tetraalkyltins and by the decrease of the reactivity when moving from tetraaryltins (or tetraalkyltins) to monoaryltin (or monalkyltin) trihalides. About a dozen biaryl derivatives were isolated in 48–93% yields (Scheme 18), starting from a large variety of substituted aryl bromides and after a workup procedure involving a diethyl ether extraction (5 × 10 mL for 3 mL of PEG 400 used as reaction medium) followed by a flash chromatography, which

also allows the recovery of PEG 400. Similarly, five *n*-butylaryl derivatives were synthesized in 42–66% yields.

4.2. Reaction in Aqueous Media

The use of water in organic^{138,139} and organometallic^{140–142} reactions can be considered beneficial, when a minor amount of organic solvent is required to recover the products at the end of the reaction, because it is more environmentally benign than volatile and sometimes quite toxic organic solvents. In addition, water is abundant, cheap, and can stabilize polar or ionic intermediates.

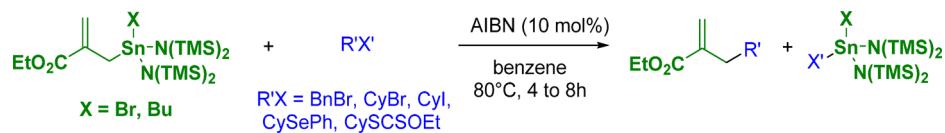
As in other fields, water has been sometimes considered as a solvent when organostannanes were used in organic synthesis to improve the elimination of environmentally unfriendly tin byproducts. The main advantage brought by the use of water as solvent is the possibility to achieve the reactions with water-soluble mono-organotin trihalides. They display low toxicity in comparison to triorganotin halides and afford nontoxic inorganic tin salts as reaction byproducts. Because every undesired tin byproduct is soluble in water, weakly polar organic products can be easily extracted. These contributions have been mainly devoted to the Stille cross-coupling reaction and the allylation of aldehydes.

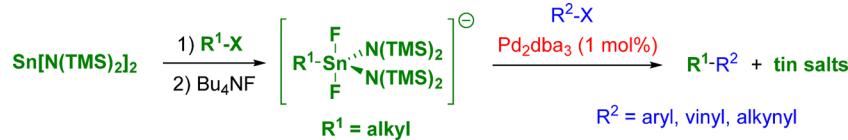
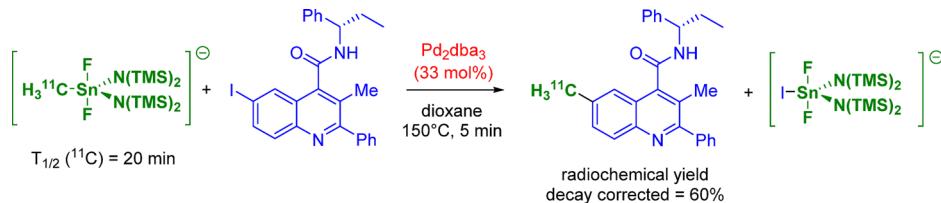
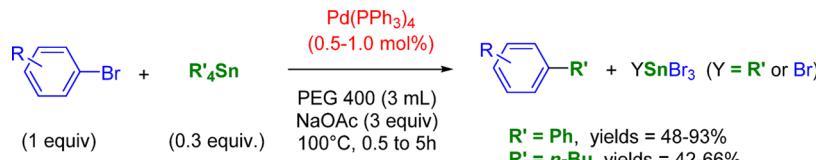
4.2.1. Stille Cross-Coupling Reactions in Aqueous Media and Highly Polar Solvents. The Stille cross-coupling reaction in aqueous media was first reported by Bumagin and Beletskaya and was devoted to the reaction between tetramethyltin and aryl diazonium salts catalyzed by Pd(OAc)₂ in aqueous acetonitrile at 20 °C.¹⁴³ The same group extended this cross-coupling in aqueous media first to diaryliodonium salts¹⁴⁴ and then to the cross-coupling of organotrimethyltins with aryl diazonium salts.¹⁴⁵ In a close area, Kang has reported the cross-coupling of organic iodides with organostannanes catalyzed by a silica-supported sulfur–palladium catalyst in aqueous acetonitrile.¹⁴⁶ Achievement of the reaction in CH₃CN:H₂O (4:1) at 80 °C for 5 h afforded the cross-coupling product in 70–83% yield. This method allows straightforward separation of the product from the catalyst, which can be reused despite a decrease in the yields along the cycles. However, no consideration of the advantages related to the purification and no evaluation of the amount of remaining tin residues in the reaction products were explicitly mentioned.

Bumagin and Collum simultaneously reported the reaction of mono-organotin trihalides RSnX₃ (X = Br or Cl) with aqueous soluble aryl, vinyl, and alkyl halides.^{147–149} Both studies involve PdCl₂ as catalyst and the presence of KOH to generate a pentacoordinated tin atom to facilitate the cross-coupling reaction (Scheme 19).

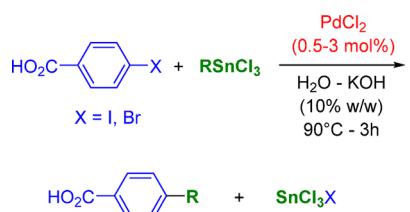
In several cases, the use of a water-soluble phosphine PhP(*m*-C₆H₄SO₃Na)₂ or Ph₂P(*m*-C₆H₄SO₃Na) is required to improve the yield. This procedure displayed a large scope with an easier purification of the cross-coupled products because the tin species derived from SnX₄ and RSnX₃ remain in water, but no evaluation of the poorly toxic residual tin derivatives in the cross-coupled products was carried out in these studies. Later, this reaction was also found to be catalyzed by dendrimer-

Scheme 15. Free Radical Allylation of Organic Halides or Analogues with Fouquet's Reagent



Scheme 16. $C_{sp^2}-C_{sp^3}$ Stille Cross-Coupling Reaction Using Mono-organotins**Scheme 17.** Example of ^{11}C Labeling of a PET Tracer**Scheme 18.** Stille Cross-Coupling Involving Tetraphenyltin and Tetrabutyltin in Polyethylene Glycol

R = electron withdrawing group; reaction carried out on 1 mmol.

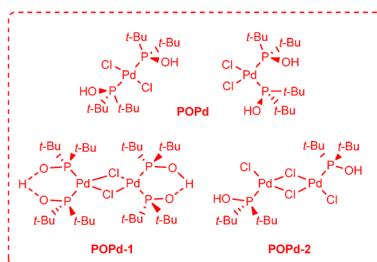
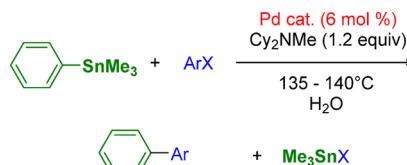
Scheme 19. Stille Cross-Coupling of Organic Halides with Mono-organotin Trihalides in Basic Aqueous Media

encapsulated Pd nanoparticles, which limit the amount of residual palladium in the products.^{150,151}

Wolf and Lerebours described a Stille cross-coupling procedure of aryl chlorides and aryl bromides in neat water.¹⁵² By using a water-soluble palladium catalyst (**POPd**, **POPd-1**, or **PdOPd-2**), the use of a cosolvent was not required when using phenyltrimethyltin as a reagent (**Scheme 20**).

The recyclability of one of the catalysts (**POPd**) was shown to be possible but exhibited a slight decrease of the yields after four runs. However, while describing a procedure that facilitates the isolation of the reaction product by extraction from water, neither the tedious purification of the coupled product from the toxic trimethyltin halide obtained after cross-coupling reaction nor the evaluation of its residual presence in the products were discussed. Because the reaction seems to be limited to aryltrimethyltins, its benefits are far from being granted. More interestingly, hydrosoluble Pd(II) complexes used at pH 10.5 in water at 100 °C afford a turnover number of 50 000 with 0.002 mol % of catalyst and a turnover frequency of 15 000 with 0.02 mol % of catalyst for the cross-coupling of aryltin trichlorides with 3-iodobenzoic acid (**Scheme 21**).¹⁵³

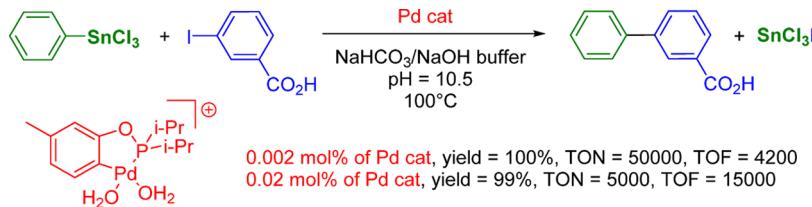
In a close area, Lipshutz et al. investigated the use of surfactants to achieve metal-catalyzed organic transformations in water^{154,155} and reported recently a contribution related to the use of a surfactant for the Stille cross-coupling reaction.

Scheme 20. Stille Cross-Coupling in Water According to Wolf and Lerebours

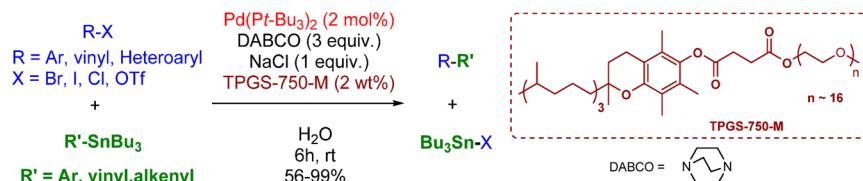
This reaction catalyzed by $\text{Pd}(t\text{-Bu}_3)_2$ in the presence of an excess of 1,4-diazabicyclo[2.2.2]octane (DABCO) proceeds at room temperature (or at 50 °C with less reactive substrates) thanks to the presence of 2 wt % polyethanol- α -tocopherylsuccinate (TPGS-750-M), which formed nanomicelles in water (**Scheme 22**).¹⁵⁶ Aryl chlorides, aryl bromides, as well as alkenyl halides or pseudohalides were coupled efficiently in these mild experimental conditions. Additionally, no homocoupling and no Z-to-E isomerization were observed, and the Z isomer was isolated with a high selectivity (up to 99/1). The aqueous medium can be recycled up to 5 cycles if an additional amount of catalyst is added after each run because the product extraction with hexanes is not selective enough toward palladium species.

More recently, improved yields have been reported using β -sisterol methoxy polyethylene glycol succinate (NOK), a less expensive amphiphile that is phytosterol based.¹⁵⁷

Scheme 21. Stille Cross-Coupling in Water

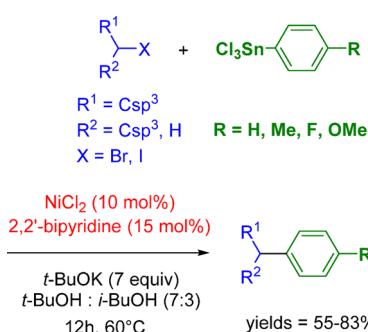


Scheme 22. Stille Cross-Coupling Reaction in Water in the Presence of Surfactant TPGS-750-M



Fu et al. have also considered the use of aryltin trichlorides (Cl_3SnPh) in the Stille reaction with secondary and primary alkyl halides, using $\text{NiCl}_2/2,2'$ -bipyridine as catalyst in basic conditions, with an excess of $\text{KO}t\text{-Bu}$ in a $t\text{-BuOH}/t\text{-BuOH}$ mixture. These mono-organostannanes efficiently avoid contamination by tin residues (with a fraction lower than 5 ppm in comparison to the reaction products) but require substrates insensitive to highly basic conditions (Scheme 23).¹⁵⁸

Scheme 23. Stille Cross-Coupling of Aryltin Trichlorides with Bromo and Iodoalkanes



Recently, Wu et al. reported the Stille cross-coupling in water catalyzed by nickel nanoparticles stabilized by a phosphine dendrimer. Biaryls could be obtained at room temperature in good yields (Scheme 24).¹⁵⁹ The reaction products were

Scheme 24. Stille Cross-Coupling Catalyzed by Nickel Nanoparticles in Water



extracted from the crude with hexanes, which also induced the precipitation of the catalyst. The latter could be separated from water by centrifugation, and its recycling was shown to be possible up to seven runs without any decrease of the yield. In addition, no nickel leaching was observed by ICP-MS measurement carried out on the products, indicating that the reaction was really heterogeneous. Unfortunately, the amount

of residual tin contained in the cross-coupling products was not evaluated.

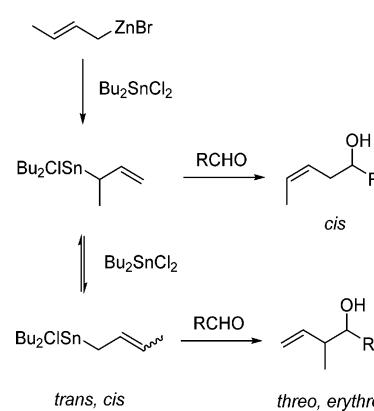
Finally, it is worth noting that the Stille cross-coupling reaction of phenyltributyltin using Pd/CaCO_3^{160} or Pd/BaSO_4^{161} was also reported in a mixture of ethanol and water.

4.2.2. Allylstannation in Aqueous Media. The allylstannation of aldehydes and ketones can be performed in the presence of water, in general by using allyltin trihalides or diallyltin dihalides prepared in situ by the reaction of metallic tin (as a powder or an anode) with an allylic halide.^{162–166} Thanks to the hydrolysis of the obtained tin alkoxide, the problem due to the reversibility of the allylstannation¹⁶⁷ can be circumvented, affording higher yields in the desired homoallylic alcohols.¹⁶³

Regarding regio- and stereochemistry of the reaction, when crotyltin reagents are involved, branched adducts are usually obtained with a poor *anti* selectivity under these experimental conditions.^{163,168} However, when the preparation and the reaction of the crotyltin halide is attempted in the presence of Zn through preliminary trapping with Bu_2SnCl_2 , an increased *anti* selectivity was obtained together with an important contamination by *Z*-linear homoallylic alcohols, due to the reaction of the branched secondary (but-1-en-3-yl)tin with the aldehyde (Scheme 25).

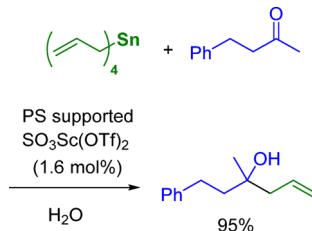
Tetraallyltin can also be used in the presence of water for the allylation of aldehydes and ketones. The advantage is an easier elimination of tin residues as poorly toxic mixed tin hydroxides

Scheme 25. Crotylstannation of Aldehydes by Crotyldibutyltin Chloride in Aqueous Media



when the reaction is performed in the presence of copper or scandium triflate,^{169–171} which can be supported on polystyrene¹⁷² or in acidic aqueous mixtures^{173,174} (Scheme 26).

Scheme 26. Allylstannation of 4-Phenylbutenone in Water Catalyzed by a Supported Scandium Triflate



In the latter case, the aldehydes are shown to be preferentially allylated in comparison to ketones, in agreement with previous studies in methanol^{175,176} and with pioneering work of Pereyre in nonaqueous conditions.¹⁷⁷ Unfortunately, while the reaction was claimed as clean in terms of pollution by tin residues, no information was given for assessing tin at trace level.

This type of reaction is also applicable in polar solvents like methanol or DMSO.^{175,176,178} While high yields can be obtained with aldehydes, ketones, or acetals using diallyltin dihalides in neutral conditions, the use of tetraallyltin allows a good chemoselectivity in favor of aldehydes as previously observed without such a polar solvent. A similar preference was observed by McCluskey using neat water as a solvent, allowing a straightforward isolation of the products.¹⁷³

Baba et al. studied the allylstannation of aromatic aldehydes in water catalyzed by *n*-Bu₄NBr/PbI₂ (10 mol %).¹⁷⁹ Under such conditions at room temperature, a high *syn* selectivity was observed both with *E* and with *Z* crotyltributyltins supporting the occurrence of an open transition state (of the Yamamoto type).²⁷

In conclusion, a few contributions involving water as a solvent have been reported in the literature. Improving the yield upon use of water can be explained by the prevention of the possible reversibility of the allylstannation reaction through hydrolysis of the obtained alkoxyorganotins and by a smoother workup resulting from the inorganic nature of the tin byproducts. Unfortunately, although all of these studies are very valuable, no determination of tin remnants at the ppm level has been performed.

4.3. Reactions on Silica Gel and on Alumina

The affinity of tin oxides for silica has been considered in research on the reduction of aldehydes and ketones by tributyltin hydride in the presence of a cyclohexane slurry of dried silica gel.¹⁸⁰ Reduction products were obtained in good yields at room temperature. The reaction was completed within 0.5–6 h with reduction rates decreasing as aldehyde > dialkylketone > arylalkylketone > diarylketone. Under these experimental conditions, most of the tin byproducts were immobilized on the silica, and the alcohols were much more easily recovered by extraction with diethyl ether. With stoichiometric proportions, a selective reduction of aldehydes versus ketones was observed,¹⁸⁰ as previously reported with tributyltin hydride in methanol (Scheme 27).¹⁸¹

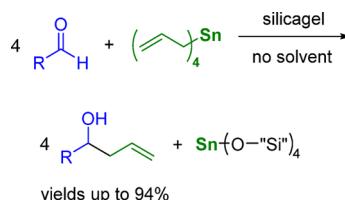
Inanaga has used this type of strategy for the allylation of aldehydes.¹⁸² By reacting tetraallylstannane and aldehydes in the presence of wet silica gel, the obtained stannoxanes were

Scheme 27. Reduction of Carbonyl Compounds by Tributyltin Hydride on Dried Silica



trapped by silica gel, and a simple elution of the homoallylic alcohols with diethyl ether afforded the desired products containing less than 10 ppm of tin residues (Scheme 28). In addition, it was shown that silica gel can be reused. This procedure was also used more recently for the one-pot reduction of imines prepared from aldehydes and aniline.¹⁸³

Scheme 28. Allylation of Aldehydes by Tetraallyltin on Silica Gel



Potassium fluoride on alumina was also used by Villemain in Stille cross-coupling reactions without solvent under monomode microwave irradiation.¹⁸⁴ The main advantage of this methodology is the adsorption of the organotin residue on KF/Al₂O₃, which allows an easy elution of the cross-coupling products (Scheme 29). However, no tin residue values in the final products have been provided.

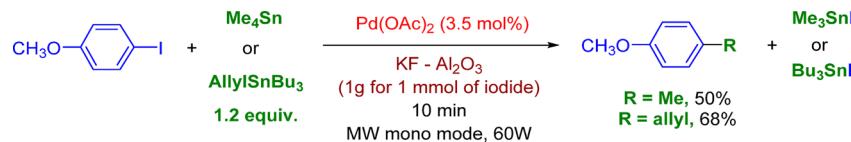
More recently, Prieto et al. also described the Stille cross-coupling reaction under microwave irradiation. In this work, no KF salts were necessary to synthesize in good yields polyheteroaryl derivatives bearing a (1*H*)-1,2,4-triazole moiety.¹⁸⁵ In this case, the absence of solvent for the reaction presents some advantages in terms of cost and environmental impact and allows an easier workup, but once more, this contribution does not report details concerning the amount of residual tin in the desired cross-coupling products.

It is worth noting that use of Celite-supported reagents in organic synthesis, including tools for an easier removal of organotin residues, has been recently reviewed.¹⁸⁶

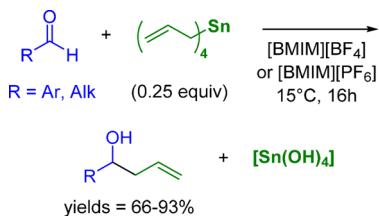
4.4. Reactions in Ionic Liquids

Ionic liquids (ILs) are organic salts, which are liquids at ambient temperature. These salts have been first used as a medium for electrochemical applications and have been subsequently considered as a new type of solvent for organic synthesis during the last 20 years. Their interest is due to their low volatility, high chemical and thermal stability, broadly accessible temperature range, low vapor pressure, and possible recyclability.^{187,188} All of these features have made ILs as possible candidates for an environmentally benign reaction medium for organic and organometallic synthetic chemistry.^{189–198} Among the different studies involving organometallic reagents reported in the literature, some of them focused on organotin reagents, which have been compiled in previous reviews.^{14,199}

4.4.1. Allylation of Aldehydes in ILs. Gordon and McCluskey have been the first to consider ionic liquids as

Scheme 29. Microwave Promoted Stille Cross-Coupling in the Presence of KF/Al₂O₃

solvents for organotin chemistry. Their work concerned the known synthesis of homoallylic and allylic alcohols from tetraallyltin and aldehydes, ketones or epoxides.¹⁷⁷ Using 1-butyl-3-methylimidazolium tetrafluoroborate, [BMIM][BF₄]⁻, and hexafluorophosphate, [BMIM][PF₆]⁻, the reaction proceeded in high yields (**Scheme 30**),^{200,201} and the adducts were

Scheme 30. Allylation of Aldehydes in Ionic Liquids

extracted by diethyl ether while the tin salts were kept in the ionic liquid. In addition, it was shown that the ionic liquid could be recycled (up to 3 cycles) without a meaningful decrease of the yield.

The stereoselectivity of the allylation of α -methoxyketones and the possibility to promote the reaction with a Lewis acid like Sc(OTf)₃ added to the ionic liquid were also reported.²⁰² The results exhibit a general trend in line with the ionic allylation.²⁷ While easy, the efficiency of the purification has not been compared to other methodologies, and the residual tin in the homoallylic alcohols has not been evaluated.

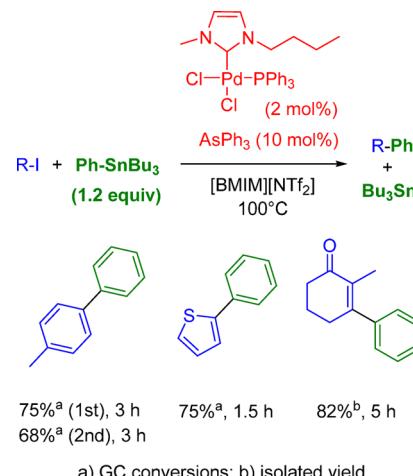
4.4.2. Stille Cross-Coupling in ILs. The Stille cross-coupling reaction in ILs has also been extensively investigated, and the first contribution has focused on the use of [BMIM][BF₄]⁻ as solvent.²⁰³ The reaction between vinyl or aryltributyltin and α -idoenones was found to proceed efficiently at 80 °C when catalyzed by PdCl₂(CN)₂/Ph₃As. Moreover, [BMIM][BF₄]⁻ and the palladium catalyst have been recycled five times without loss of activity. The scope of this reaction was recently extended by Cai et al., who considered other aryl halides in reaction with arylstannanes and alkynylstannanes.²⁰⁴ Using Pd(PPh₃)₄ as catalyst in [BMIM][PF₆]⁻ at 80 °C, cross-coupling products were obtained in good yields. A recycling experiment also demonstrated that ILs and the catalyst can be reused five times without any loss of activity after extraction of the reaction product by diethyl ether. The reaction was also extended to the cross-coupling of PhSeSnBu₃ and BuSeSnBu₃ with aryl and alkyl halides.²⁰⁵ Additionally, Chiappe et al. evaluated 10 different ILs on the Stille cross-coupling reaction involving iodobenzene and vinyltributyltin, tetrabutyltin, or tetramethyltin. The influence of the different properties of the medium on the transfer of vinyl and alkyl groups was investigated by considering a broad range of ILs. [BMIM][C₈H₁₇SO₄]⁻, [BMIM][Tf₂N]⁻, [bpyrr][Tf₂N]⁻, and [HPy][Tf₂N]⁻ (with bpyrr = N-butyl-N-methylpyrrolidinium, HPy = N-hexylpyridinium) were found to be the more interesting ones for this reaction (**Scheme 31**).²⁰⁶

These authors have also considered the efficiency of the extraction process according to the nature of the ILs and found

Scheme 31. Stille Cross-Coupling in Ionic Liquids

that it was possible to work in the absence of arsenine or phosphine ligand. König et al. extended this work by considering the use of sugar-urea-salt as a medium and obtained quantitative conversion with tetravinyltin and phenyltributyltin, moderate yields with tetramethyltin, and low yields with tetrabutyltin because of the β -elimination.²⁰⁷

Later, Ryu et al. investigated the use of [BMIM][NTf₂]⁻, a low viscosity ionic liquid as solvent for carbon–carbon cross-coupling reaction.²⁰⁸ *p*-Iodotoluene, 3-iodo-2-methyl-2-cyclohexen-1-one, and 2-iodothiophene were considered for a reaction with phenyltributyltin using a palladium carbene complex as catalyst in the presence of triphenylarsine at 100 °C (**Scheme 32**). Good yields in cross-coupling products together

Scheme 32. Stille Coupling Reaction Conducted in [BMIM][NTf₂]⁻

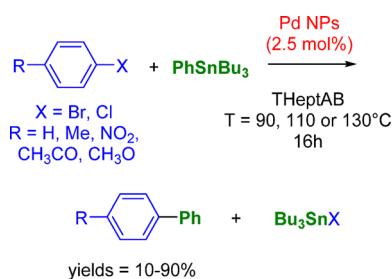
a) GC conversions; b) isolated yield

with a small amount of biphenyl (homocoupling product) were obtained. In the case of 4-iodotoluene, [BMIM][NTf₂]⁻ could be recycled for a second experiment but with a slightly lower yield (68% against 75%).

Similarly, Nacci et al. reported the cross-coupling reaction of aryl bromides and aryl chlorides with phenyltributyltin in tetraheptylammonium bromide (THepAB) at 90 °C catalyzed by palladium nanoparticles and demonstrated that the catalytic system can be reused at least five times with only minor activity loss in the reaction involving *p*-bromotoluene (**Scheme 33**).²⁰⁹

The cross-coupling of aryl halides with vinyl, phenylalkenyl, or phenyltributyltin catalyzed by copper oxide (Cu₂O) in the

Scheme 33. Stille Coupling Reaction Conducted in THepiAB



presence of $\text{P}(o\text{-tol})_3$ and KF was also shown to proceed efficiently in TBAB.²¹⁰ Moreover, the $\text{Cu}_2\text{O}/\text{P}(o\text{-tol})_3/\text{TBAB}$ association can be recovered and reused three times without any activity loss in the reaction involving aryl iodides and activated aryl bromides.

In a close area, Radhakrishnan et al. reported a palladium-catalyzed C–N bond cleavage reaction of bicyclic hydrazines with allyl and phenyltributyltin.²¹¹ The reaction proceeded in good yield when catalyzed by a Lewis acid in toluene and faster when carried out in [BMIM][PF₆]. Moreover, in the absence of Lewis acid, the reaction requires a longer reaction time but afforded a similar yield.

While the possibility to achieve the Stille reaction in ILs is clearly pointed out in all of the contributions above, none focused on the power of ILs to avoid contamination by organotin residues at the trace level.

4.4.3. Esterification Reaction in ILs. The esterification and transesterification reactions that are often catalyzed by organotin oxides or organotin carboxylates^{36,37} have also been considered in ionic liquids, affording the desired esters in good yields.^{212,213}

In summary, the use of ILs as solvents in reactions involving organotins generally allows a smoother purification method based on biphasic media, a strategy that facilitates products extraction and decreases the amount of organotin residues in the products. However, these procedures involve often numerous extractions with a high volume of diethyl ether (or petroleum ether), and sometimes additional washings with saturated aqueous potassium fluoride without avoiding the need of a column chromatography to purify the obtained products. Therefore, even sometimes published as “green methodologies”, the workup does not always fit satisfactorily with the green appeal of the concept. In addition, the elimination of ILs is a delicate issue cumulating to the toxicity of some of them.²¹⁴ Moreover, none of these studies reports the quantification of tin at the trace level in the reaction products.

5. MODIFIED ORGANOTIN REAGENTS NONGRAFTED ON A SUPPORT

By modifying appropriately one or several organic substituents of organotin reagents, the physical properties of organotin byproducts obtained during the reaction can be modified allowing an easier elimination and/or a decrease of their toxicity. Numerous studies have been developed in this context with the aim to obtain smooth partitions between two phases.

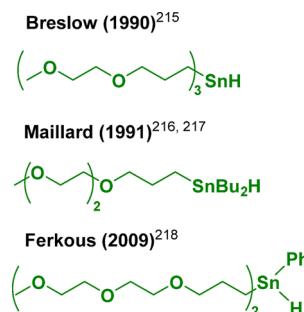
5.1. Polar Organotin Reagents Containing Oxygen Atoms

The modification of an organotin reagent by inserting one or several highly polar groups in the hydrocarbon chain constitutes one of the strategies developed to limit residual

tin byproducts in desired products. The main objective is to facilitate the elimination of organotin byproducts, taking advantage of the presence of the polar group on the tin atom favoring either the interactions between organotin residues and the stationary phase during the purification step on silica gel, or their solubility in aqueous phase during extraction.

In this way, Breslow et al. have prepared a tin hydride functionalized with three polyethylene glycol side chains, which efficiently facilitates the purification of products of radical dehalogenations of alkyl halides. The organotin reagent, being either in the hydride or in the halide form, is soluble in aqueous phase. At the reaction end, products can be straightforwardly isolated by extraction. The tin hydride can be regenerated by reduction of the obtained tin halide with $\text{BH}_3\cdot\text{THF}$ (Scheme 34).²¹⁵

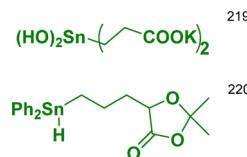
Scheme 34. Tin Hydrides Containing Polyethylene Glycol Side Chain(s)



In a similar approach, Maillard et al. have prepared a tin hydride bearing a polyethylene glycol side chain, which allows a facile separation of the nonpolar organic products of the reaction by column chromatography due to the much longer retention time of the stannylated ethylene glycol derivatives (Scheme 34).^{216,217} More recently, Ferkous et al. have also developed a phenyltin hydride with two diglyme-type side chains (Scheme 34).²¹⁸ This reagent was used for the reduction of hexadecyl halides in the presence of AIBN in refluxing toluene and also for the reductive alkylation of ethyl-chloromalonate. Very high yields were obtained in the former reaction, while 65% yield was obtained in the later one when AIBN/reflux was substituted by $\text{Et}_3\text{B}/\text{O}_2$.

In a close concept, Collum et al. have synthesized an organotin reagent bearing two potassium propanoate chains to make it soluble in aqueous phase (Scheme 35).²¹⁹ This reagent

Scheme 35. Organotin Derivatives Allowing Elimination of Tin Residues as Carboxylates



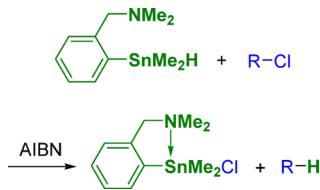
was employed in the presence of NaBH_4 in dehalogenation reactions as well as in tin hydride promoted radical cyclizations of halogenated compounds and allows the elimination of organotin byproducts thanks to their solubility in the aqueous phase. Similarly, a tin hydride functionalized by a 1,4-dioxolan-2-one was developed by Clive et al. and engaged in radical

reduction of alkyl halides and Barton–McCombie deoxygenation (Scheme 35).²²⁰ In all cases, the increased solubility of the organotin side chains in water allows an easy purification of the products, but no data were given for the evaluation of tin at the trace level.

5.2. Polar Organotin Reagents Containing Nitrogen Ligands

5.2.1. Organotin Reagents Containing an Amine Group. Vedejs et al. have developed a tin hydride reagent containing an amine function and have considered its use for the reduction of halogenated derivatives.²²¹ Because of this amine group, a pentacoordinated organotin halide was generated at the end of the reaction (Scheme 36), and was easily removed from the crude thanks to its crystallization in diethyl ether.

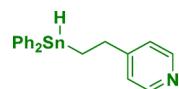
Scheme 36. Vedejs' Tin Hydride



This tin hydride was also used in the radical reduction of ketones and in the Barton McCombie deoxygenation. In both cases, the efficiency of the reagent was demonstrated, and the polar tin byproducts could be eliminated by chromatography on silica gel.

According to this work, Clive et al. have prepared a tin hydride with a β -(pyridin-4-yl) ethyl chain (Scheme 37).²²²

Scheme 37. Organotin Hydride Including a Pyridinyl Side Chain



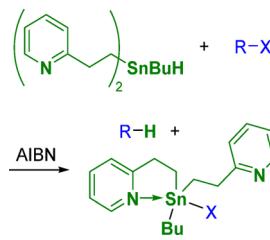
This polar reagent has been used efficiently in radical dehalogenation and in Barton McCombie deoxygenation, allowing the elimination of tin byproducts from the desired products by chromatography on silica gel.

Taking this work into account, Yoshida et al. have described tin hydrides linked in the 2-position of the pyridine.²²³ Accordingly, the organotin halide formed during the radical reduction of alkyl halides with bis(2-pyridinyl-ethyl)butyltin hydride is stabilized by an intramolecular nitrogen–tin coordination and contains a pyridine function, which allows again smooth removal from the organic target products by acid extraction (Scheme 38).²²⁴

Finally, chiral organotin hydrides containing a dimethylamino group have been reported by Schiesser to facilitate the removal of organotin residues in enantioselective reductions.²²⁵

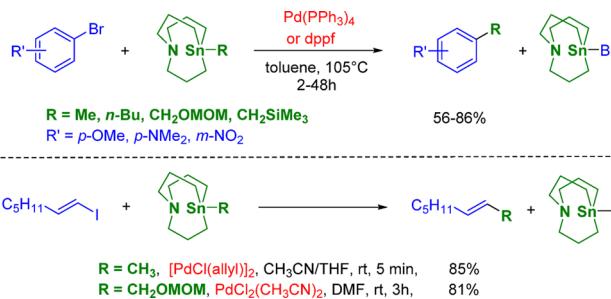
5.2.2. Organostannatranes and Related Compounds. Vedejs et al. have prepared 5-organo-1-aza-5-stannabicyclo[3.3.3]undecanes, which exhibit a good reactivity in the Stille cross-coupling with aryl bromides thanks to the lengthening of the Sn–R bond in the apical position related to the nitrogen of the stannatrane. At the end of the reaction, the precipitation of the 5-halogeno-1-aza-5-stannabicyclo[3.3.3]-

Scheme 38. Tin Hydride with β -(Pyridin-2-yl)ethyl Ligands



undecane allows its removal from the crude mixture (Scheme 39).²²⁶

Scheme 39. Use of a Stannatrane in Stille Cross-Coupling Reaction



Apart from their ability to facilitate reaction mixture workup, stannatranes have also been used for the improvement of their Sn–C reactivity as for example in the Stille coupling of an aminomethyl stannatrane used for a carbapenem synthesis,^{227,228} or those of aziridiny²²⁹ or alkyl stannatranes²³⁰ (Scheme 40).

Similarly, Gaston et al. developed soluble γ -amino-organotins, which were used in Stille cross-coupling reaction and in radical dehalogenation of iodo benzoic acids (Scheme 41).²³¹

Unfortunately, although these studies aimed to facilitate the workup procedures involving organotin reagents, no quantification of the remaining tin byproducts has been carried out; the evaluation of the efficiency of the procedure was only based on the analysis of the NMR spectra of the reaction products.

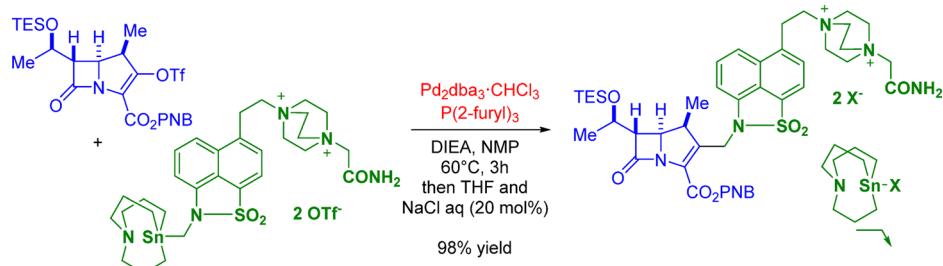
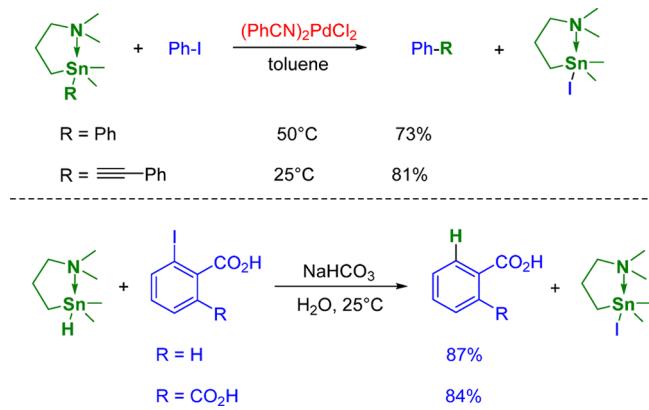
5.3. Organotin Reagents Grafted on a Pyrene Backbone

Gastaldi and Stien have synthesized organotin reagents grafted on a polyaromatic hydrocarbon (a pyrene derivative), to remove easily tin byproducts from the reaction mixture thanks to the adsorption of the aromatic moiety on activated carbon (Scheme 42).^{232,233} These reagents have been used in radical dehalogenation, radical and ionic allylations, and Stille cross-coupling reactions. According to this process, at the reaction end, the stannylated polyaromatic hydrocarbon byproducts were adsorbed on activated carbon, allowing a smooth isolation of the reaction products. Concentrations of the residual tin in the products were found in the range of 0.2–0.77% (2000–7700 ppm) through an approach hampered by the highly carcinogenic nature of pyrenes.

5.4. Perfluoroalkyltins

Fluorine-based methodologies have also been applied to organotins used in organic synthesis both to facilitate crude mixture workup and to reduce tin contamination in the products. After the pioneer work of Horváth and Ràbai on the fluorous biphasic catalysis concept applied to the rhodium-catalyzed hydroformylation of alkenes in 1994,²³⁴ there has

Scheme 40. Transfer of an Aminomethyl Group through a Stille Cross-Coupling Reaction

Scheme 41. Gaston's γ -Amino-organotins Used in Stille and Reduction Reactions

Scheme 42. Organotin Reagents Grafted on a Pyrene Backbone



been a strong development of catalyst separation/recovery exploiting the physical-chemical properties of the perfluoroalkyl tags and their interaction with perfluorocarbons. This methodology is based on the fact that fluorous solvents are immiscible with water and also with most organic solvents. Therefore, two phases (organic, fluorous) or three phases (organic, water, fluorous) can be obtained, and molecules with a sufficient number of fluorine atoms will be extracted in the fluorous liquid phase while other molecules will be extracted into the organic one or in water. Moreover, perfluorocarbons (PFC)

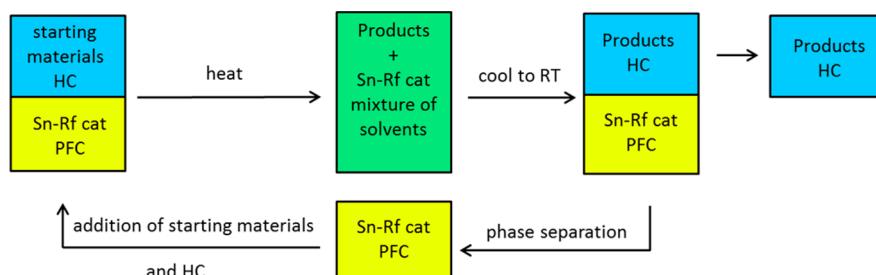
and hydrocarbons (HC) present thermomorphic properties, which offer ideal conditions to conduct homogeneous catalysis at high temperature where only a single phase is obtained and to achieve subsequently a facile liquid/liquid phase separation at ambient temperature where two phases are present. Therefore, the product isolation is easy and the catalyst recovery possible (Scheme 43).

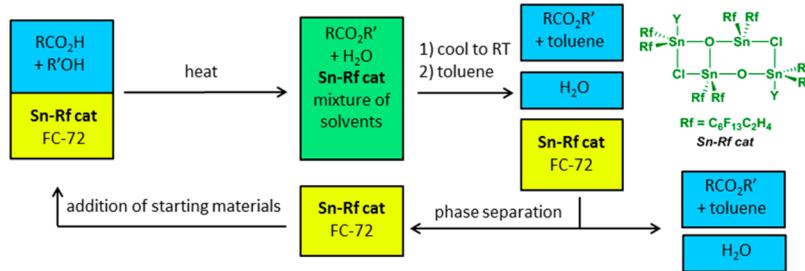
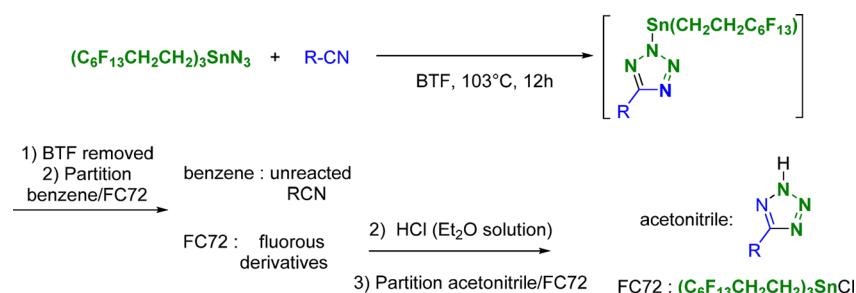
In this context, Curran and Ryu applied this fluorine-based methodology to the catalytic hydroxymethylation of organic halides promoted by a fluorous tin hydride in the presence of carbon monoxide.²³⁵ In that case, a three-phase workup (water, dichloromethane, perfluorohexane) afforded an efficient separation of the fluorous tin hydride from the one-carbon homologated alcohols, which were obtained in good yields. In a close area, Otera et al. have exploited the extreme hydrophobicity of PFC to develop very powerful esterification and transesterification methodologies using a fluorinated distannoxane catalyst (Scheme 44).^{236–238}

When the reactions are carried out at the 10 mmol scale, the pure ester is recovered after decantation, without addition of toluene. The efficiency of this methodology has been demonstrated by performing 10 cycles (reaction, separation, recycling). For each cycle, the yield in isolated ester was >99.5%, and, furthermore, 99.5% of the initial catalyst was recovered after the 10th cycle. The high efficiency of the methodology is due to the very low solubility of water in the PFC that allows a shift of the equilibrium toward the formation of the ester, making this esterification nearly perfectly irreversible without procedures involving dehydration, an excess of alcohol, or activation of the carboxylic acid. Nishikido et al. also investigated the esterification reaction^{239,240} and extended this strategy to the Baeyer–Villiger reaction^{240–242} using a tin(IV) bis(perfluoroalkanesulfonyl)amide, which was likewise found to be recyclable.

While the first contributions were devoted to catalysis, the fluorous technology has been rapidly extended to stoichiometric transformations. Curran et al. reported the use of a

Scheme 43. Reaction Catalyzed by a Fluorous Tin Catalyst (Sn-Rf cat) in a Mixture of Perfluorocarbon (PFC) and Hydrocarbon (HC)



Scheme 44. Esterification Reaction Catalyzed by a Fluorinated Distannoxane in a PFC/HC Biphasic System**Scheme 45.** Stille Cross-Coupling Using Fluorous Tagged Aryltin Derivatives**Scheme 46.** Tetrazole Synthesis with a Fluorous Organotin Azide

fluorous tin hydride, $(C_6F_{13}CH_2CH_2)_3SnH$, in radical reactions^{243–245} and of a fluorous aryltin, $(C_6F_{13}CH_2CH_2)_3SnAr$, in Stille cross-coupling under classical heating conditions^{246,247} and microwave heating.²⁴⁸ This reaction was achieved with several halides or triflates and four different aryltins tagged with a $CH_2CH_2C_6F_{13}$ chain (**Scheme 45**).

After being heated, the reaction mixtures were evaporated and partitioned in a three-phase extraction between water, dichloromethane, and FC72 (perfluorohexane). Evaporation of FC72 provided 80–90% of $(C_6F_{13}CH_2CH_2)_3SnX$ ($X = Cl, Br$), which can be recycled, while the dichloromethane phase afforded the crude reaction product, which was purified by flash chromatography.

Such a methodology was also applied by Gladysz et al. to the preparation and purification of a perfluorophosphine $P-(CH_2CH_2CH_2(CF_2)_7CF_3)_3$ starting from 3-(perfluoroctyl)-prop-1-ene and allyltributyltin,²⁴⁹ and by Curran et al. to the [2 + 3] cycloaddition between a nitrile and a tagged tin azide, which affords 5-substituted-tetrazoles.²⁵⁰ In the latter reaction, using $(C_6F_{13}CH_2CH_2)_3SnN_3$, it was shown that by using a fluorous/organic phase partition, it was possible to obtain pure 5-substituted-tetrazoles even when the nitrile was used in excess (**Scheme 46**). At the end of the reaction carried out in benzotrifluoride (BTF, trifluoromethylbenzene), the solvent was removed to allow a first benzene/FC72 partition to separate the tagged tetrazole from the unreacted organic starting material. After an acidic hydrolysis, the 5-substituted-tetrazoles were separated from $(C_6F_{13}CH_2CH_2)_3SnCl$ by a second partition between CH_3CN and FC72. On the basis of the 1H NMR spectrum of the reaction mixture, the procedure was estimated to be efficient but the global assessment is

mitigated by the fact that these two partitions involve benzene, acetonitrile, and FC72, which are not harmless in terms of hazards and environment.

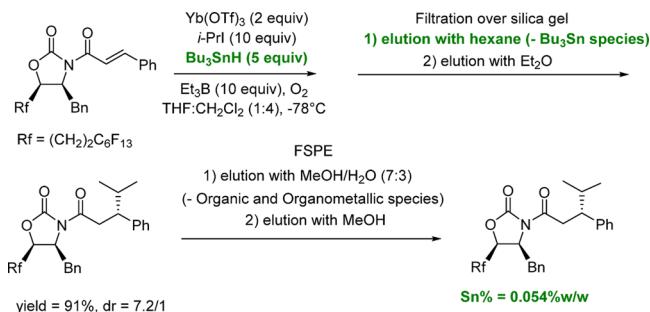
By its very nature, this methodology implies some limitations regarding the scope of the reagents that can be considered, and the efficiency of the liquid/liquid partition is directly dependent on the number of fluorine atoms in the PFC (it is generally observed that at least 60% of the molecular weight has to be fluor to ensure a good partition).

As PFCs are expensive solvents and present the risk of persistence in the environment due to their extreme stability, many efforts have been engaged to develop methodologies limiting both the number of fluorine atoms on fluorous-tagged reagents and the required volume of PFC to be used. In this context, Curran et al. have developed the chemistry of partially fluorinated molecules (called “light fluorous compounds” with usually less than 40% w/w of fluorine), which can be easily separated from nonfluorous ones by fluorous solid-phase extraction (FSPE).^{251–253} This method consists of charging a crude reaction mixture containing both fluorous and non-fluorous derivatives onto a column packed with fluorous silica gel. The nonfluorous derivatives are eluted first with fluorophobic solvents (70–80% $MeOH-H_2O$, 50–60% CH_3CN-H_2O , 80–90% $DMF-H_2O$, or 100% DMSO), while fluorous compounds are retained on the silica gel and are only eluted along with a second elution with a fluorophilic solvent (dry $MeOH$, CH_3CN , THF, etc.). In addition to this simple purification procedure, this approach presents the advantage to use light fluorous reagents having good solubilities in conventional organic solvents and reactivities similar to those of their reference analogues.

Curran et al. developed first this method for the allylstannation of aldehydes and demonstrated that it allows a fast and efficient purification of the products.^{254–257} More recently, the FSPE method was also used for the iododestannylation reaction and the production of radio-iodinated compounds.^{258–261}

Sibi et al. applied the FSPE methodology to the asymmetric conjugate radical addition (Scheme 47).²⁶² Accordingly,

Scheme 47. Example of Improved Separation of Products in the Asymmetric Conjugate Radical Addition Using FSPE Methodology

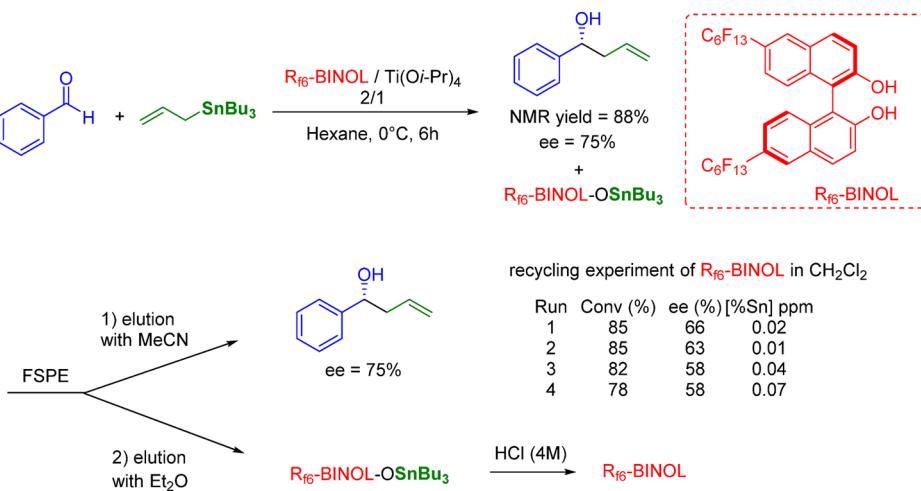


alkylated fluorous oxazolidinones were easily isolated with about 0.06% w/w of tin species in the reaction product, even though tributyltin hydride was used in large excess. This study demonstrates the interest of FSPE using a fluorous chiral auxiliary when comparing the results with those involving nonfluorous oxazolidinones, which require an additional flash chromatography to obtain less than 0.1% w/w of organotin residues in the products.

This method has also been applied to the preparation of α -perfluorohexyloligothiophenes obtained through an iterative sequence including an α -bromination of the thiophene moiety followed by a microwave promoted Stille cross-coupling reaction.²⁶³ While the synthesis and the purification were quickly performed, the cleavage of the fluorous tag has not been addressed, and the purity of the oligomer was only measured by GC–MS analyses.

Stuart et al. have reported the asymmetric allylstannation of benzaldehyde with allyltributyltin mediated by $\text{Ti}(\text{O}-i\text{-Pr})_4$ complexed with a fluorous (*R*)-BINOL ($\text{R}_{f6}\text{-BINOL}$) (Scheme 48).

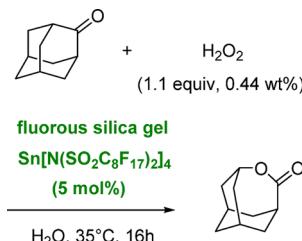
Scheme 48. Asymmetric Allylstannation of Benzaldehyde Using $\text{R}_{f6}\text{-BINOL}$



48).²⁶⁴ When the reaction was carried out in hexane instead of dichloromethane, conversion and enantiomeric excess (ee) were similar to those obtained with (*R*)-BINOL. The reaction product was purified by FSPE and was found to contain only 0.02% of residual tin species. The chiral auxiliary was also isolated as a $\text{R}_{f6}\text{-BINOL-OSnBu}_3$ derivative and was found to be reusable at least three times after hydrolysis with aqueous HCl (4 M). However, conversion and ee slightly decreased during the four successive runs, while residual tin concentration in the products slightly increased, indicating an acceptable but imperfect recyclability.

Fluorous silica gel was also considered to immobilize fluorous Lewis acid to have easier recovery of the catalyst. This concept was studied by Nishikido et al., who developed the Bayer–Villiger oxidation catalyzed by $\text{Sn}[\text{N}(\text{SO}_2\text{C}_8\text{F}_{17})_2]_4$ immobilized on fluorous silica gel.^{265–267} The reaction was carried out in water using a tin Lewis acid immobilized on fluorous silica gel by fluorine–fluorine London forces. In this way, the catalyst can be recycled up to four times, but progressive decreases in yield (79% to 71%) and in selectivity (100% to 91% of lactone from converted 2-adamantanone) were observed (Scheme 49). When the reaction was carried out

Scheme 49. Bayer–Villiger Reaction Catalyzed by $\text{Sn}[\text{N}(\text{SO}_2\text{C}_8\text{F}_{17})_2]_4$ Immobilized on Fluorous Silica Gel by Fluorous–Fluorous Interactions



at a lower temperature (25°C) but with 4.4 wt % of H_2O_2 (instead of 0.44), a stable 88% yield of lactone was obtained along four cycles, and the selectivity remained stable around 90%.

In conclusion, fluorous techniques involving perfluoroalkyltins have been very appealing thanks to their efficiency in separation procedures. However, these methodologies appear

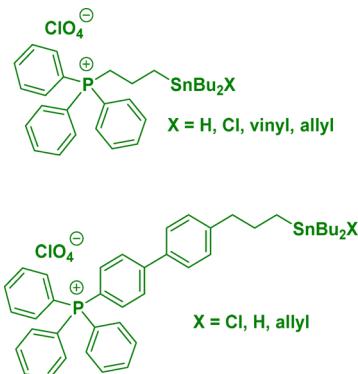
to be less considered nowadays, presumably because of the required tedious preparation of perfluoroalkyltins and of the use of expensive fluorous solvents, combined with non-negligible environmental drawbacks.

6. REAGENTS OR SUBSTRATES GRAFTED ON ORGANIC OR INORGANIC MATRIXES

6.1. Organotin Reagents Grafted on Phosphonium Salts

The use of tetraarylphosphonium moiety as a solubilizing group has been developed by Charette et al. The phosphonium reagents are very soluble in chlorinated solvents and can be precipitated from any reaction mixture upon diethyl ether, hexane, or toluene addition. This methodology was first applied to the Mitsunobu reaction^{268,269} prior to being designed for organotin reagents.²⁷⁰ In Charette's work, two phosphonium-supported organotin reagents have been prepared (**Scheme 50**) and assessed in Stille cross-coupling, radical dehalogenation, radical cyclization, and carbonyl allylation reactions.

Scheme 50. Triphenylphosphonium-Supported Organotin Reagents



Thus, using Fu's catalyst and experimental conditions,²⁷¹ the reactivity of the phosphorylated vinyltin derivative shown in **Scheme 50** in Stille cross-coupling was comparable to that of its nongrafted tributyltin analogue. The workup consists of an evaporation of the solvent of the reaction mixture prior to dissolving the crude products in dichloromethane followed by a precipitation and a filtration of the tin byproduct using hexane. According to this procedure, the cross-coupling product was obtained in this way with a very low tin residue concentration (13 ppm in the crude product and <5 ppm after flash chromatography, as determined by dissolving ICP AES).

The reduction of alkyl halides using a tin hydride grafted on a phosphonium salt has also been investigated. Under Stork's conditions,⁹⁸ alkyl bromides were converted into the corresponding alkanes in high yields. After evaporation and dissolution in dichloromethane, the precipitation of the residual tin halide occurred upon hexane addition. A filtration and a concentration of the residual solution afforded the reduced product with a very low contamination by organotin byproducts, 5 ppm in the crude, as determined by ICP-AES. Moreover, it was shown that the phosphonium hydride reagent could be recycled over six runs without any loss of activity. A radical mediated cyclization and two allylation reactions of aldehydes were also considered without recycling experiments, affording the homoallylic alcohols containing only 7 ppm of residual tin.

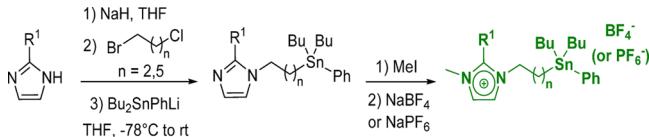
Accordingly, these organotin reagents supported by phosphonium salts appear to be very efficient, obtaining products nearly uncontaminated by any organotin byproducts.

6.2. Organotin Reagents Grafted on Ionic Liquids

In parallel with the increased use of ionic liquids (ILs) in organic and organometallic synthesis, the development of task specific ionic liquids (TSILs) also rose.^{272,273} Numerous contributions have been reported in this field^{274,275} prior to being applied to organotin chemistry.

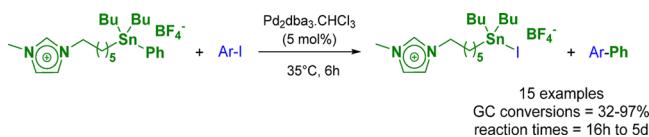
Legoupy et al.^{276,277} have applied this concept to organotin chemistry, and their first study was devoted to the preparation of a phenyltin reagent supported on $[\text{BMIM}]^+[\text{BF}_4]^-$ or $[\text{BMIM}]^+[\text{PF}_6]^-$ obtained by reaction of Bu_2SnPhLi with 1-(3-chloro-propyl)- and 1-(6-chloro-hexyl)-2-methylimidazole followed by alkylation with methyl iodide and anion metathesis with NaBF_4 or NaPF_6 (**Scheme 51**).

Scheme 51. Preparation of a Phenyltin Reagent Supported by an Ionic Liquid



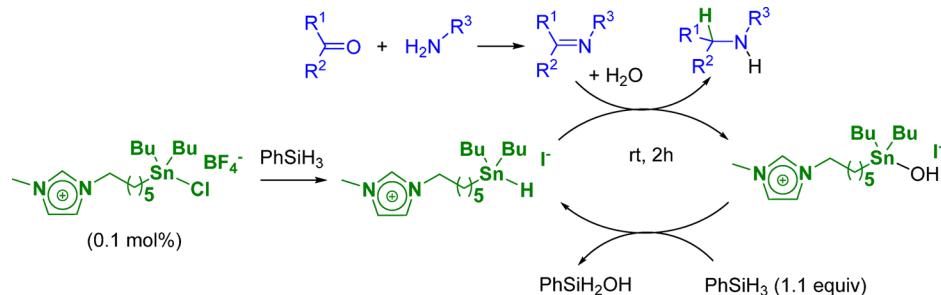
This type of reagent in Stille cross-coupling displayed good to moderate conversions in cross-coupling products along with a significant amount of biphenyl derivative. While $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ was found to afford the best results at 35°C , the reaction times were sometimes restrictively long for complete conversion of starting materials (**Scheme 52**).^{276,277} The recycling of the phenyltin reagent was evaluated in the reaction with phenyl iodide and found to be possible up to five times without any loss in conversion.

Scheme 52. Stille Cross-Coupling Using Organotin Reagents Supported by Ionic Liquids

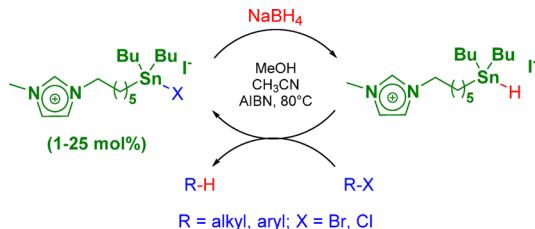


Further contributions were devoted to the reaction of phenyl, vinyl, allyl, anisyl, fluorophenyl, and thiophenylin compounds grafted onto ionic liquids with brominated substrates.^{278,279} With aryl and heteroaryl bromides, the use of $\text{Pd}(\text{OAc})_2$ without any phosphine, any copper salt or fluoride salt, at 100°C during 24 h, afforded the higher yields of cross-coupling products using this grafted phenyltin, while the vinyl transfer was improved by the use of $\text{Pd}(\text{PPh}_3)_4$ at 80°C . In the case of the ionic liquid functionalized with an allyl group, the organotin reagent was shown to be recyclable without decrease of the yields over five runs, and the residual tin pollution in the cross-coupling products was found to be below 3 ppm.

The authors extended the use of stannylated TSILs to the catalytic reduction of cyclic and acyclic imines and aldimines mediated by phenylsilane. Using 0.1 mol % of the organotin chloride grafted on the ionic liquid in the presence of PhSiH_3 , the amines were isolated in good yields after distillation (**Scheme 53**).²⁸⁰

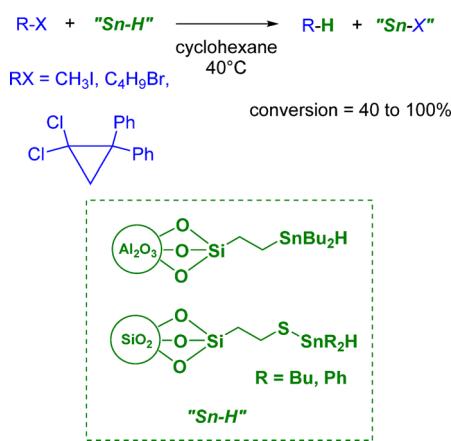
Scheme 53. Organotin Reagents Supported by Ionic Liquids in Catalytic Reduction of Imines

The AIBN promoted radical reduction of alkyl halides was also found to proceed efficiently when catalyzed by an ionic liquid-supported organotin chloride, using NaBH_4 in the presence of acetonitrile and methanol (Scheme 54).²⁸¹ ICP measurements of the residual tin in the reaction products revealed values around 10 ppm.

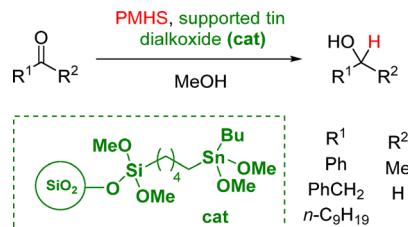
Scheme 54. Radical Reduction of Alkyl and Aryl Halides Catalyzed by an Organotin Halide Supported by an Ionic Liquid

6.3. Organotin Reagents Supported by Inorganic Matrixes

A few inorganic matrixes have been used as supports for organotin reagents. In a pioneering work, Schumann and Pachaly have prepared two organotin hydrides grafted, respectively, on alumina and silica and described their use in the radical dehalogenation of alkyl halides (four examples, conversion from 40% to 100%) (Scheme 55).²⁸² The resulting supported organotin halide ($\text{Sn}-\text{X}$) can be regenerated as a tin hydride ($\text{Sn}-\text{H}$) by treatment with diisobutylaluminum hydride (DIBAL-H) in a mixture of diethyl ether/toluene, but a loss of activity over 50% was observed upon reuse.

Scheme 55. Organotin Hydrides Grafted on Alumina or Silica Matrixes Used for Reduction of Organic Halides

Meanwhile, Matlin et al. described the use of organotin dialkoxides grafted on a silicate type support (Corasil II silica) as catalysts for the polymethylhydrosiloxane (PMHS) reduction of ketones and aldehydes (Scheme 56).²⁸³ The authors report that a batch of catalyst was recycled throughout four successive reduction sequences without noticeable activity lowering.

Scheme 56. Reduction of Ketones and Aldehydes Catalyzed by Organotin Dialkoxides Grafted on Silica

When refluxed in toluene with silica, reagents of the type $\text{Cl}_3\text{Si}-(\text{CH}_2)_3-\text{SnCl}_3$ or $[(\text{Cl}_3\text{Si}-(\text{CH}_2)_3)_2\text{SnCl}_2]$ afford grafted species containing organotin trichloride or dichloride, which have been proved to be efficient catalysts for esterification and transesterification reactions by achievement of the esterification of phthalic anhydride with 2-ethyl-hexanol.²⁸⁴

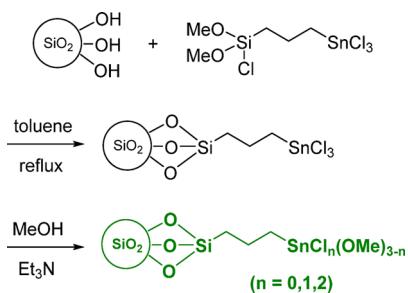
Later, this contribution was taken up by Tsang and co-workers who grafted a similar tin monohydride onto various inorganic matrixes such as Al_2O_3 , ZrO_2 , activated carbon, TiO_2 , and SiO_2 with loadings between 5.4 and $810 \mu\text{mol g}^{-1}$ of active $\text{Sn}-\text{H}$ (with $\text{SiO}_2 > \text{Al}_2\text{O}_3 > \text{TiO}_2 > \text{C} > \text{ZrO}_2$ being the decreasing order of loadings).²⁸⁵ The use of a tin hydride reagent supported by one of these inorganic matrixes afforded high yields in the reduction products of 6-bromohex-1-ene.

Similarly, Fan et al. have synthesized a series of methoxyorganotin chlorides immobilized on mesoporous silica (Scheme 57),^{286,287} and used them as catalysts for the synthesis of dimethyl carbonate from methanol and carbon dioxide.

The authors have pointed out that the activity of these catalysts can be improved by adding the 1,4-bis(triethoxysilyl)-benzene to the condensation reaction to incorporate a phenyl group into the inorganic framework.²⁸⁸ The higher activity observed in this case was explained by a more hydrophobic surface combined with the presence of a larger number of hexacoordinated Sn species and the formation of small Sn oxides clusters. This new material also exhibits a higher stability upon recycling.

Silica matrixes have also been used for the immobilization of tin halides used as Lewis acids to obtain heterogeneous recyclable catalysts for conversion of alcohols into silyl ethers²⁸⁹ or for achievement of key terpenic precursors.^{290,291} In the

Scheme 57. Preparation of Mixed Alkoxytin Halides Supported by a Mesoporous Silica



latter case, tin tetrachloride was supported by a mesoporous silica (MCM41) functionalized by tetraalkylammonium chlorides (**Scheme 58**).

These supported Lewis acid catalysts were used in the Prins condensation of isobutene and formaldehyde for the synthesis of 3-methyl-but-3-en-1-ol (MBOH), which is an important intermediate for the preparation of industrially valuable terpenes. The catalyst exhibited a high selectivity for the unsaturated alcohols (yield of MBOH > 90%) in comparison to the corresponding nonmodified silica analogue, which led to a mixture of compounds (MBOH yield <49%). These results have been explained by the higher concentration of active sites per/g of this supporting material when compared to silica support.

More recently, Toupane et al. also reported the synthesis of an organotin trichloride grafted on silica with an undecyl spacer through a sol–gel processing (**Scheme 59**).²⁹² After a full characterization by HR-MAS ^{119}Sn and CP-MAS ^{29}Si NMR, N_2 -sorption, and TEM measurements, the hybrid silica obtained was further used as a catalyst for the transesterification reaction of ethyl acetate by *n*-octanol. While its parent tricyclohexyltin derivative was not active in this reaction, the supported mono-organotin trichloride afforded 95% of conversion after 20 h, to be compared to about 3 h for the homogeneous analogue. The catalyst was found to be stable under reaction conditions and was recycled four times with at least 95% of the previous activity. In addition, the residual tin concentration was found to be about 10 ppm in the reaction

products, adding a further benefit to the easy workup brought by this silica anchored catalyst.

Apart from the organotin reagents or catalysts supported by metal oxides, it is worth mentioning the synthesis of solid tin hydride reagents by reaction of phenyltin trichloride with di-Grignard reagents (**Scheme 60**).²⁹³ After successive treatments with Br_2 and with NaBH_4 , recyclable insoluble tin hydride reagents exhibiting efficiency similar to Bu_3SnH were obtained and used in the stoichiometric radical dehalogenation of alkyl and aryl halides.

6.4. Organic Polymers Used as Supports

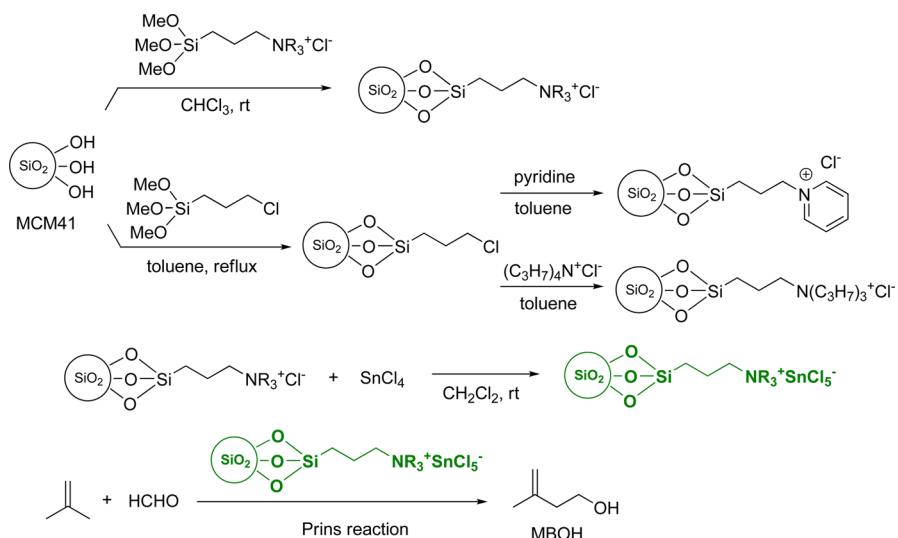
6.4.1. General. Many types of polymeric supports with a variety of compositions and properties have been used for organic synthesis.^{294–297} Among them, non-cross-linked soluble polymers can be distinguished from cross-linked insoluble ones. These polymeric materials have been considered to graft organotin reagents, and among them poly(ethylene glycol) (G), polystyrene (noncrossed linked, Ps), and cross-linked polystyrene (P) have been most often used (**Scheme 61**). Several contributions have also considered the use of polyethylene (PE), polynorbornene (PN), or polyfluorene (PF). Depending on the planned application, each type has its own advantages and drawbacks.

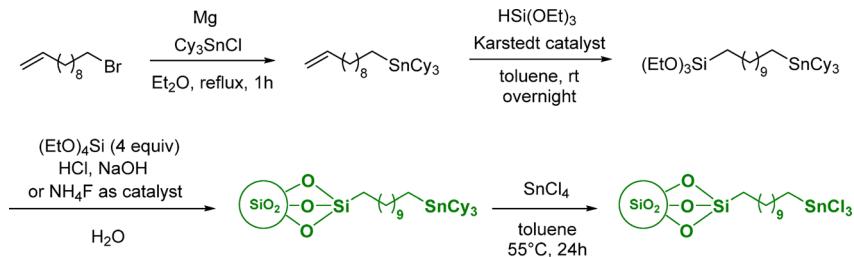
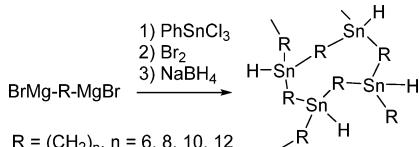
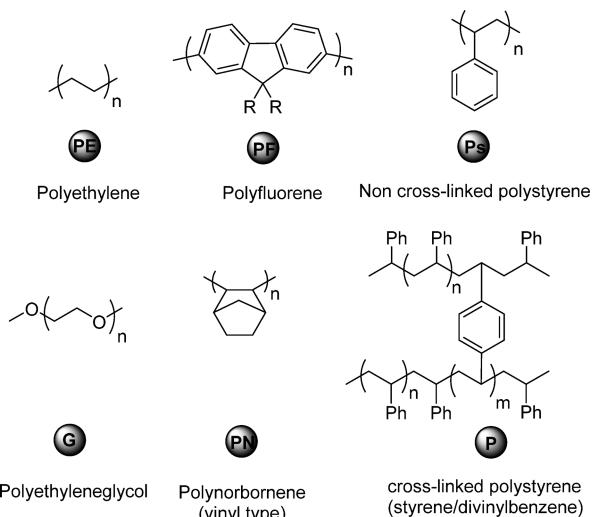
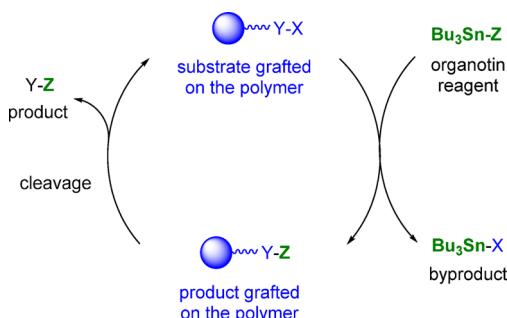
While contributions in this field have been mainly devoted to the development of methodologies involving polymer-supported organotin reagents, several efforts have also focused on grafting the substrate onto the polymer to use a non-immobilized R_3SnZ reagent.

6.4.2. Methods Involving a Polymer-Supported Substrate and a Soluble Organotin Reagent. In this case, the substrate is bound to the polymer and reacts with a soluble nonbound organotin reagent. Therefore, after reaction, the product linked to the polymer can be precipitated (in the case of a soluble polymer) or directly filtrated (in the case of an insoluble one) to remove the soluble tin byproducts. A cleavage reaction is then necessary to liberate the desired product (**Scheme 62**).

6.4.2.1. Methods Involving Substrate Supported by Insoluble Organic Polymers. This methodology has been mainly applied to syntheses involving the Stille cross-coupling reaction. Deshpande has first reported the reaction of an aryl

Scheme 58. Synthesis and Use of a Lewis Acid Immobilized on Mesoporous Silica



Scheme 59. Synthesis of a Silica-Supported Organotin Trichloride Useful in Transesterification Reactions**Scheme 60.** Preparation of a Polymeric Network of Tin Hydride**Scheme 61.** Organic Polymers More Commonly Used To Support Organotin Reagents**Scheme 62.** Use of a Substrate Linked to a Soluble (or an Insoluble) Polymer

iodide bound to an insoluble polymer (a Rink amide or a Wang resin) with aryl and vinyl stannanes, which afforded the cross-coupling products in good overall yields after treatment of the linked product with TFA (**Scheme 63**).²⁹⁸

De Mesmaeker et al. also reported the use of an insoluble polystyrene (Rink resin) as substrate support in a Stille reaction catalyzed by $Pd_2dba_3/AsPh_3$, which was found to be more

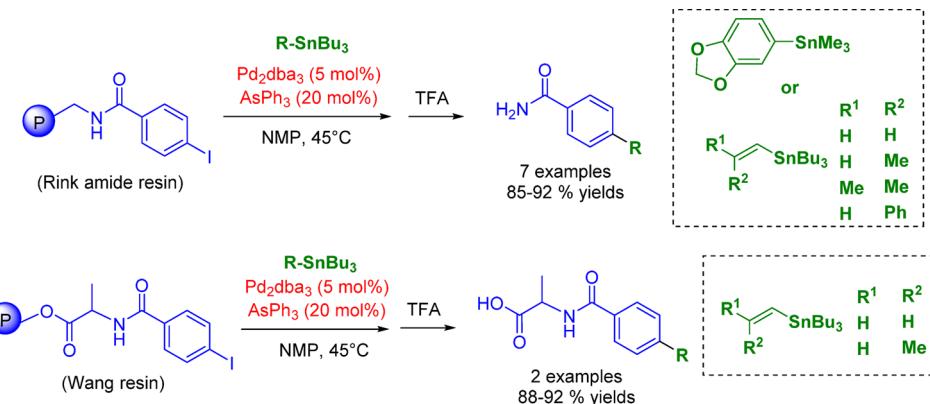
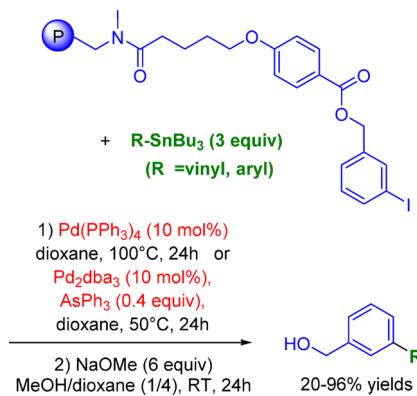
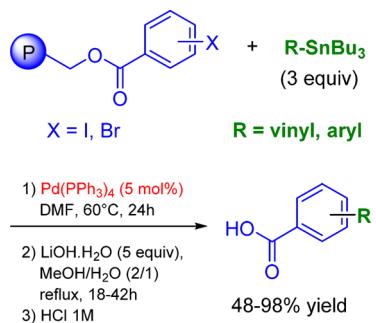
efficient than $Pd(PPh_3)_4$.^{299,300} Good yields were obtained in cross-coupled products, which were recovered after saponification. It is worth noting that this procedure requires a higher charge of catalyst, a longer reaction time, and a large excess of stannanes (3 equiv) to provide comparable yields with respect to the reaction achieved in homogeneous conditions (**Scheme 64**).

Simultaneously, Snieckus et al. were also interested in the evaluation of the Stille cross-coupling reaction on solid support.³⁰¹ Using an insoluble Merrifield polystyrene resin (reticulated with 1% of DVB), high yields were obtained in substituted benzoic acids recovered after LiOH cleavage and subsequent acidification (**Scheme 65**).

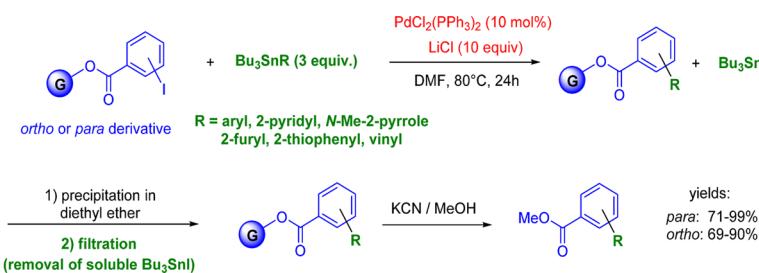
The Stille reaction in the presence of carbon monoxide was also considered by Yun et al. for diarylketones synthesis through a carbonylative Stille cross-coupling prior to preferring the reverse reaction with a polymer-supported phenyltin reagent.³⁰² Guillaumet et al. have used this method for the synthesis of 2,4-disubstituted thiazoles and aminothiazoles.³⁰³ Thus, again, an insoluble polystyrene was used (a Rink resin), and thiazoles were synthesized in 61–90% yields. Apart from contributions devoted to the Stille cross-coupling reaction, it is worth noticing the use of this method for the radical allylation of α -bromoesters with allylstannanes using AIBN as initiator.³⁰⁴ In this case, the Wang resin was found to be the more efficient one, despite chemical yields lower than those obtained with the analogous soluble substrate. In addition, a simple washing with solvents allowed an alternative to the usual problematic purification encountered after radical allylation reaction producing tributyltin halides. De Mesmaeker also applied this methodology involving insoluble polymer-supported substrate to the radical cyclization of *o*-iodobenzyl enamines.^{300,305}

6.4.2.2. Methods Involving a Substrate Supported by a Soluble Organic Polymer. The concept of the grafted substrate was also considered by Janda et al. with a soluble polyethylene glycol, for Stille cross-coupling reactions.³⁰⁶ Thus, 2- or 4-iodobenzoates-substituted polymers were reacted with several tributyltin reagents to afford methyl esters after precipitation with diethyl ether, separation of the polymer-supported product from Bu_3SnI , and transesterification. In this case, the purity of the product is controlled by the efficiency of the precipitation step to ensure a good and optimal removal of the soluble tin byproducts from the polymer (**Scheme 66**).

Unfortunately, none of these contributions has evaluated the efficiency of this method by reporting a careful quantification of the residual tin derivatives remaining in the reaction products. In addition, this method often requires the use of an excess of tin reagents to ensure a complete conversion of the polymer-supported substrate, a drawback that disfavors a low residual tin concentration in the reaction products. It should also be noted that this method, even improving efficiently the purification

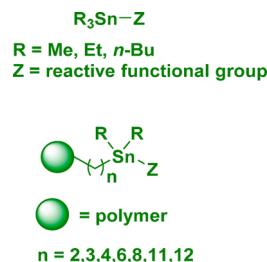
Scheme 63. Use of an Aryl Iodide Bound to an Insoluble Polymer in the Stille Cross-Coupling with Vinyl or Aryl Stannanes**Scheme 64.** Stille Cross-Coupling Involving an Aryl Iodide Grafted on an Insoluble Rink Resin**Scheme 65.** Stille Cross-Coupling Involving an Arylhalide Grafted on an Insoluble Merrifield Resin

workup, does not automatically suppress the purification by flash chromatography, which remains necessary to separate the reaction product from the unreacted substrate because both are

Scheme 66. Use of a Soluble Polyethylene Glycol-Supported Iodoarylester in Stille Cross-Coupling

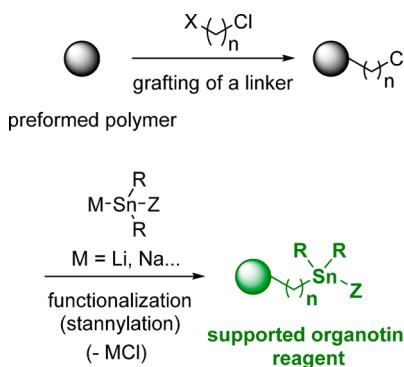
released by the reaction cleavage (transesterification, hydrolysis, etc.) used for the product recovery.

6.4.3. Methods Involving a Polymer-Supported Organotin Reagent. In this case, the substrate is in solution, and the organotin reagent is grafted onto an organic polymer. The direct grafting of the organotin moiety on the polymer imposes that the Sn–C bond of the linkage must be unreactive to avoid tin leaching and ensure reactivity centered on the “Z” moiety of the supported reagent (**Scheme 67**). The “linker-SnR₂” moiety

Scheme 67. From Triorganotin Reagents to Polymer-Supported Organotin Reagents

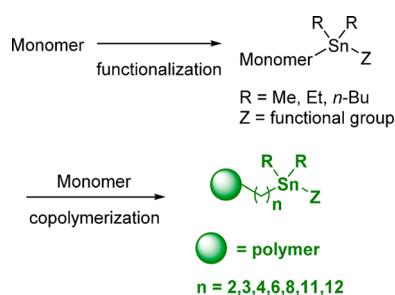
is often a mimic of the usual triorganotin reagents; therefore, R is usually a methyl, an ethyl, or a butyl group, and the linker is an alkyl chain with a length of 2–12 carbons (with a β -elimination issue with 2 carbons). In practice, the R group is often an *n*-butyl group and the linker a 4 carbon chain to be as similar as possible to the tributyltin derivatives.⁶⁸

For this purpose, the organotin unit can be introduced onto the polymer chain either by grafting the organotin reagent onto the preformed polymer (**Scheme 68**) or by copolymerization of a stannated monomer with styrene (or another olefinic monomer).

Scheme 68. Stannylation of a Preformed Polymeric-Support

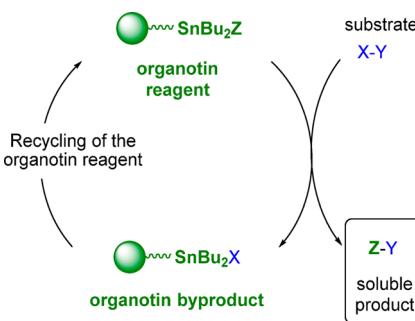
The first route, as for instance the functionalization of cross-linked polystyrene, is by far the prevalent route to prepare polymer-supported tin reagents because it avoids the polymer synthesis steps. However, anchoring the desired reactive species onto the polymer requires several steps that need to be quantitative to obtain acceptable reproducibility in the loadings due to the impossibility to achieve separations and removal of grafted impurities that usually cross-interfere in target processes. Obviously, once synthesized, these supported tin reagents should be washed thoroughly several times to remove the soluble organotin species resulting from their synthesis for further use under appropriate conditions.

The other synthetic route involves the copolymerization reaction between a monomer and a stannylated monomer and therefore may allow an easier control of the tin loading by using an appropriate ratio of monomers (**Scheme 69**).

Scheme 69. Copolymerization of a Functionalized Monomer

Using such supported organotin reagents, the reaction products are obtained in solution and therefore can be isolated by a simple filtration (in the case of an insoluble polymer), or after precipitation followed by a filtration of the supported organotin byproducts (in the case of a soluble one) (**Scheme 70**). After separation, it is possible to consider recycling of the immobilized tin byproduct.

Finally, a methodology where the R_3Sn moiety is grafted onto the polymer through a secondary functional group (FG) has also been considered. This method allows a good removal of organotin residues but cannot be considered for recycling. In this case, the reaction product remains on the polymer support while the organotin byproducts are in solution. An additional step is necessary to obtain the reaction product from the polymeric support by an appropriate cleavage achieved after separation of the organotin byproducts from the polymer, which can be either soluble or insoluble (**Scheme 71**).

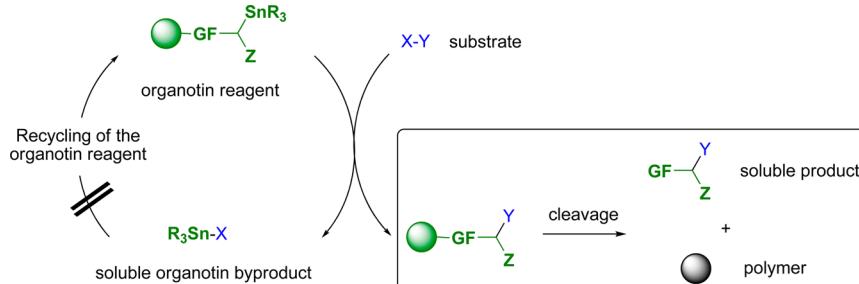
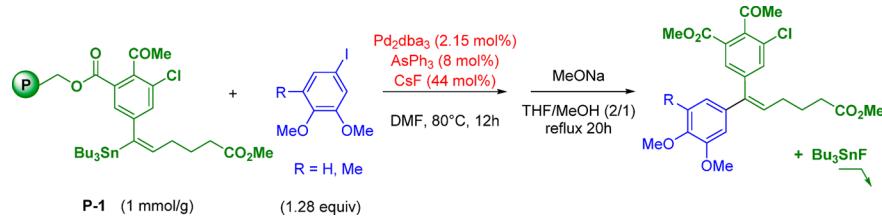
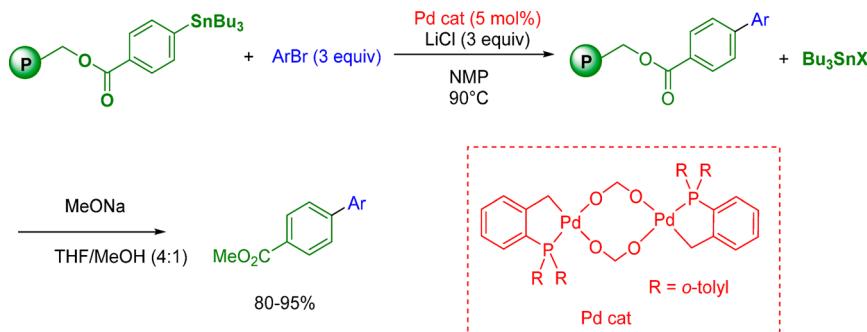
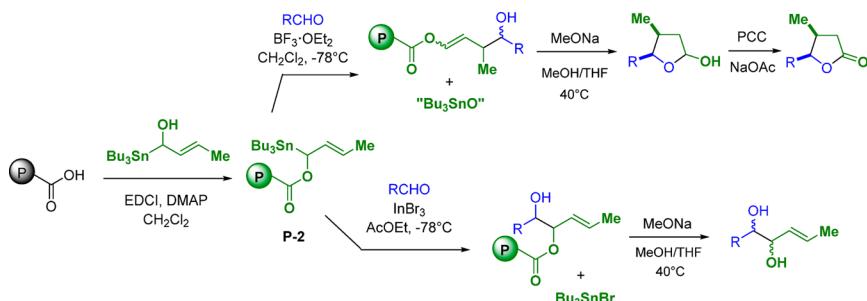
Scheme 70. Use of an Organotin Reagent Permanently Anchored to a Soluble or an Insoluble Polymer

Whatever the supported organotin reagent used, the common point of these strategies is that one specific component (substrate, byproduct, product) is soluble in the organic layer while the other components of the reaction mixture (byproduct, product) remain grafted to the polymeric support. These supported reagents avoid difficult purification steps and therefore minimize the tin contamination of the products.³⁰⁷ However, the temporary grafting is less attractive than the permanent one, because it is less general, and it requires one more step to release the product from the polymeric support, and it is also incompatible with an immediate regeneration of the supported organotin reagent.

Nevertheless, several contributions illustrate its potential. Using an insoluble aminomethyl polystyrene³⁰⁸ or a polystyrene with a silicon-based tether,³⁰⁹ Ellman has elaborated a library of 1,4-benzodiazepines via Stille cross-coupling. The interest of this strategy is based on the fact that the reaction products are still grafted to the insoluble polymer allowing the five following steps at the liquid–solid interface, until achievement of a TFA cleavage to afford the 1,4-benzodiazepines. Hone et al.³¹⁰ and later Cushman et al.³¹¹ also considered this method for the Stille cross-coupling reaction. In the latter case, alkenyldiarylmethane derivatives were synthesized to propose non-nucleosides HIV-1 reverse transcriptase inhibitors. Two derivatives were prepared from a Wang resin anchoring a vinyltin reagent (**P-1**) through a Stille cross-coupling.³¹² The alkenyldiarylmethanes were recovered after a sodium methoxide cleavage, with however a poor chemical purity of 75–85% as established by 1H NMR, which required further purification by flash chromatography (**Scheme 72**).

This strategy was also used by Finn et al. for the functionalization of bromoarenes via Stille cross-coupling. An arylstannane grafted onto a Merrifield resin (polystyrene cross-linked with 1% of divinylbenzene) was reacted with bromoarenes in *N*-methylpyrrolidone (NMP).³¹³ A pallada-cycle complex was found to be more efficient or more stable than $Pd(PPh_3)_4$, $Pd_2(dbu)_3$, or $Pd(AsPh_3)_4$. After cleavage with a catalytic amount of MeONa in a mixture of THF/MeOH, the reaction products were isolated in high yields (**Scheme 73**).

The concept of temporary anchored organotin reagents has also been used in the reactions of α -(hydroxymethyl)-allenyltributyltin and α -hydroxycrotyltributyltin with aldehydes. In these cases, the polymer was a microporous carboxylic polystyrene and the primary products of the reaction were the supported homopropargylic or homoallylic alcohols, which afford the corresponding diols or their cyclized derivatives upon cleavage (**Scheme 74**).

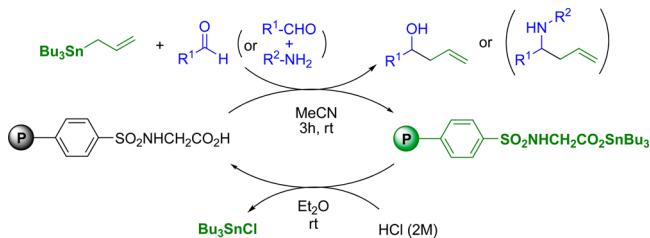
Scheme 71. Use of an Organotin Reagent Temporary Grafted to a (Soluble or Insoluble) Polymer via a Functional Group (FG)**Scheme 72.** Use of a Temporary Linked Vinyltin in a Stille Cross-Coupling Reaction**Scheme 73.** Use of a Temporary Linked Aryltin in a Stille Cross-Coupling Reaction**Scheme 74.** Use of α -Hydroxycrotyltributyltin Temporary Linked to a Microporous Polymer

Thus, after transesterification, the cleavage step, eventually followed by an oxidation, a variety of homopropargylic alcohols³¹⁴ and 1,2-diols, lactols, or γ -lactones^{315,316} were obtained with satisfactory yields and with selectivities similar to those obtained with nonsolid-supported tributyltin analogues. As expected, the products obtained exhibit no significant NMR resonances from tin residues within the sensitivity limits of the NMR. Note that the organotin residues are released into the liquid phase and washed away prior to the desired release of target organic compounds.

A close concept but more in line with the “catch and release” method has been applied later by Zhao et al. to the allylation of aromatic aldehydes and aldimines by allyltributyltin.³¹⁷ Thanks to the carboxylic function of a polymer-supported *N*-

sulfonamide of *N*-glycine, homoallylic adducts were readily isolated, while organotin alkoxide or tin amide was trapped by the carboxylic function of the polymer to give the filterable organotin carboxylates (Scheme 75). The unreacted allyltin was also removed by the presence of an excess of polymer through protolysis. Upon treatment with HCl (2 M), residual organotins were recovered as tributyltin chloride, which can be used for the regeneration of allyltributyltin. The latter was shown to be efficient after three cycles despite a lowering in the activities. According to this methodology, the obtained homoallylic alcohols or amines were obtained efficiently and cleanly within the ¹H NMR sensitivity limits, but no tin trace levels were available.

Scheme 75. “Catch and Release” Concept Applied to the Synthesis of Homoallylalcohols and Homoallylamines



6.4.3.1. Organotin Reagents Grafted onto Soluble Polymers. **6.4.3.1.1. General.** Soluble polymers have been widely used in organic synthesis.^{318–320} Polyethylene glycol **G** and non-cross-linked polystyrene **Ps** are the most often used starting materials for the preparation of the supported organotin reagents in the case of soluble polymers. These latter correspond to the linear polymer obtained from the polymerization of inexpensive monomers such as ethylene oxide or styrene using standard conditions. The resulting grafted polymers are soluble in common solvents used in organic synthesis, and therefore allow the desired reactions to be carried out in homogeneous phase.^{321–323} In addition, NMR analysis of any functionalized polymer-bound intermediates is possible in a nondestructive manner using routine NMR analyses and spectrometers for their characterization.^{307,324–326}

Supported reagents of type **G** exhibit good solubility in a wide range of solvents including DMF, dichloromethane, toluene, acetonitrile, and water, but are nearly insoluble in hexane, diethyl ether, isopropanol, and cold ethanol. Therefore, the latter solvents are generally used to induce precipitation of the polymer-supported reagents and of the supported by-products. Furthermore, it is worth noting that when reactions are carried out at low temperature, **G** derivatives have a very low solubility, while **Ps** modified reagents are soluble in dichloromethane, chloroform, toluene, ethyl acetate, and acetonitrile even at low temperatures (-78°C) but are insoluble in methanol and water. Therefore, dilute solutions of these polymers allow a rapid and unimpeded access of reagents to the functionalized support, allowing high conversions due to the homogeneity of the reaction medium.

After completion of the reaction in homogeneous phase, the polymer-supported organotin compounds can be recovered by precipitation upon cooling and addition of methanol or by aqueous extraction after addition of dichloromethane in the case of **Ps**-type polymer, or by precipitation with diethyl ether in the case of **G**-type polymer.

6.4.3.1.2. Preparation of Organotin Reagents Grafted onto Soluble Polymers and Their Evaluation as Tin Hydrides

in Reduction of Organic Halides. Among the reactions involving organotin reagents, the reduction reaction of alkyl halides carried out using triorganotin hydrides has been one of the most frequently studied. Therefore, several reports have considered the grafting of both organotin chlorides (as precursors of tin hydrides) and tin hydrides on soluble polymers to facilitate the reaction workup with the objective to minimize the amount of the organotin residues in the products.

In a pioneering work, Bergbreiter et al.³²⁷ grafted successfully dibutyltin chloride on polyethylene and polystyrene matrixes to obtain the corresponding supported tin chlorides **PE-3** and **Ps-6**, respectively,³¹² of which the application as catalysts (in association with NaBH₄) was highlighted for the reduction of alkyl halides and aryl halides.³²⁷ These two polymer-supported dibutyltin chlorides were respectively prepared by anionic polymerization of ethylene and polystyrene promoted by *n*-butyllithium followed by electrophilic trapping of the resulting anionic species with dibutyltin dichloride, a strategy that was also applied to other supported organotin chlorides (Scheme 76).

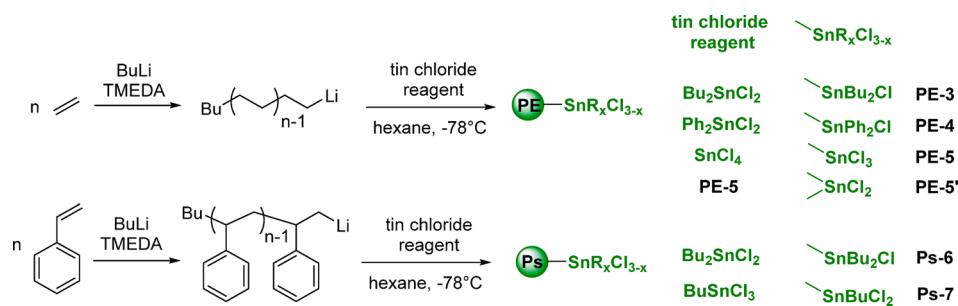
The resulting stannylated polymers were fully characterized by ¹H and ¹¹⁹Sn NMR, and their tin loading was evaluated to be 0.3–0.6 mmol Sn/g by ICP analysis.

Typically, for the reactions performed in refluxing toluene (110°C), the tin reagents were used as cocatalysts (ca. 10%) in the presence of an excess of NaBH₄ with 10–20% of the benzo 15-crown-5 ether, which was used as a phase transfer catalyst. Under these conditions, the reaction of NaBH₄ with **PE-3** and **Ps-6** affords the corresponding supported tin hydrides, which are able to reduce efficiently primary and secondary alkyl halides as well as aryl halides (Scheme 77). In both cases, the yields were comparable to those obtained for the tributyltin hydride reductions.

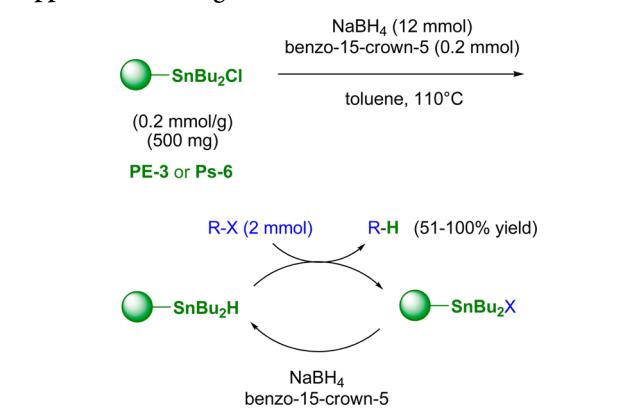
Following a similar synthetic strategy, soluble polystyrene-supported *n*-butyltin dichloride **Ps-7**, polyethylene-supported tin trichloride **PE-5**, and polyethylene-supported diphenyltin chloride **PE-4** have also been prepared using BuSnCl₃, SnCl₄, or Ph₂SnCl₂ as an electrophile (Scheme 76) and were used in reduction reactions. Reduction products were obtained in good yields, but the double functionality on tin induced side reactions (for instance, ditin formation) especially when performed at high temperature (110°C). Polymers **PE-3** and **Ps-6** were reused with no significant loss of activity, while recycling attempts of tin catalysts **PE-5**, **PE-5'**, and **Ps-7** led to 30–50% of catalytic activity loss.

In a different approach, Enholm and Schulte³²² reported the synthesis of another organotin chloride supported by a soluble polystyrene polymer **Ps-8** and its use in the reduction of

Scheme 76. Synthesis of Organotin Chlorides Supported by Soluble Polymers

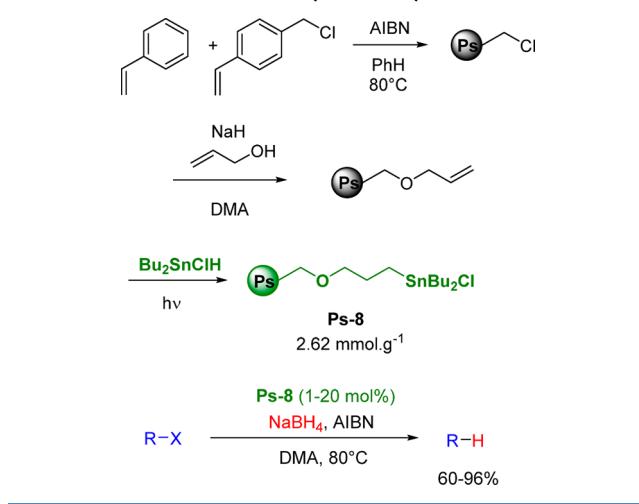


Scheme 77. Reduction of Alkyl and Aryl Halides Using Supported Tin Reagents PE-3 and Ps-6



organic halides. A free radical polymerization initiated by AIBN was used to prepare the chloromethyl functionalized polystyrene with halogen loadings varying from 3% to 50%, tuning the styrene to 4-vinylbenzyl chloride ratio. The resulting chloromethyl polymers were subsequently reacted with the prop-2-en-1-ol alcoholate to obtain the corresponding allylethers. Upon hydrostannylation, the latter afforded the polystyrene-supported tin chlorides **Ps-8** in 65% overall yield (**Scheme 78**).

Scheme 78. Synthesis of an Organotin Chloride Anchored to a Soluble Polymer by an O-Containing Linker (Ps-8), and Its Use in the Reduction of Alkyl and Aryl Halides

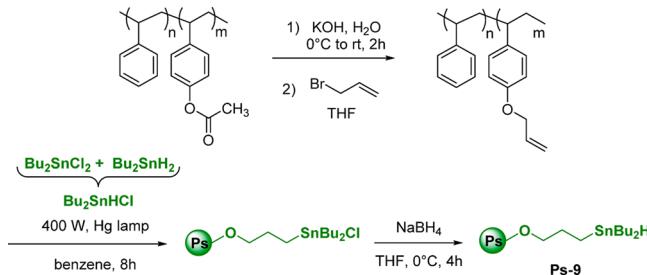


According to the reaction described in **Scheme 78**, most of the reduction reactions were successfully performed in good yields with primary, secondary, and tertiary alkyl halides as well as with aryl halides using only 0.1 equiv of the supported organotin reagent and an excess of sodium borohydride (1.5 equiv). Most reactions are going to completion within 2.5 h with yields ranging from 60% to 96% (**Scheme 78**). In each case, the recovery of the products was much easier than with soluble tributyltin hydride, and very low tin residue levels were measured in the products (5–11 ppm for the reported examples).

Maillard et al. have also synthesized several soluble copolymers of polystyrene with different molecular weights (depending on *n/m* ratio) and different degrees of tin hydride functionalities (depending on *m* value for acetoxystyrene) using

atom transfer radical polymerization. Chemical modifications were carried out to prepare the desired supported tin hydrides **Ps-9** (**Scheme 79**), which have been well characterized by different techniques including IR and NMR spectroscopy and size exclusion chromatography.³²³

Scheme 79. Synthesis of Soluble Polymer-Supported Tin Hydrides Ps-9 with an O-Containing Linker



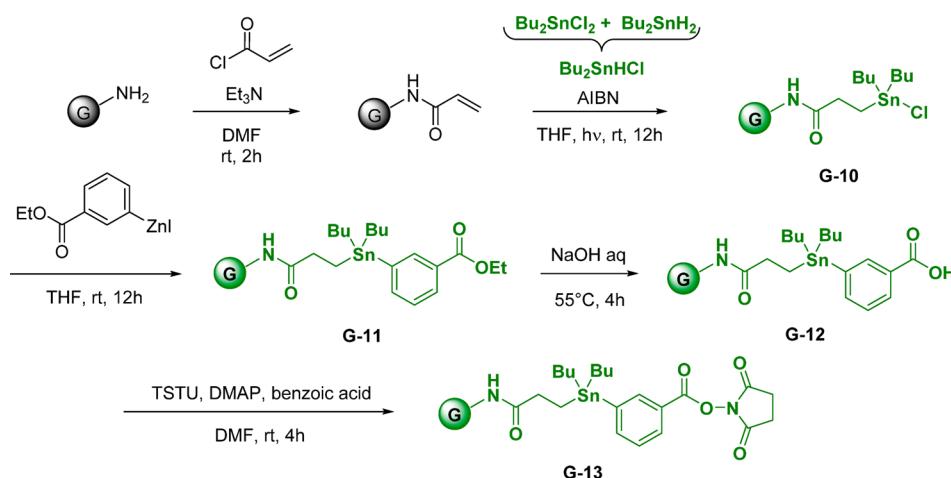
The efficiency of these soluble polymer-supported tin hydrides has been demonstrated through the reduction of 6-bromohexene. In comparison to tributyltin hydride, higher yields were obtained in shorter reaction times with these reagents for reactions adjusted to have the same concentration of tin hydride. The H transfer constant *k*_H increases as the functionalization degree of the polymer decreases, a result that was explained by the change in solution viscosity.³²³

6.4.3.1.3. Organotin Reagents Grafted onto Soluble Polymers in Halodestannylation Reactions. Recently, Gifford et al. reported a polymer-supported approach for ¹²⁵I radiolabeling of organic substrates to avoid the need of postlabeling purification prior to conjugation to biological macromolecules.³²⁸ In this case, the supported aryltriorganotin precursor was grafted on a polyethylene glycol polymer via a C_{sp}³–Sn bond. Thus, aryltins substituted on the *meta* position by a carboxylic ester **G-11** or by a *N*-succinimidyl ester **G-13** have been synthesized according to **Scheme 80** and assessed for radioiodination purposes.

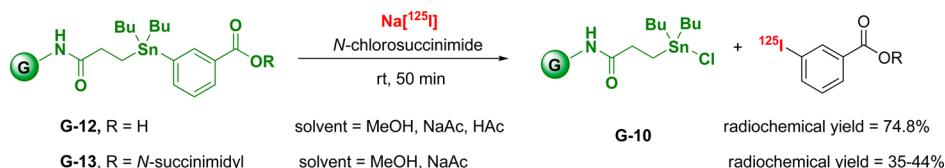
Iododestannylation by Na^{[125]I} of **G-11** and **G-13** in aqueous solvent or methanol during 50 min at room temperature released the corresponding radiolabeled ¹²⁵I compounds, whereas unreacted tin precursors and byproducts remain grafted to the resin beads, enabling an easy separation from the radioiodinated product by a simple filtration or extraction step (**Scheme 81**). Good chemical yields (up to 75%) and good radiochemical purities (80–92%) were obtained depending on the solvent and the precursor.³²⁸ This approach improves the process of radiolabeling of proteins and peptides via the conjugate radiolabeled group approach because by reducing the need of postiodination purification of the prosthetic group prior to conjugating it, the radiochemical yield is also logically improved. Because of the fast reaction and workup, this method is also compatible with radioisotopes having a shorter half-life like ¹²³I (*t*_{1/2} = 13.2 h).

6.4.3.1.4. Organotin Reagents Grafted onto Soluble Polymers in Allylation Reactions. Both radical substitutions and heterolytic additions have been widely used for the selective formation of C–C bonds in organic synthesis. Here again, the difficulty of removing organotin residues in the target products is the main drawback when working with tributyltin derivatives, and the polymer-supported strategy constitutes an efficient route to improve this point.

Scheme 80. Synthesis of a Stannylated G-Based Polymer Containing Ethyl-(dibutylstanny)benzoate (G-11) and N-Succinimidyl-(dibutylstannyl)benzoate (G-13) Units

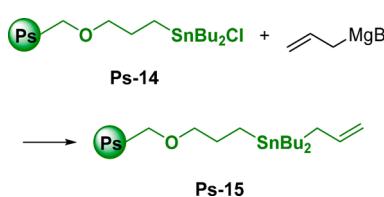


Scheme 81. Preparation of Radiolabeled Benzoic Acid Derivatives by Iododesstannylation of Supported Aryltriorganotins



Enholt and Schulte have reported the preparation and the use of a non-cross-linked polystyrene allyltriorganotin **Ps-14** (with a loading from 0.3 to 5 mmol g⁻¹) in the radical allylstannation of organic halides.³²¹ A series of alkyl halides was submitted to the allylic transfer reaction, and, surprisingly, hindered tertiary bromides poorly reactive with allyltributyltin appear to be more reactive with the soluble-supported allyltin, affording the desired products in good yields (*Schemes 82* and

Scheme 82. Synthesis of an Allyltin Grafted on a Soluble Polymer, **Ps-15**

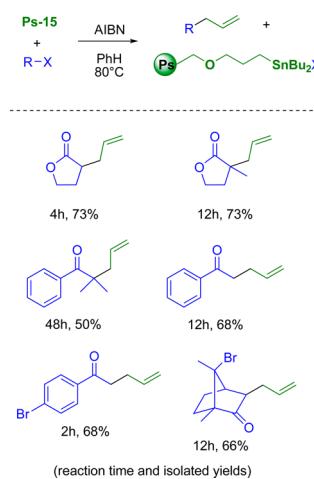


83). The authors explained this reactivity by an increased nucleophilicity of the supported allylstannane. A strong effect of the substituents present on the alkyl halides was found: substrates containing withdrawing groups (as for instance α -bromoacarbonyl function) appear to be the most reactive ones, while substrates containing electron-donating groups appear poorly reactive or nonreactive.

In the case of α -bromoacetophenone, a tin contamination of 6.9 (first run) and 15.6 ppm (second run) in the product was found using **Ps-15**. These values were compared by the authors with values of 53 and 79 ppm (first and second runs, respectively) obtained with allyltributyltin evidencing the relevance of the methodology.

6.4.3.1.5. Organotin Reagents Grafted onto Soluble Polymers in Stille Cross-Coupling Reactions. Tin reagents grafted onto soluble polymers have also been used in Stille

Scheme 83. Allylation of Organic Halides with Polymer-Supported Tin Reagent **Ps-15**

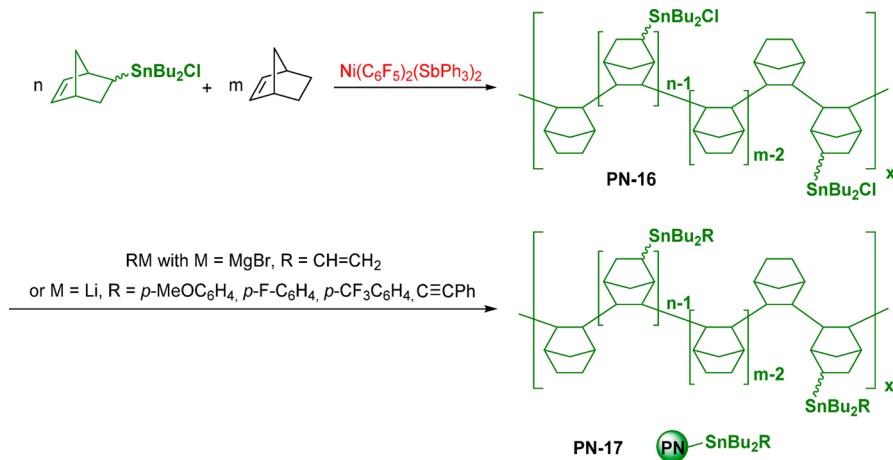


cross-coupling reactions to facilitate the purification of the products, a field that has been previously reviewed.^{14,329,330}

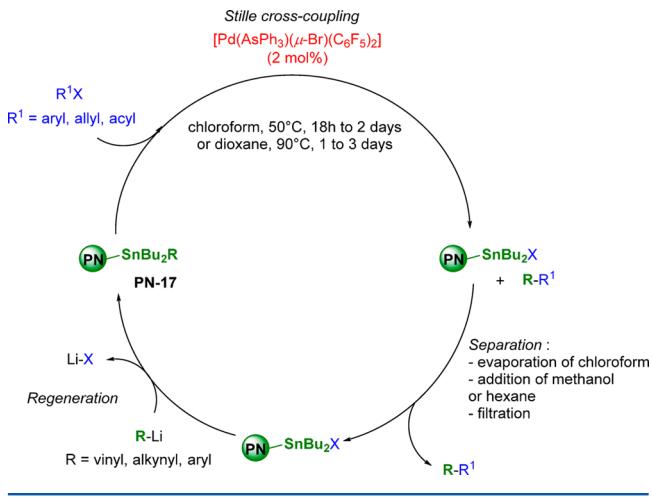
Espinet et al. have synthesized a soluble stannylated vinylidene polynorbornene **PN-17** (via **PN-16**) by copolymerization of norbornene with a norbornen-4-yl dibutyltin chloride, catalyzed by [Ni(C₆F₅)₂(SbPh₃)₂] and subsequent substitution of the tin halide by organometallic reagents (*Scheme 84*).³³¹

These polymers have been used as R-transfer reagents in Stille couplings, providing separation of the polymer-supported tin halides byproducts from the coupling products by precipitation of the soluble polymer in methanol or *n*-hexane followed by a filtration (*Scheme 85*).^{331,332} Good yields were obtained, but a long reaction time was necessary (18 h to 3 days). Interestingly, the stannylated polymers were shown to be recyclable at least five times without any yield loss (95% for

Scheme 84. Synthesis of Polynorbornene-Supported Tin Reagents



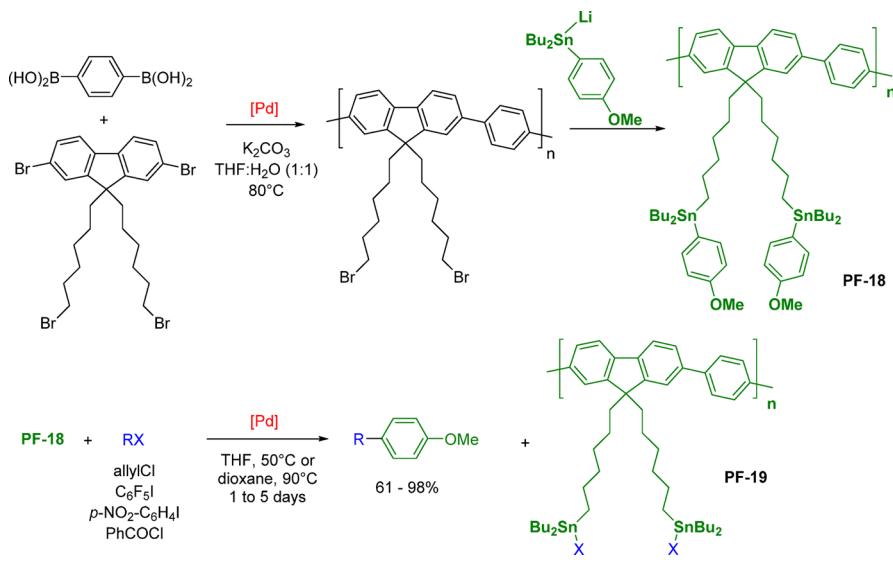
Scheme 85. Stille Reactions Involving Polynorbornene-Supported Organotins with Sn-Vinyl, Sn-Aryl, or Sn-Alkynyl Functionalities and Recycling



each run). Low tin residue concentrations (0.02–0.05 wt %) were found in the reaction products using this new polymeric reagent from the second run.

A fluorene-based polymer PF-18 was also used to graft the *p*-anisyl dibutyltin moiety, and the efficiency of this new reagent was evaluated in the Stille cross-coupling reaction (Scheme 86).³³³ Despite the soluble nature of the organotin reagent, long reaction times (1–5 days) were required to observe a complete conversion in the four considered examples. The workup procedure consists of a precipitation of the polymer by addition of methanol (500 mL for 5 g of polymer used) and its filtration to obtain a solution, which affords the cross-coupling products after evaporation of the solvent. The recycling of the polymer was shown to be possible for at least four runs but needs additional treatments (washing with MeOH (4 × 50 mL)), then the coupling product was subjected to diethyl ether and treated with activated charcoal prior to an ultimate filtration through silica gel. In addition, it was noted that the more the polymer was recycled, the less it became soluble, a fact that can explain the decrease of the remaining tin in the cross-coupling products as the number of runs increases without efficiency loss. It is noteworthy that the fluorescence

Scheme 86. Preparation of a Fluorene-Supported Organotin Reagent and Its Use in a Stille Cross-Coupling

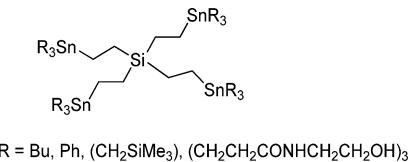


properties of the fluorene were found to underestimate the residual tin concentrations in the cross-coupling products as compared to results obtained by ICP-MS, which exhibits about 2.5 and 0.1 wt % of tin content after the first and the fourth cycles, respectively.

In summary, while useful and efficient, the perfect separation of soluble polymers from the products is often less simple than claimed and generally not fully quantitative. Therefore, the primary advantages associated with the use of soluble polymeric supports (homogeneous reaction conditions, possibility to utilize standard analytical techniques like ^1H , ^{13}C , or ^{119}Sn NMR, etc.) have been often disregarded considering this drawback. Accordingly, these types of soluble polymers have not been extensively developed in organic synthesis when compared to insoluble ones (*vide infra*).

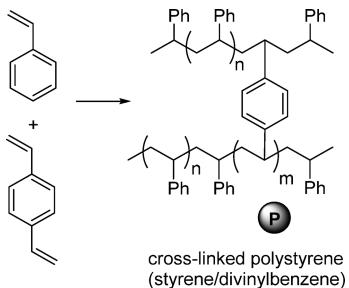
The problem due to low loadings might be circumvented by the use of stannylated dendrimers, but even though these have been synthesized and characterized, to our knowledge, none of them has been yet evaluated as a tool for organic synthesis ([Scheme 87](#)).^{334–338}

Scheme 87. Stannylated Dendrimers



6.4.3.2. Organotin Reagents Grafted onto Insoluble Organic Polymers. **6.4.3.2.1. General.** In the case of organic insoluble polymers, a cross-linked agent is added during the polymerization reaction so that the polymer chains are covalently interconnected to generate a network, which is insoluble in all solvents ([Scheme 88](#)). Cross-linked polystyrene

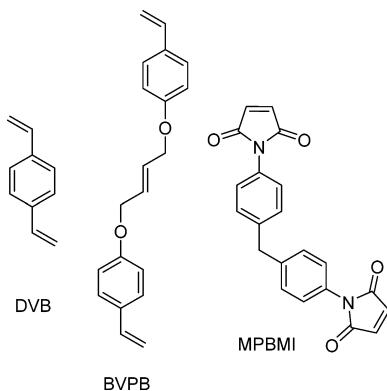
Scheme 88. Cross-Linked Polystyrene



polymers (**P** type) remain among the most popular polymeric supports. Depending both on the percentage and on the type of added cross-linking agent, their properties can be significantly modulated, in particular their swelling ability upon addition of a solvent.

Various types and ratios of cross-linking reagents can be incorporated into the **P** resins; divinylbenzene (DVB) is generally used, but 1,4-bis (4-vinylphenoxy) but-2-ene (BVPB),^{339,340} allylether, or 1,1-(methylenedi-1,4-phenylene) bis maleimide (MPBMI)³⁴¹ have also been considered to give solvation properties different from those of the polymer ([Scheme 89](#)). According to the literature, the cross-linked polymers are classified into microporous polymers (also called

Scheme 89. Example of Cross-Linking Agents Used in the Synthesis of Insoluble Polymers



gel-type resins) and macroporous polymers depending on the polymerization conditions and swelling behaviors.

Microporous polymers are prepared by suspension polymerization of vinyl monomers and small amounts of cross-linking agents (0.5–2%). These types of polymers are characterized by the absence of permanent pores and by a low external area. Therefore, the swelling of the resin in the solvent is of great importance to achieve the chemical reactions. Thus, in an appropriate solvent, they can have a gel-type behavior, which readily allows penetration of reagents into the beads where the chemistry is taking place. Microporous polymers with less than 1% cross-linking agent usually have low mechanical stability and are highly sensitive to fragmentation and to osmotic pressure even under careful handling.³⁴² Practically, resins with about 2% of cross-linking agent provide a satisfactory compromise, allowing an easy penetration of the soluble reagents combined with an acceptable mechanical stability.

Macroporous polymers are obtained when a higher quantity of cross-linking agent (5–20%) is incorporated in the synthesis. In fact, 20% of cross-linking agent is the usual amount used for the preparation of a macroporous insoluble polymer. Consequently, the latter shows good mechanical stability and good resistance to pressure.³⁴² These materials can have a much higher specific area in the dry state, typically ranging from 50 to 1000 $\text{m}^2 \text{ g}^{-1}$, than gel-type resins. Unlike microporous resins, macroporous resins do not need to swell in a solvent to allow access of reactants inside of the matrix because they possess a permanent porous structure due to the use of an appropriate porogen during their preparation by copolymerization. Indeed, reactive reagents in solution should simply fill the pores throughout the polymer beads regardless of the reaction media. In contrast to soluble polymers, NMR analysis of any polymer-bound intermediates requires studies on solid samples using a NMR spectrometer fitted with a magic angle spinning probe. The ^{119}Sn is routinely used to monitor reactions and to evaluate the reaction conversion rates. When a higher characterization is necessary, then high-resolution MAS (hr-MAS) NMR spectroscopy is required. Willem et al. have particularly developed this technique and applied it to insoluble polymers anchored organotin reagents.^{343–346}

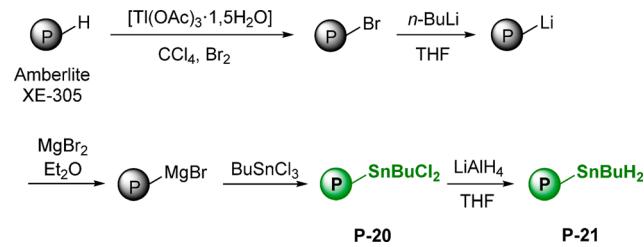
Herein, to avoid redundancies, the applications of organotin reagents supported by insoluble polymers are presented by reaction whatever the nature of the polymer (macroporous or microporous).

6.4.3.2.2. Use of Tin Hydrides Grafted onto Insoluble Organic Polymers. **6.4.3.2.2.1. Use of Tin Hydrides Grafted**

onto Insoluble Polymers Obtained by (Post) Functionalization of the Polymer. In this series, the DVB cross-linked polystyrene resin was generally the starting material, and a functionalization of a preformed polymer was carried out to obtain the target-supported organotin reagents.

The pioneers in this field have used an insoluble macroporous and commercially available polystyrene matrix, Amberlite XE 305.^{347,348} The latter was used as a support and directly functionalized to afford a “ SnBuCl_2 ” Amberlite XE 305 (**P-20**), which was converted into corresponding dihydrides (**P-21**) according to Scheme 90. This method

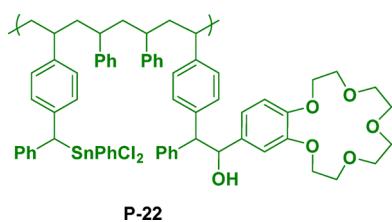
Scheme 90. Synthesis of Tin Dihydride Reagent Supported on Amberlite XE 305



allows the grafting of about 2 mmol of the tin dihydride functionality per gram of polymer. This supported tin dihydride was able to reduce alkyl and aryl halides, aldehydes, and ketones in good yields, but difficulties were encountered with recycling because only 60–30% of the originally active tin dihydride was regenerated after the reaction, due to significant undesired formation of ditin species, which preclude goods yields for further uses. This situation cannot be considered as unexpected, because tin dihydrides are known to be more reactive than tin monohydrides but also much less stable.

Using the efficiency of 15-crown-5 ethers as phase transfer catalysts for reactions involving sodium salts,³²⁷ the sodium borohydride reduction of the supported tin dichloride into tin dihydride can be improved. Accordingly, Blanton reported the preparation of an original macroporous polymer containing both dichlorobutyltin moiety and a pendant crown ether linked to the polymer **P-22** (Scheme 91).³⁴⁹ Thanks to the proximity

Scheme 91. Macroporous Resin Prepared and Used by Blanton

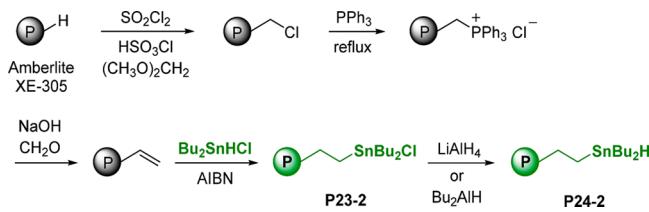


of the crown-ether to the PhSnCl_2 moiety, the NaBH_4 reduction of the $\text{Sn}-\text{Cl}$ bond into $\text{Sn}-\text{H}$ bond was improved, allowing a more efficient reduction of alkyl halides with yield increases by 40–50%.³⁴⁹

Considering that the proximity of the resin backbone and of the incorporated reactive tin moiety could be a major drawback in terms of kinetics because of the steric hindrance, Herschberger synthesized organostannanes (tin chloride **P-23-2** and tin hydride **P-24-2**)³⁵⁰ supported on Amberlite XE 305 (polystyrene reticulated with 12% of DVB) with a two-

carbon spacer incorporated between the metal and the aromatic ring of polystyrene (Scheme 92). This synthesis involves four

Scheme 92. Incorporation of a Tin Hydride Function on a Styrene-DVB Polymer through Hydrostannylation of a Vinyl Group

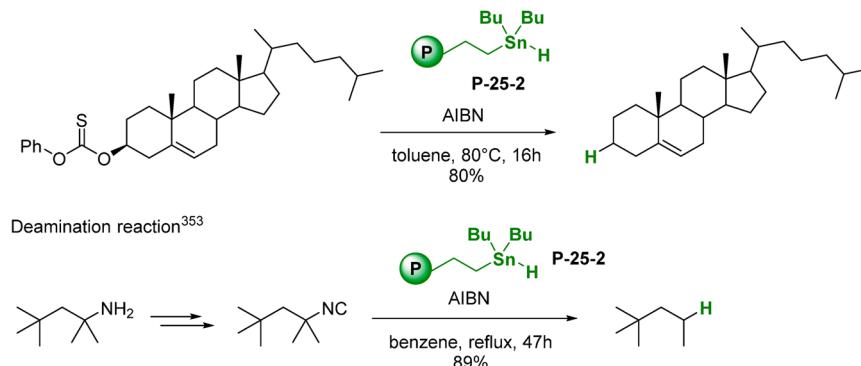
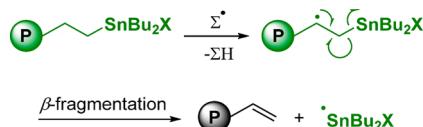
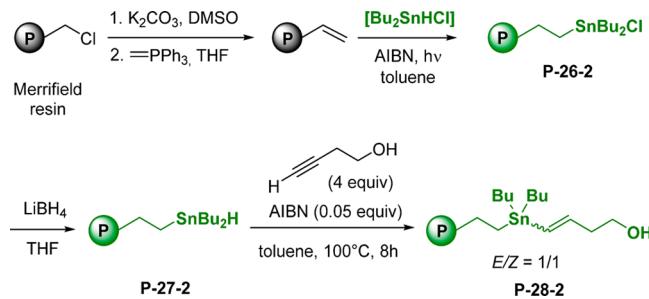


successive reactions: a chloromethylation, a Wittig reaction, an hydrostannylation, and a reduction affording the polymer-supported tin hydride with a loading ranging from 1.5 to 1.7 mmol g^{-1} of reactive $\text{Sn}-\text{H}$.³⁵¹

With a similar approach, Neumann et al.^{351–355} reported the synthesis of two different supported tin hydrides: one grafted on Amberlite XE 305³⁴⁸ and the second grafted on Lewatit OC1018 (7% of DVB).^{352,353} The application of the above strategy to Amberlite XE 305 allows a loading of 1.5 mmol g^{-1} of SnBu_2H (**P-24-2**) as well as ditin species (0.15 mmol g^{-1}) and tri-*n*-butylstannylated species (0.1 mmol g^{-1}), while the same strategy conducted on Lewatit OC1018 (7% DVB) gave lower amounts of $\text{Sn}-\text{H}$ (0.9 mmol g^{-1}) (**P-25-2**) and higher amounts of ditin compounds (0.3 mmol g^{-1}). The efficiency of these new supported tin hydrides was assessed on the most frequently used free radical reactions, dehalogenation of organic halides and radical cyclization (Scheme 93).^{352–354,356} Barton–McCombie deoxygenation of alcohols,^{354,357} deamination of alkyl amines,^{354,356} and rearrangement reactions (such as ring enlargement of cyclohexadiones).³⁵⁸ Whatever the type of reaction in this series, the reactive polymer matched completely the reactivity and selectivity of tributyltin hydride. Moreover, besides the versatility of its uses, the main advantages of the tin hydride anchored on insoluble polymers are the simple workup, the limitation of problems with organotin wastes, and the possibility of regeneration of the reagent for multiple uses.

These first examples show that the polymer-supported tin hydride with a two-carbon spacer is chemically as efficient as tributyltin hydride and, as expected, allows an easier purification of the products. However, the level of organotin contamination in the products remains high in these reactions (about 2000 ppm) and can reasonably be assigned to a β -stannylation via a readily formed benzylic radical on the polymer (Scheme 94).³⁵⁹

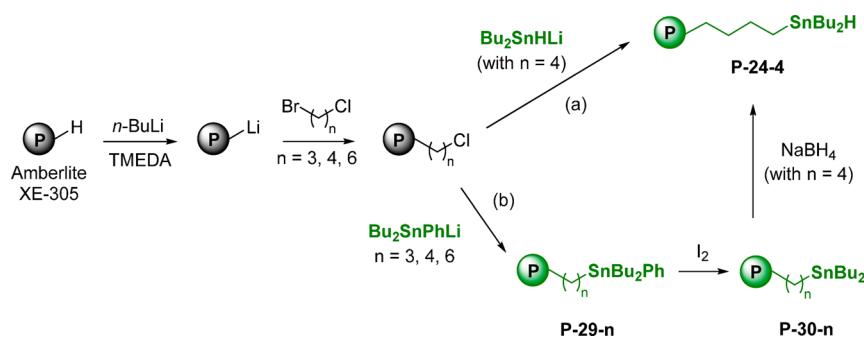
Nicolaou et al. have also considered a microporous polymer (a Merrifield polymer) displaying a two-carbon spacer (with a β -fragmentation as latent drawback) for the total synthesis of macrocycles (Scheme 95).³⁶⁰ In this case, the chloromethyl resin was submitted to an oxidation followed by an olefination affording a vinylic bond, which was hydrostannylated by Bu_2SnHCl generated in situ. The hydrostannylation of but-3-yn-1-ol with the obtained supported tin hydride afforded the corresponding vinyltin in good yield (94% starting from the supported organotin chloride). Unfortunately, in the reported example, no stereoselectivity (*E/Z* = 1/1) was obtained for the vinyltin **P-28-2**, and this pathway was subsequently discarded for the synthesis of (*S*)-zearalenone (vide infra, Scheme 118).

Scheme 93. Reductive Processes Using a Supported Tin Hydride Anchored by a C₂ SpacerReductive rearrangement of 6-bromohex-1-ene^{352,353}Barton Mc Combie deoxygenation of alcohol derivatives^{353,357}**Scheme 94. β -Fragmentation of Polystyrene-Supported Organotin Reagents with a C₂ Linker****Scheme 95. Preparation of a Microporous-Supported Tin Hydride and Its Use for the Preparation of a Supported Vinyltin**

To avoid the β -fragmentation, which prohibits very low levels of organotin residues in the products and limits the number of

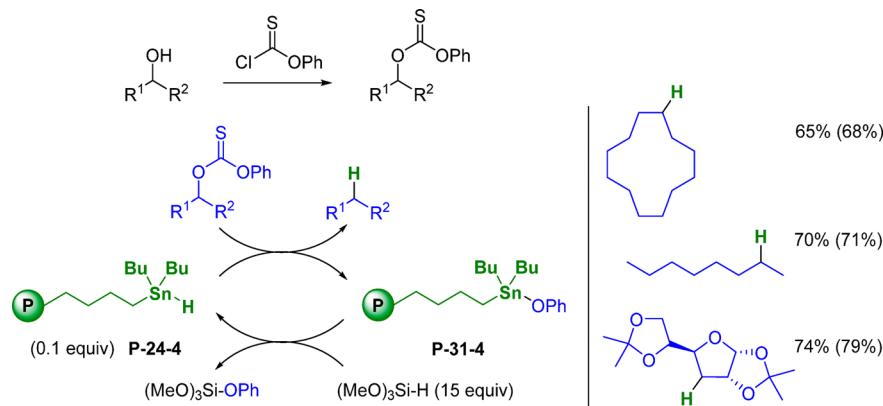
cycles in the recycling process, Dumartin et al. have developed supported organostannanes with longer spacers than the two-carbon unit. Amberlite XE 305 was used as support and was initially functionalized with a terminal chloroalkyl spacer in which the chloride was subsequently substituted by an appropriate stannyl anion. Accordingly, supported aryltins, tin halides, and tin hydrides can be obtained efficiently with modulation of the spacer length. The addition of an appropriate stannyl anion affords directly (route a) or after two steps more (route b) the polymer P-24-4 (Scheme 96).^{361–365}

Using this route, longer spacers could be used and the tin hydride P-24-4 could be obtained directly by reaction of the chloroalkyl resin with Bu₂SnHLi,^{364,366} but due to the poor reproducibility of the reaction, the route involving three steps and Bu₂PhSnLi has to be preferred. The last step leads to an organotin hydride of ~1.2 mmol g⁻¹ loading when polymer P-30-4 is reduced into P-24-4 with NaBH₄,³⁶¹ a value that can be improved to 1.4 mmol g⁻¹ using LiAlH₄.³⁶⁷ These reagents have been used as a hydrogen source both in stoichiometric and in catalytic reductions of haloalkanes (with in situ reduction of Sn-X by NaBH₄).³⁵⁹ The spacer length has been proved to be important both for the efficiency of the reaction (higher yields obtained due to a higher accessibility to the metal) and for the limitation of the presence of organotin residues in the products.

Scheme 96. Incorporation of an Organotin Function Linked by 3C–6C Spacers

AD

Scheme 97. Catalytic Reduction of Thiocarbonates by a Supported Tin Hydride Generated in Situ



With a four-carbon spacer, the β -fragmentation is avoided, and therefore the residual organotin observed was mainly due to abrasion of the polymer. The pollution of the products by organotin residues at trace level was evaluated via inductively coupled plasma mass spectrometry (ICP-MS) showing the presence of a very low residual amount of tin, less than 5 ppm when P-30-4 was used in a catalytic amount and around 50 ppm when P-24-4 was used in a stoichiometric amount. Furthermore, contamination decreases generally after the two first cycles of use due to the initial leaching of residual soluble organotin byproducts remaining from the synthesis of the supported reagent.

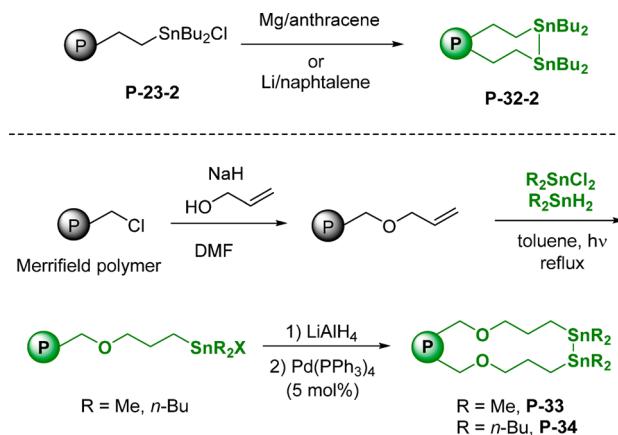
In addition to the reduction of organic halides, which is the usual test experiment for an evaluation of the grafted reagent quality,^{359,361} these supported tin hydrides can also be used in the hydrostannylation of alkynes^{367–369} or in the Barton–McCombie deoxygenation of alcohols.³⁷⁰ In the latter case, a catalytic variant was reported using hydrogenosilanes for the inside regeneration of the tin hydride. While polymethylhydrosiloxane was found to be ineffective for the regeneration of supported tin hydride P-24-4 because of its inability to penetrate into the polystyrene beads, trimethoxysilane was found to be efficient for this regeneration from the tin phenoxide byproduct P-31-4. Three examples were considered with yields in the range of those obtained with a stoichiometric amount of tributyltin hydride (Scheme 97).

Finally, supported ditin reagents have been prepared by dehydrogenation of supported organotin hydrides in the presence of $Pd(PPh_3)_4$ ^{371,372} according to Beletskaya^{373,374} and Mitchell³⁷⁵ or by reductive coupling of supported organodibutyltinchloride P-23-2 with Mg/anthracene or Li/phenanthrene (Scheme 98).³⁷⁶

These reagents were proposed for generation of tin centered radicals useful as promoters of free radical cyclizations involving organic bromides or iodides especially when tin hydrides are poorly effective because of the too easy hydrogen transfer (Scheme 99).

For instance, Neumann³⁷⁶ and Kilburn³⁷² found that supported ditin compounds could be used to promote atom transfer cyclization of ϵ -unsaturated iodoacetates or iodoamides using UV irradiation (Scheme 99). In the latter case, tin contamination was found in the range of 5–34 ppm using 0.1 equiv of ditin reagent of which recycling was shown to be possible despite a lower activity. These ditin reagents have been also used to promote free radical addition of organic iodides to triple bonds (Scheme 99).³⁷⁷

Scheme 98. Preparation of Supported Ditin Reagents P-32-2, P-33, and P-34

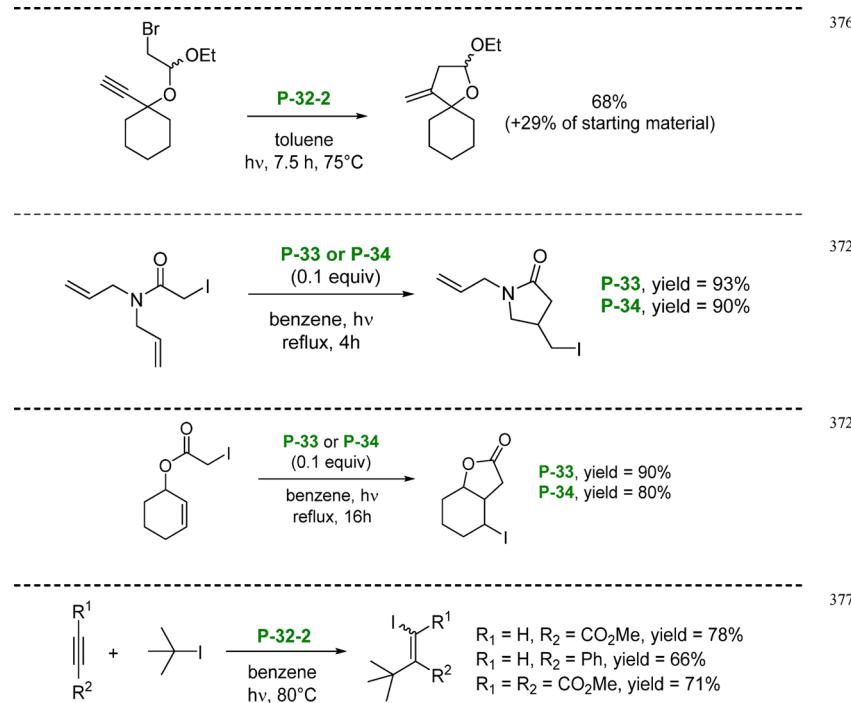
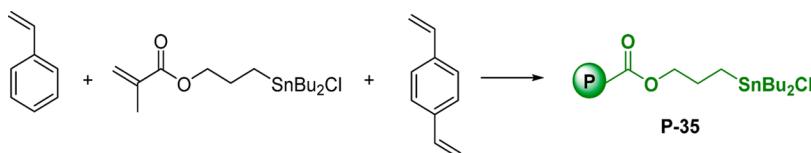
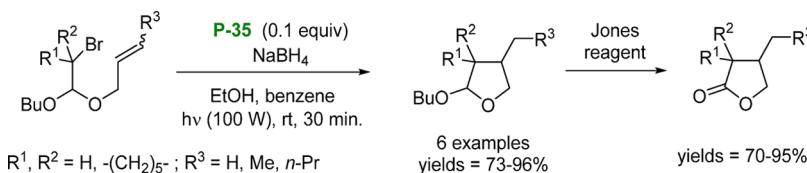


6.4.3.2.2. Use of Polymer-Supported Tin Hydrides Obtained by Copolymerization. To obtain an improved loading of the polymer, several reports have been devoted to the preparation of supported tin reagents by copolymerization of styrene and DVB with an organostannyl monomer. This approach was first developed in a pioneering work by Ueno et al.,³⁷⁸ which considered the possibility to prepare a resin bound tin chloride P-35 by copolymerization between styrene/DVB and [γ -(chlorodibutylstannyl) propyl] methacrylate to obtain a tin loading in the polymer in line with the amount of polymerizable organotin monomer used in its preparation (Scheme 100).

In this case, P-35 was obtained with a loading of 0.5 mmol g^{-1} of tin chloride and was converted into supported tin hydride by $NaBH_4$. This polymer was used for the synthesis of 2-alkoxytetrahydrofurans and subsequently for γ -butyrolactones through a free radical cyclization of the corresponding halides (Scheme 101).

The reactions afford higher yields when the couple P-35/ $NaBH_4$ was used to promote the radical cyclizations instead of $Bu_3SnH/AIBN$ in homogeneous conditions, thanks to the easier purification. Through this route, several reagents have been prepared from methacrylic analogues containing a SnX_3 moiety ($X = Br, Cl, OMe$) with tin incorporation depending on the nature of X. A loading of 0.9 mmol g^{-1} was obtained for $SnBr_3$, 0.7 mmol g^{-1} for $Sn(OMe)_3$, 1 mmol g^{-1} for $SnCl(OMe)_2$, and 1.5 mmol g^{-1} for $SnBr(OMe)_2$. These

Scheme 99. Examples of Free Radical Cyclizations Promoted by a Supported Ditin Reagent

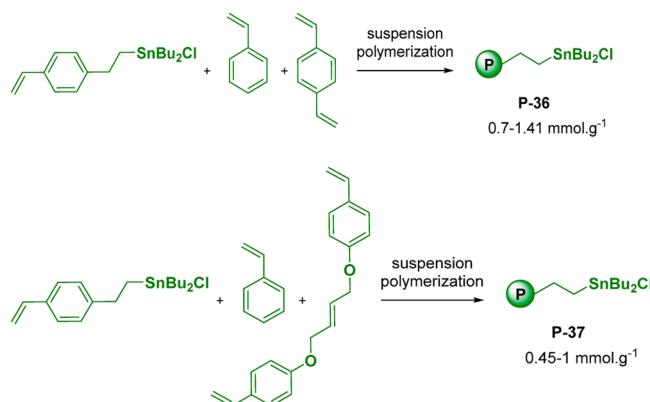
Scheme 100. Polymer Obtained by Copolymerization of Styrene/DVB with γ -(Chlorodibutylstannyl) propyl MethacrylateScheme 101. Ueno's Synthesis of 2-Alkoxytetrahydrofurans and γ -Butyrolactones

reagents have been used in various transesterification reactions.³⁷⁹

Using this strategy based on the copolymerization of a stannylated styrene (obtained by hydrostannylation of DVB with Bu_2SnHCl) with styrene and divinylbenzene in the range 15–45%, Deleuze et al. have prepared a supported macroporous polymer functionalized by an organotin chloride **P-36** with various tin loadings ($0.7\text{--}1.35\text{ mmol g}^{-1}$) (Scheme 102).³³⁹ They also used (*E*)-1,4-bis-(4-vinylphenoxy)but-2-ene in place of DVB as a cross-linking reagent to obtain the polymer **P-37**, which exhibited higher swelling abilities in organic solvents but lower tin loading ($0.45\text{--}1\text{ mmol g}^{-1}$).

The grafted reagents **P-36** and **P-37** used in a 10% molar ratio in the presence of $NaBH_4$ (2 equiv) were found to be as efficient as Bu_3SnH in the reduction of 1-bromoadamantane.³³⁹ However, they also revealed that the nature of the cross-linking agent has a major influence on solvent swelling. Thus, **P-37** swells twice as much as **P-36** in a larger range of solvents and is more reactive than **P-36**. In addition, the amount of cross-linking agent has no significant effect on the reactivity of these

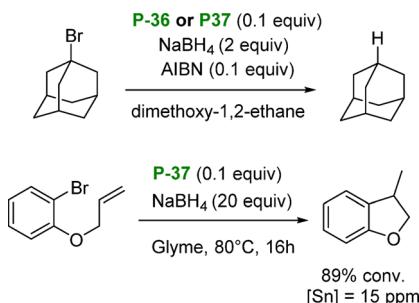
Scheme 102. Copolymerization with Incorporation of a Stannylated Unit on a 2C Spacer



reductive reagents. Reagent **P-37** was also used for the preparation of 2,3-dihydro-3-methylbenzofuran by radical cyclization obtained with 89% conversion and with a

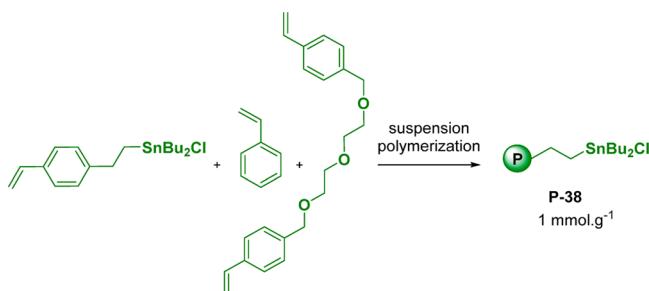
concentration of tin residues estimated at 15 ppm (**Scheme 103**).³⁸⁰

Scheme 103. Use of P-36 and P-37 in 1-Bromoadamantane Reduction and P-37 in Radical Cyclization



Recycling of P-36 and P-37 could be achieved in the reduction reaction of 1-bromoadamantane up to 10 and 5 runs, respectively, while P-37 could not be recycled in the radical cyclization. Therefore, another copolymer (P-38) using di(4-vinylbenzyloxy)ethyl ether as a cross-linker was prepared to generate a polymer more compatible with polar solvents such as glyme (**Scheme 104**). When this radical cyclization was

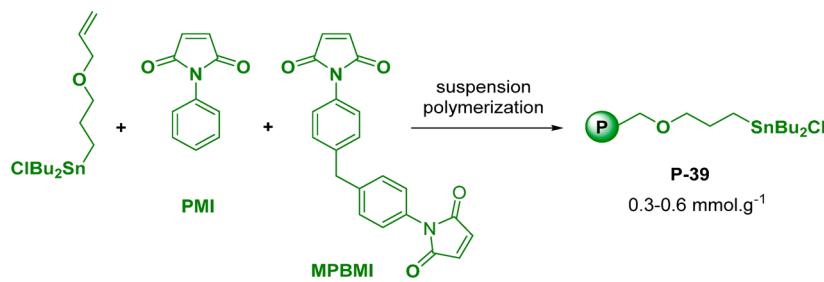
Scheme 104. Preparation of Polymer P-38



investigated using 10 mol % of P-38 and 10 equiv of NaBH₄ in glyme at 80 °C for 3 h, a high conversion was obtained (99%) for the first run. This reaction remained possible in a second run, requiring however a longer reaction time (93% after 20 h), but a third run failed.

In an attempt to improve swelling and stability of polymers P-36, P-37, and P-38 in toluene, a non styrenic macroporous polymer tin reagent P-39 was obtained by suspension polymerization of chloro(dibutyl)[3-allyloxypropyl]tin and N-phenylmaleimide (PMI) monomers in the presence of 1,1'-(methylene-di-4,1-phenylene) bismaleimide (MPBMI) used as cross-linking agent (**Scheme 105**).³⁴¹

Scheme 105. Synthesis of a Stannylated Polymer Using a (Bis) N-Aryl Maleimide as Cross-Linking Agent



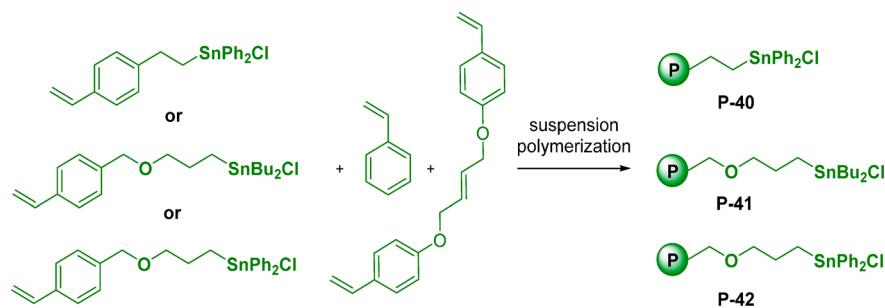
P-39 used as catalyst (0.1 equiv) in the presence of NaBH₄ (5 equiv) for the reduction of 1-bromoadamantane displayed an activity similar to that of tributyltin hydride. While the swelling degree of P-39 was higher than for polymers P-36–P-38, its loading was quite low (0.5 mmol g⁻¹), and it appeared less stable especially at high temperatures (95 °C).³⁴¹ In practice, the tin concentration in the final products was found to be around 220–270 ppm when the reaction was carried out at 65 °C but increased to 410–800 ppm when a temperature of 95 °C was used. Another contribution reports the influence of both the substituent (butyl or phenyl) and the length of the spacer between the tin moiety and the polymer backbone on the reactivity and on tin leaching.³⁸¹ Three different organotin styrenic monomers were prepared and involved in suspension polymerization with styrene in the presence of (E)-1,4-bis-(4-vinylphenoxy)but-2-ene used as cross-linking agent, affording P-40, P-41, and P-42 (**Scheme 106**). Considering once more the reduction of 1-bromoadamantane, dibutyltin polymers were found more stable than their diphenyl analogues, allowing successive reuse without loss of activity up to six runs. The residual tin in the products turned out to be only 0.6% of the tin amount incorporated into the polymer, suggesting its thermal degradation because β-stannylation fragmentation in polymers P-41 and P-42 is not expected a priori to occur.

Finally, Deleuze et al. also developed polyHIPE-supported organotin reagents P-43 and P-44.^{382,383} The High Internal Phase Emulsion (HIPE) polymerization, leading to polyHIPE polymers initially discovered by Bardy and Hag,³⁸⁴ affords a porous polymer having a more regular structure. Thanks to their permanent porosity, these polymers allow a wider range of solvents for use in organic synthesis in comparison to polymers obtained by suspension polymerization, thus enabling better diffusion of reagents into the matrix (**Scheme 107**). These polyHIPE organotin reagents were found to be efficient for reduction of alkyl halides and for radical cyclizations.

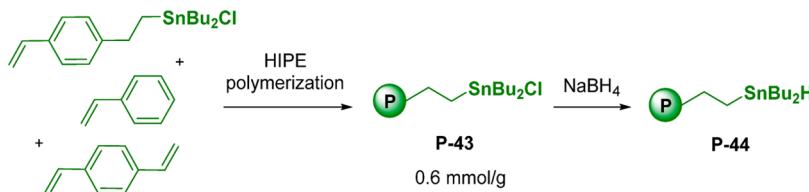
More recently, Gaina described also the synthesis of an organotin carboxylate maleimide copolymer, but no applications in organic synthesis were reported.³⁸⁵

It is worth noting that recycling supported tin hydrides is often affected by minor side reactions, as for instance dimerization of stannyl radicals to ditin species, which hamper quantitative recycling of the supported tin hydride. Obviously, the unwanted formation of ditin species can be minimized when the reactions are performed in the catalytic mode because of lower radical concentration. Another problem encountered with free radical reactions is the possible hydrogen atom abstraction, particularly on benzylic positions, a reaction that can induce a β-stannylation fragmentation of an organotin radical from the supported organotin reagent when two-carbon spacers are used.

Scheme 106. Preparation of Stannylated Polymers with Diphenyl and Dibutyl [(4-Vinylphenyl)methylenoxypropyl] Tin Chloride



Scheme 107. Preparation of polyHIPE-Supported Organotin Chloride



To have an immediate comparison of the different types of polymer-supported tin hydrides, the more meaningful ones (or their precursors when generated *in situ*) are gathered in Table 1 with information about their chemical nature, their loading, and their solubility, together with the type of applications for which they have been used, as well as their advantages and drawbacks in terms of recycling and prevention of tin pollution.

As was already emphasized in this Review, organotin monohydrides can be reasonably well recycled, in contrast to organotin dihydrides, which give ditin species as side products (see, for instance, polymer P-21 as compared to P-24-4).

Regarding the efficiency of these supported reagents to limit the presence of organotin byproducts, reagents with a 3, 4, or 6 carbon chain as spacer, or those bearing a propyl ether unit, appear to be much more efficient than the more easily prepared polymers with a 2 carbon spacer, a result that is explained by the absence of β -fragmentation in the former, as supported by residual tin amounts in the reaction mixtures of 5–50 ppm against 250–2500 ppm. However, when a low tin concentration was obtained (under 50 ppm), the comparison between two stannylated polymers has to be done carefully and only for experiments performed under similar conditions. For instance, a tin amount measurement achieved after several cycles often exhibits a lower concentration of organotin residues in comparison to that after the first run, because of leaching of remaining traces of free diffusing organotins used in the synthesis of the polymer (especially when the polymer was functionalized *a posteriori*). Therefore, when no information is given on recycling, the evaluation of the grafted stannylated polymers in terms of ability to prevent pollution by tin residues on the basis of the trace amount of tin has to be considered as indicative. Only when a support is the carrier of various tin reagents and provides high efficiency and low pollution in different types of reactions like reduction, cross-coupling reactions, allylation, or transesterification reactions, etc. (*vide infra*) can it be considered as an efficient and reliable grafted reagent to prevent pollution.

6.4.3.2.3. Use of Organotins Containing a Reactive Sn–C Bond and Supported on an Insoluble Polymer. Starting from the polymer-supported tin halide, simple supported organotin

reagents of the type polymer-SnBu₂R can be easily obtained with R = allylic groups,^{388,389} vinylic groups,^{367,388} aryl groups,^{388,390} or heteroarylgroups³⁹¹ by substitution of the halide using nucleophiles or organometallic reagents. When poorly functionalized tin reagents are prepared, Grignard reagents or organolithium reagents can be used, but when highly functionalized reagents are required, organozinc reagents can be more appropriate, as for instance for the synthesis of allyl reagents containing a cyano or an alkoxy carbonyl group.³⁸⁹ Obviously, hydrostannylation of alkynes by supported tin hydrides provides a route to functionalized vinyltins,^{367,369} which can be used in cross-coupling reactions (see below). Even though they have not really been investigated yet, supported stannylanions can in principle also be generated and used for the synthesis of reactive reagents, as supported by the results obtained in crotylltin series.³⁶⁹

6.4.3.2.3.1. Use of Insoluble Polymer-Supported Organotin Reagents for Halodesannylation Reactions. The halodesannylation of vinyl or aryltins provides an efficient route to vinyl or aryl halides, and can be especially useful when radiolabeled compounds are targeted to take advantage of the easy cleavage of the Sn–C bond. The iododesannylation reaction is fast, regio- and stereoselective, and allows high yields under mild experimental conditions.³⁹² Accordingly, when a quick and easy workup is required because of short half-life times of the isotope, using supported organotin reagents is very convenient, thanks to their high reactivity associated with an expeditious purification of the products.

Thus, several contributions have reported the use of grafted organotin precursors onto insoluble polymer support to achieve the synthesis of vinyl halides^{368,393,394} and aryl halides^{395,396} through halodesannylation reaction.

As biological studies have shown the presence of selective estrogen receptors in the tumor cells of some breast and ovarian cancers, radioiodinated estrogens like 17 α -(iodovinyl) estradiol and derivatives have been prepared by iododesannylation and used as medical imaging agents both for diagnosis and for radiotherapy.^{392,397,398} In this context, the synthesis of iodinated estrogens such as 17 α -(¹²⁷I)-(iodovinyl) estradiol and analogues has been achieved using insoluble polymer-supported

Table 1. Comparison of the Different Polymer-Supported Tin Hydrides (and Precursors)

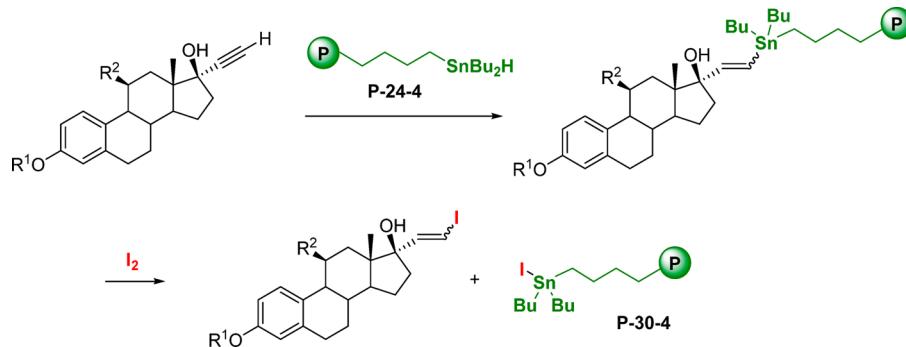
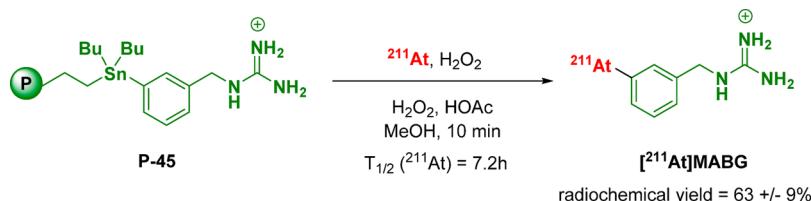
Tin hydride or tin hydride precursor	P ⁿ ³¹²		Soluble or Insoluble	Loading (mmol of Sn/g of polymer) ^a	Residual tin contents in the reaction products	Recycling	Comments	Ref
SnBu ₂ Cl	Ps-3	Polyethylene (MW ≈ 1420)	soluble	0.2	n.d.	+	- The Sn-H polymer was formed <i>in situ</i> and used as catalyst in the presence of an excess of NaBH ₄ (6 equivalents) in the presence of 10–20% benzo-15-crown-5; - several polymers investigated (with loading from 0.1 to 0.4 mmol of Sn/g of polymer) - loading of 0.2 mmol of Sn/g of polymer gave the best results; yields = 51 to 100% - One Polymer was reused 4 times without loss of activity	327
SnBu ₂ Cl	Ps-6	polystyrene	soluble	0.2	n.d.	+		327
SnBu ₂ Cl	Ps-8	polystyrene	soluble	2.62	5 to 11 ppm	-	- The Sn-H polymer was formed <i>in situ</i> and used as catalyst (0.1 equivalent) in the presence of 1.5 equivalents of NaBH ₄ ; yield = 60–93%	322
SnBu ₂ Cl	Ps-9	polystyrene	soluble	n.d.	n.d.	-	- The Sn-H polymer was used in stoichiometric amount - 84–95% conversion (GC evaluation)	323
SnBuH ₂	P-21	polystyrene with 12% of DVB (Amberlite XE 305)	insoluble	2	n.d.	+	Recycling experiments were carried out but only 30 to 60% of the original tin hydride was regenerated.	347,348
[15,5-crown ether]-SnPh ₂ Cl ₂	P-22	polystyrene	insoluble	0.4	n.d.	-	Used as catalyst in the presence of an excess of NaBH ₄ (10 equivalents) for the reduction of 1-bromodecane	349
SnBu ₂ Cl	P-23-2	polystyrene with 12% of DVB (Amberlite XE 305)	insoluble	n.d.	530 ppm (with 0.4 equivalent of P-30-2) to 1975 ppm (with 0.7 equivalent of P-30-2)	+	The Sn-H polymer was formed <i>in situ</i> and used as catalyst (0.3 to 0.6 equivalent) in the presence of 2.5 equivalents of NaBH ₄	359,386
SnBu ₂ H	P-24-2	polystyrene (Amberlite XE 305)	insoluble	1.5–1.7	250 ppm	-	Used for the reduction of 1-bromoadamantane	387
SnBu ₂ H	P-24-4	polystyrene with 12% of DVB (Amberlite XE 305)	insoluble	1.2–1.4	45 ppm	-	The polymer was used in stoichiometric amount for the reduction of 3-iodo-5-cholestone.	365
SnBu ₂ H	P-25	polystyrene with 7% of DVB (Lewatit OC 1018)	insoluble	0.9–1.5	2000 ppm ^b	-	Used for the dehalogenation of bulky or multifunctional halides	352–354,356
SnBu ₂ Cl	P-26-2	polystyrene with different cross-linking agents and cross-linking levels (15% to 45%)	insoluble	0.7–1.35	n.d.	+	Different macroporous organotin have been prepared and used for catalytic reduction of 1-bromoadamantane in the presence of 5 equivalents of NaBH ₄ . The corresponding Sn-H polymer was prepared <i>in situ</i> and used for reduction of 1-bromoadamantane	339,383
SnBu ₂ I	P-30-4	polystyrene with 12% of DVB (Amberlite XE 305)	insoluble	0.9	26 ppm (when 0.5 equivalent was used) 34 ppm (when 0.9 equivalent was used)	-	- The Sn-H polymer was formed <i>in situ</i> and used as catalyst (0.3 to 0.6 equivalent) in the presence of 2.5 equivalents of NaBH ₄ . - The reducing ability of P-30-4 was evaluated by reduction with bromodecane.	359,386
SnBu ₂ I	P-30-3	polystyrene with 12% of DVB (Amberlite XE 305)	insoluble	n.d.	5 ppm (when 0.6 equivalents of P-30-3 was used)	+	The Sn-H polymer was formed <i>in situ</i> and used as catalyst (0.3 to 0.6 equivalent) in the presence of NaBH ₄ (2.5 equivalent).	386
SnBu ₂ Cl	P-36	Polystyrene with DVB (15 to 45%) as cross-linking agent	insoluble	0.7–1.41	n.d.	+	The Sn-H polymer was formed <i>in situ</i> and used as catalyst (0.1 equivalent) in the presence of NaBH ₄ (2 equivalents) in the reduction of 1-bromoadamantane. Conversion = 45–60% in 30 min; Recycled up to 10 runs	339
SnBu ₂ Cl	P-37	Polystyrene with (E)-1,4-bis(4-vinylphenoxy)but-2-ene as cross-linking agent	insoluble	0.45–1	n.d.	-	The Sn-H polymer was formed <i>in situ</i> and used as catalyst (0.1 equiv) in the presence of NaBH ₄ (20 equiv) in the reduction of 1-bromoadamantane. Conversion = 75% in 30 min and 90% in 60 min; Recycled up to 5 runs	339
SnBu ₂ Cl	P-39	PMI with MPBIMI as cross-linking agent	insoluble	0.5	280–800 ppm at 65°C 410–800 ppm at 95°C	+	The Sn-H polymer was formed <i>in situ</i> and used as catalyst (0.1 equiv) with NaBH ₄ (10 equiv) for the reduction of 1-bromoadamantane. The polymer is less stable at 95°C and must be used at 65°C to avoid the limit of tin residues in the products.	341
SnPh ₂ Cl	P-40	Polystyrene with (E)-1,4-bis(4-vinylphenoxy)but-2-ene as cross-linking agent	insoluble	0.8	n.d.	-	The Sn-H polymer was formed <i>in situ</i> and used as catalyst (0.1 equiv) with NaBH ₄ (2 equiv) for the reduction of 1-bromoadamantane. Conversion = 70% in 60 min.	381
SnBu ₂ Cl	P-41	Polystyrene with (E)-1,4-bis(4-vinylphenoxy)but-2-ene as cross-linking agent	insoluble	1.1	0.6% of the tin initially present	+	The Sn-H polymer was formed <i>in situ</i> and used as catalyst (0.1 equiv) with NaBH ₄ (2 equiv) for the reduction of 1-bromoadamantane. Recycled up to 6 runs	381
SnPh ₂ Cl	P-42	Polystyrene with (E)-1,4-bis(4-vinylphenoxy)but-2-ene as cross-linking agent	insoluble	0.6	0.6% of the tin initially present	-	The Sn-H polymer was formed <i>in situ</i> and used as catalyst (0.1 equiv) with NaBH ₄ (2 equiv) for the reduction of 1-bromoadamantane	381
SnBu ₂ Cl	P-43	Polystyrene with DVB as cross-linking agent (PolyHIPE)	insoluble	0.6	n.d.	+	The Sn-H polymer was formed <i>in situ</i> and used as catalyst (0.1 equiv) with NaBH ₄ (2 equiv) for the reduction of 1-bromoadamantane; Conversion = 100% in 30 min. Recycled up to 5 runs.	383
SnBu ₂ H	P-44	Polystyrene with DVB as cross-linking agent (polyHIPE)	insoluble	0.6	n.d.	-	The Sn-H polymer used in stoichiometric amount or as catalyst (0.1 equiv) with NaBH ₄ (2 equiv) for the reduction of 1-bromoadamantane; Conversion = 77% in 60 min.	382

^an.d. = not determined. ^bThe important amount of tin residues is due to the β-fragmentation of the supported tin reagent.

organotin precursors. Good yields were reported after a simple filtration to separate the reaction product from the tin byproducts grafted on a solid support, without requirement of further purification (**Scheme 108**).³⁶⁸ Therefore, a similar methodology can be applied to the synthesis of radioiodinated compounds as exemplified by the preparation of 2-(¹²⁵I)-iodolisuride, an antagonist of the dopamine D2 receptor.³⁹⁹

A similar procedure has been used for other radiopharmaceuticals, especially for molecules tagged with short-lived radionucleides such as ²¹¹At ($t_{1/2} = 7.2$ h) as exemplified by the synthesis of [²¹¹At]astatobenzylguanidine ([²¹¹At]MABG).

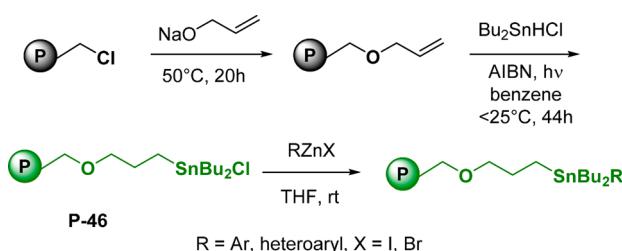
Because *meta*-iodobenzylguanidine [¹³¹I]MIBG as well as other radiohalogenated analogues such as ^{77/76}Bromo-, ¹⁸Fluoro-, and ²¹¹Astato-labeled benzylguanidines have shown their ability to accumulate in neuroendocrine tumors, they have been considered to be possible targeted radiopharmaceuticals for medical imaging and radiotherapy applications. For these reasons, Zalutsky et al. have reported a synthesis of [²¹¹At]-MABG using a tin precursor anchored to a polymer support (**P-45**). Good radiochemical yields were reported with a surprising low residual tin contamination (<1 ppm) for an

Scheme 108. Synthesis of 17α -(^{127}I)-Iodovinyl)estradiolScheme 109. Synthesis of [^{211}At]Astatobenzylguanidine ($[^{211}\text{At}]$ MABG)

organotin grafted on the polymer through a 2 carbon spacer (Scheme 109).⁴⁰⁰

Noteworthy, Carroll and Zhu have described the preparation of organotin reagents supported on a Merrified resin using aryl zinc^{401,402} and aryl Grignard⁴⁰³ reagents with the objective to prepare radiopharmaceuticals such as [^{125}I]-3- β -(4-iodophenyl)-tropane-2 β -carboxylic acid methyl ester ($[^{125}\text{I}]$ -RTI-55 hydrochloride) (Scheme 110). Unfortunately, to the best of our knowledge, this contribution did not result in biomedical applications.

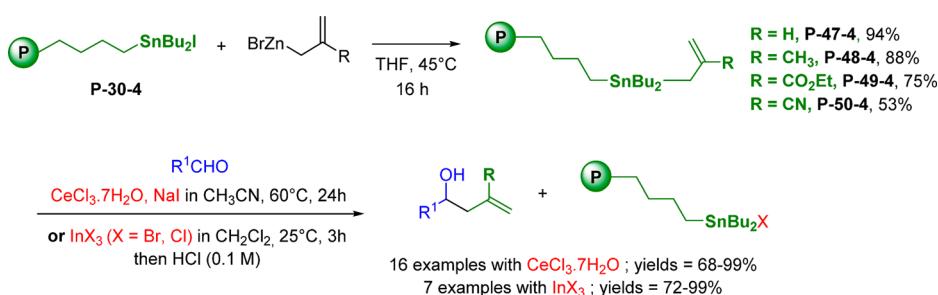
Scheme 110. Synthesis of Merrified-Supported Aryltin Reagent Using Arylzinc Halides

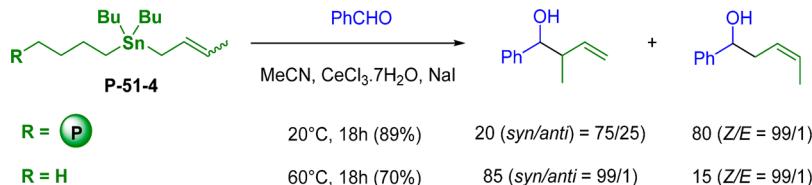
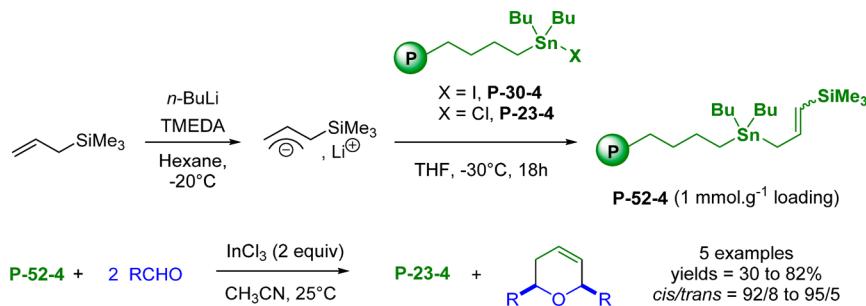


6.4.3.2.3.2. Use of Insoluble Polymer-Supported Organotin Reagents in Allylation Reactions. While possibly used in free radical reactions like Giese reaction,⁴⁰⁴ most applications in this

field have been devoted to allylation of carbonyl compounds. The use of a macroporous-supported allyltin in the ionic allylation of *p*-bromobenzaldehyde has been reported in a pioneering work by Dumartin.³⁶¹ The reaction of the polymer-supported dibutylallyltin reagent was achieved at -78°C in CH_2Cl_2 under anhydrous conditions in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ and afforded the homoallylic alcohol (75% of conversion measured by GC). In the case of α -substituted γ -alkoxyallyltins, monoprotected α -diols were obtained with a shift of stereoselectivity from a *syn* to an *anti* preference when increasing the size of the α -group³⁶⁹ as was already observed with tributyltin derivatives.⁴⁰⁵ We have investigated further this allylation of aldehydes using a macroporous polystyrene-supported allyltin, and demonstrated that the reaction can be achieved at 60°C in acetonitrile using $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}/10\%$ NaI as a promoter when an allyl or a methallyl unit is involved. When indium tribromide was used as a promoter, the reaction took place at 25°C in dichloromethane for a range of unfunctionalized and functionalized allyl units (P-47-4 to P-50-4) (Scheme 111).³⁸⁹ Thanks to the mild experimental conditions (room temperature to 60°C and orbital stirring), the recycling of the supported reagent can be smoothly achieved without significant loss of reactivity (yields decreased from 95% to 90% over five cycles) and with a remarkable control of residual tin contamination under 5 ppm and no measurable cerium contamination.³⁸⁹

Scheme 111. Preparation of Supported Functionalized Allyltins and Lewis Acid Assisted Allylstannation of Aldehydes



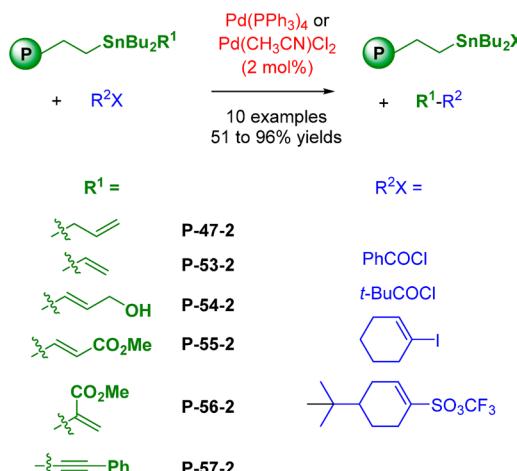
Scheme 112. Influence of the Matrix Effect on Stereoselectivity in the Crotylation of Benzaldehyde by Crotyltriorganotins**Scheme 113.** Synthesis of a Polymer-Supported γ -Silylated Allyltin and Its Use for the Synthesis of 2,6-Disubstituted Dihydropyrans

With a similar approach, a polymer-supported crotyltin P-51-4 was prepared and used for the crotylation of various aliphatic and aromatic aldehydes in the presence of $\text{BF}_3\cdot\text{OEt}_2$, $\text{CeCl}_3\cdot7\text{H}_2\text{O}/10\%$ NaI , or indium salts.⁴⁰⁶ Under these conditions, high yields of homoallylic alcohols nearly uncontaminated by organotin residues (less than 5 ppm) were obtained. It is worth noting that a matrix effect favorable to branched over linear isomers was observed when reacting supported crotyltin with aldehydes in acetonitrile and when $\text{CeCl}_3\cdot7\text{H}_2\text{O}/10\%$ NaI was used as Lewis acid (**Scheme 112**).

We also successfully attempted a useful extrapolation of the tandem carbonylation/Prins cyclization of aldehydes for the synthesis of dihydropyrans.⁴⁰⁷ A new macroporous polymer-supported (γ -trimethylsilylallyl) dibutyltin P-52-4 was prepared in a single step by adding under argon a solution of lithiated allyltrimethylsilane to a mixture of precooled solid-supported di-*n*-butyltin halide P-23-4 or P-30-4 in THF (**Scheme 113**).⁴⁰⁸ The formation of the polymer-supported bimetallic reagent was unambiguously evidenced by IR as well as solid-state ^{119}Sn and ^{29}Si MAS NMR analysis.

The resin P-52-4 was proved to be efficient in the tandem reaction carbonyl allylation/silyl Prins cyclization because 2,6-disubstituted dihydropyrans were obtained in good yields and with a low organotin contamination (<20 ppm). The recovered resin can be regenerated and reused several times without appreciable activity loss, and the one-pot two-steps procedure can be also employed to prepare dissymmetric 2,6-disubstituted dihydropyrans.⁴⁰⁸

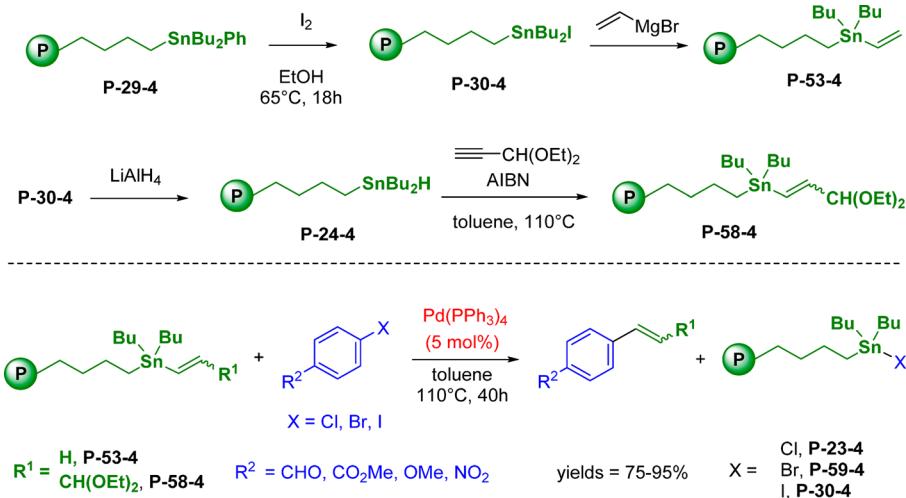
6.4.3.2.3.3. Use of Organotin Reagents Supported by Insoluble Polymers in Stille Cross-Coupling Reactions. The first use of macroporous polymers-supported tin reagents containing a reactive Sn–C bond (allyl, vinyl, and alkynyl) in the Stille reaction was reported by Neumann (**Scheme 114**).³⁸⁸ The functionalized resin was synthesized via hydrostannylation of one of the double bonds of divinylbenzene and subsequent radical polymerization of the resulting monomer. The Stille coupling products were obtained with moderate to good yields, and the recycling of these polymers was attempted three times but no specific conversion data were given for each cycle.

Scheme 114. Neumann's Supported Tin Reagents Used in the Stille Reaction

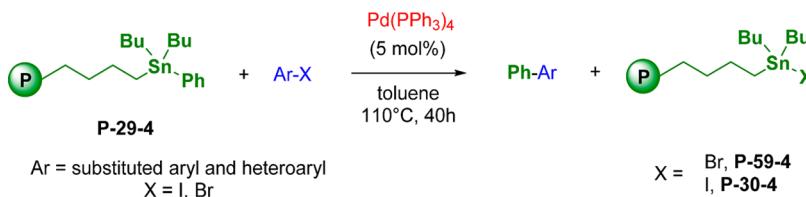
A Stille cross-coupling involving a supported allyltin has also been achieved by Dumartin on 4-bromobenzaldehyde affording a chemoselective reaction (the Stille cross-coupling was observed without any allylstannation of the aldehyde).³⁶⁵

In the course of their study on soluble polymer-supported organotin reagents,^{331,409} Albéniz and Espinet observed that their soluble norbornene polymers became insoluble in common organic solvents when they were heated in DMF at 120°C for 24 h. Therefore, the workup and the recycling became easier and less solvent consuming. Subsequently, a new generation of stannylated norbornene-based polymers affording an insoluble material by heating in DMF was prepared. The yields obtained in cross-coupling products were similar to those obtained with organotins grafted on a soluble polymer, but the purification was easier and the tin contamination lower (0.007–0.099% wt). They also dispersed these polymers in SiO_2 in a polymer: SiO_2 weight ratio = 1:10, and performed the Stille reaction in batch or in a thermostated column. In the latter case, yields were unaffected, and the resulting easier workup reduced the tin contamination by a factor of about 10 in

Scheme 115. Synthesis of Vinyltins Anchored on an Insoluble Organic Polymer and Their Use in Stille Cross-Coupling



Scheme 116. Use of Aryltins Supported by Insoluble Organic Polymers in Stille Cross-Coupling Reactions



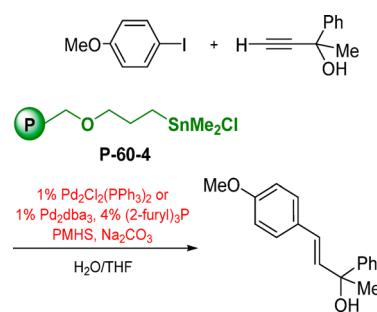
comparison to the case of the soluble polymer analogues. This low level held on during six recycling experiments.^{409,410}

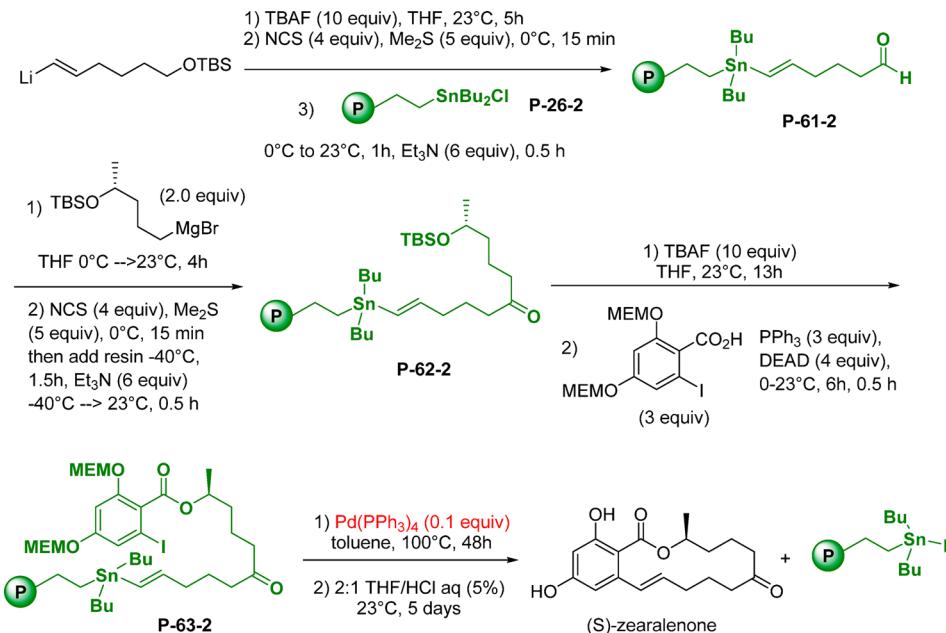
We have recently reported the synthesis of various organotin reagents bearing a vinyl or 3,3-diethoxyprop-1-en-1-yl substituent grafted on an insoluble macroporous polymer (Amberlite XE305) using the reaction sequence in Scheme 115. Vinyl groups were introduced in this polymer either by reaction of the tin halide with vinylmagnesium bromide or by hydrostannylation of alkynes to afford P-53-4 or P-58-4, respectively, after conversion of the polymer-supported tin halide into its tin hydride analogue. These vinyltin reagents anchored on an insoluble organic polymer were subsequently used in Stille cross-coupling reactions with aryl halides to obtain substituted styrenes in good yields and with a very low contamination by organotin residues (<10 ppm).^{367,390} We also used the insoluble polymer-supported phenyltin for the synthesis of diaryl derivatives through a Stille cross-coupling reaction (Scheme 116).³⁹⁰ The cross-coupling products were isolated in good yields with a very low contamination by tin (10 ppm) and palladium (1 ppm) residues after removal of the residual-supported organotin halide by filtration. The regeneration and recyclability of the supported phenyltin reagent were also proved possible after palladium cleaning of the polymer with 2,4,6-trimercapto-s-triazine prior to the next cycle. To reach aryl-heteroaryl or bis(heteroaryl) cross-coupling, a series of supported organotin reagents have been successfully prepared by reacting appropriate Grignard or heteroaryllithium reagents with supported organotin halides.³⁹¹

All of these supported tin reagents were analyzed using solid-state ¹¹⁹Sn MAS NMR and ¹H/¹³C/¹¹⁹Sn hr-MAS NMR in 2D experiments (¹H/¹³C HSQC, ¹H/¹¹⁹Sn HSQC, and ¹H NOESY) allowing unambiguous assignment of their isomeric distribution.³⁶⁹

Organotins supported by microporous organic polymers have also been used in a catalytic Stille cross-coupling, which involves the in situ formation of a vinyltin by hydrostannylation of an alkyne, allowing the reaction to be carried out with as little as 5 mol % of tributyltin chloride as tin hydride reagent precursor.^{118,119} This concept that contributes to reduce the tin amount has been successfully used by Kilburn et al. Thus, the vinyltin intermediates were obtained in situ by conversion of either a microporous polymer-supported dimethyl- or a dibutyltin chloride into the corresponding tin hydride, using polymethylhydrosiloxane and Na₂CO₃ for the exchange, which was used in the hydrostannylation of an alkyne (Scheme 117).^{372,411} Improved results were obtained with the dimethyltin chloride-supported polymer in comparison to the dibutyltin chloride analogue thanks to a lower steric hindrance around tin. Once more, a low tin contamination was found in the cross-coupling products of the reaction by using this strategy (<5–60 ppm values in comparison to >500 ppm when

Scheme 117. One-Pot Stille Cross-Coupling Using a Methyltin Derivative Anchored on a Microporous Polymer



Scheme 118. Synthesis of the (*S*)-Zearalenone through an Intramolecular Cross-Coupling on a Polymer Support

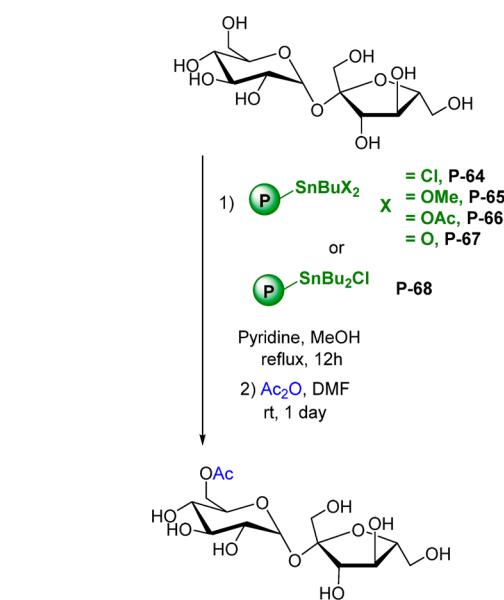
the reaction is performed in homogeneous medium with trimethyltin chloride).

In a similar context, the polymer-supported vinyltin reagent **P-61-2** was prepared by Nicolaou et al. by reacting a vinyl lithium reagent on the supported tin chloride **P-26-2** and used for the synthesis of (*S*)-zearalenone (Scheme 118).³⁶⁰ After deprotection of the alcohol and oxidation, only the *E*-vinyltin was obtained. Its intramolecular coupling reaction with the aryl iodide proceeded efficiently with 54% yield, allowing the synthesis of (*S*)-zearalenone in a 28% overall yield starting from **P-26-2** emphasizing the simplicity of the workup along the total synthesis. However, this strategy should be still improved at the level of tin trace pollution and recycling using a spacer avoiding β -fragmentation.

6.4.3.2.4. Use of Supported Organotin Polyhalides, Oxides, Hydroxides, or Alkoxides. The first contribution in this field has been reported by Macindoe and consists of grafting an organotin dialkoxide on a polymer⁴¹² to improve the methods developed in solution for the selective acylation of sugars.³⁹ For this purpose, different microporous polystyrene bearing a SnBu₂X₂ moiety (X₂ = O, **P-64**; X = Cl, **P-65**; X = OMe, **P-66**; X = OAc, **P-67**) or SnBu₂X (X = Cl, **P-68**) have been prepared and used for the regioselective acylation of sucrose (Scheme 119). Upon heating with sucrose in methanol and pyridine, the inactive supported organotin dichloride was converted into an active organotin dialkoxide, which acts as a catalyst for the acylation reaction. Using acetic anhydride and sucrose in a 3/1 ratio after use of a 65/1 sucrose/organotin ratio, a monoacetylation product on the 6-position was isolated with 65% yield. The recovered supported organotin byproduct can be recycled as a catalyst for at least six runs without activity loss.

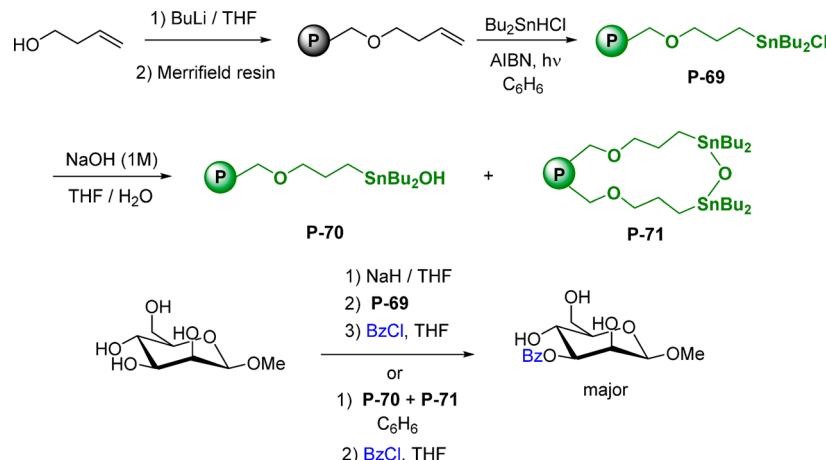
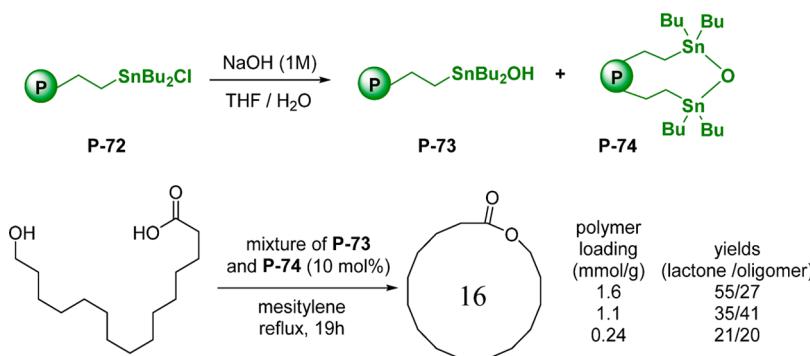
In comparison to reactions in solution, the trends are roughly the same, but the activity is better with the (bis) functionalized organotin catalysts when compared to the monofunctionalized ones (X = Cl, OR), in line with the Lewis acidity of the tin center (Cl > OAc and OMe). Furthermore, a very poor selectivity was obtained when the tin oxide was used in place of the tin dichloride.

Scheme 119. Polymer-Supported Tin Reagents for Selective Acylation of Sucroses



Whitfield and Ogawa investigated the benzoylation of methyl α -D-mannopyranoside starting from the chlorodibutylstannyl **P-69** and the hydroxydibutylstannyl **P-70** reagents grafted on a Merrified resin, the latter being obtained as mixture with the corresponding oxide **P-71**. Two different materials were used, a microporous resin with 2% of DVB and a macroporous one with 5% of DVB. A high regioselectivity favoring position 3 of the carbohydrate ring was obtained in both cases. However, the yields (10–30%) were low for the microporous resin and high (60%) for the macroporous one (Scheme 120). This result was explained by an activation of the hydroxide as a tin alkoxide combined with a matrix effect.³⁴⁰

Hunter and Roberts described the synthesis and the use of polymer-supported stannols and distannoxane as catalysts for the lactonization of hydroxycarboxylic acids.⁴¹³ These polymers

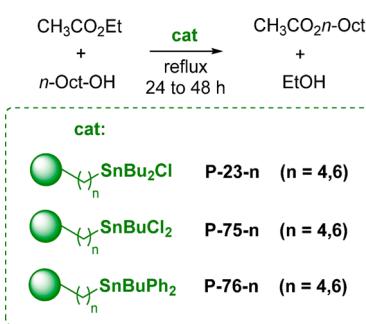
Scheme 120. Selective Benzoylation of Methyl α -D-Mannopyranoside**Scheme 121.** Preparation of Insoluble Polymer-Supported Stannol (Obtained in Mixture with the Corresponding Distannoxane) and Its Use for the Lactonization of 16-Hydroxyhexadecanoic Acid

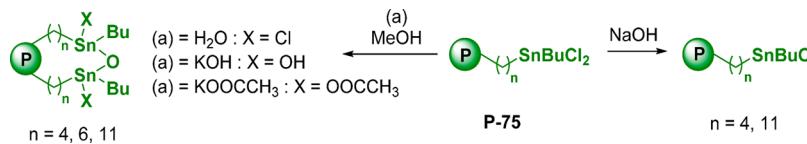
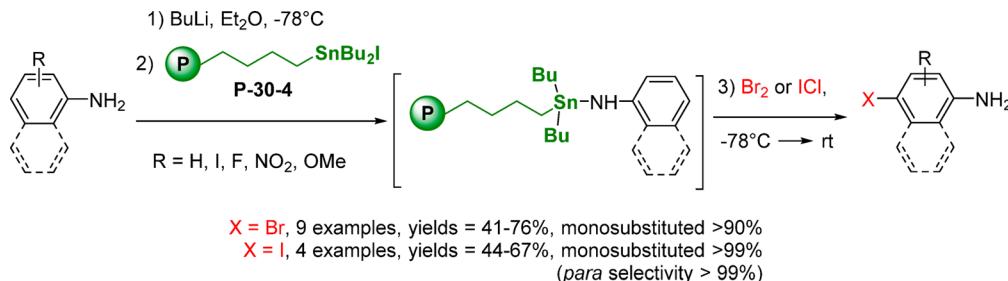
were prepared by copolymerization of 3- and 4-(2-di-*n*-butylchlorostannyl)-ethylstyrene with DVB as cross-linking agent. While no improvement was observed for the lactone to oligomer ratio, good yields in lactone up to 55% were obtained thanks to the simpler purification procedure. Moreover, the loading of the polymer has a significant impact on the reaction because a better yield was obtained with a higher loading (**Scheme 121**).

Willem and Biesemans reported several contributions on tin reagents grafted onto insoluble Amberlite XE305 (**P-23**, **P-75**, and **P-76**) and their use as catalyst in transesterification reactions (**Scheme 122**). Their pioneering work in this field was devoted to organotin catalysts grafted either by a tetra-

methylene or by a hexamethylene spacer and bearing a Bu_2SnCl (**P-23**), BuSnCl_2 (**P-75**), or SnBuPh_2 (**P-76**) moiety. These materials were initially characterized by ^{117}Sn MAS NMR,^{363,414} and subsequently by hr-MAS NMR ^1H , ^{13}C , and ^{119}Sn NMR, which was proved to be an invaluable tool for the full characterization of these insoluble tin reagents (**Scheme 123**).⁴¹⁵ Noteworthy is that the ERETIC method in ^{119}Sn hr-MAS NMR can be an alternative to elemental analysis for the determination of the tin loading.⁴¹⁶

Later, they pointed out that catalysts bearing a longer spacer (a C11 side chain, $n = 11$) were more stable upon recycling, with no alteration in the original macroscopic morphology of the beads, and also presented a higher swelling degree facilitating their hr-MAS NMR characterization. Moreover, grafts with the trichlorotin moiety were the most active catalysts and can be recycled at least 10 times in the transesterification of ethyl acetate by octanol.⁴¹⁷ When refluxing 2 h, the tin contamination was found to be around 5 ppm, but longer reaction times (24 h) caused higher contaminations (200 ppm).⁴¹⁸ Inspired by the high catalytic activities found in solution by Otera for numerous distannoxanes, in particular dimeric diorganochloro distannoxanes,^{236–238} Willem et al. also prepared the distannoxanes and the diorganotin oxides derivatives from the corresponding dialkyldichlorotin precursors (**Scheme 123**).^{419–421} While solid-state and hr-MAS ^{119}Sn NMR findings could not firmly evidence the presence of the dimeric Sn_2O_2 core in the case of the C4 and C6 grafts, its presence was unambiguously characterized in the case of the C11 grafted.⁴⁰² This feature is of importance, as Otera^{236–238}

Scheme 122. Transesterification Reaction of Ethyl Acetate with Octanol Catalyzed by Polymer-Supported Organotin Reagents

Scheme 123. Supported Mixed Organotin Oxides Used as Transesterification Catalysts**Scheme 124.** Use of Supported Tin Amide as *para* Orientating Group in Halogenation of Anilines and Naphthylamines

evidenced throughout numerous findings that the dimeric Sn_2O_2 core structure is determinant for the high catalytic activity of diorganodistannoates, which is indirectly supported by the higher efficiency of C11 grafted dibutylchlorodistannoate in comparison to the C4 and C6 ones (Scheme 123).

These supported mixed organotin oxides have also been used for the ring-opening polymerization of ϵ -caprolactone in the presence of propanol, and it was pointed out that an 11 carbon atoms spacer between polystyrene matrix and tin was the more appropriate one, to avoid the collapse of the resin beads (as observed for a 6 carbon spacer).^{421–423}

The efficiency of these catalysts in transesterification reactions was recently compared to those of organotin catalysts anchored on cross-linked polystyrene bearing an ethylene glycol chain as spacer. Through the introduction of such a polar spacer, an improved swelling and a higher site accessibility in polar media were expected.⁴²⁴ However, low conversions were obtained for the reaction between ethyl acetate and *n*-octanol, a disappointing result that has been explained by strong intra- and intermolecular donor–acceptor O → Sn interactions between ether functions and the tin center, which prohibits the catalytic process and destabilizes the catalyst, an assumption strongly supported by hr-MAS NMR investigations.

Some contributions related to the preparation of polymer-supported tin carboxylates^{425,426} and their use as chloride-selective anion carriers in polymeric-liquid-membrane potentiometric ion-selective electrodes have also been reported.⁴²⁷ These polymer-supported tin carboxylates were also evaluated as catalysts for the transesterification of ethyl acetate by different alcohols^{428,429} or of glyceryl tridodecanoate (as a model of natural triglyceride) by ethanol to mimic the preparation of biodiesel fuel.⁴³⁰

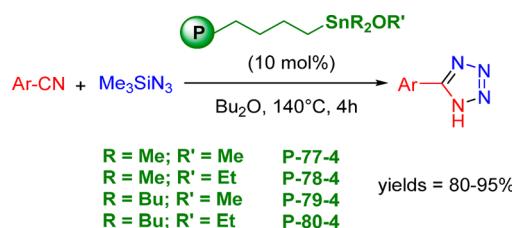
6.4.3.2.5. Use of Supported Organotins Containing a Sn–N Bond. Functional aromatic halides such as bromo- and iodo anilines are key intermediates in organic chemistry because of their usefulness for the generation of carbon–carbon bonds via cross-coupling reactions. For this purpose, numerous methods have been developed for the halogenation of aromatic compounds involving new bromination and iodination reagents. However, some of them lack regioselectivity and show low control over polyhalogenation. Even scarcely used, the Sn–N bond can be exploited both to improve the reactivity of the aromatic ring and to generate a steric hindrance at the

ortho positions allowing a high *para* selectivity. Thus, we have successfully extrapolated the previously reported tandem *N*-lithiation, *N*-trimethylstannylation/halogenation⁴³¹ to the halogenation of aromatic amines using a macroporous polymer-supported dibutyltin bromide or iodide.⁴³²

The reaction involving trimethyltin derivatives (in solution) for the halogenation of aromatic amines⁴³¹ was considerably improved in terms of safety when using a macroporous polystyrene-supported dibutyltin bromide or iodide with a four-carbon spacer. Aromatic amines exposed to *n*-butyllithium reacted with a polymer-supported organotin halide and gave the corresponding transient polymer-bound *N*-triorganostannylamines, which by treatment with bromine or iodine monochloride gave the *para*-halogenated aromatic amines with high yields and high selectivities (Scheme 124).⁴³²

It is worth noting that the supported organotin halide regenerated during the course of the halogenation reaction can be reused without loss of efficiency. Furthermore, the concentration of residual tin in the halogenated amines never exceeded 50 ppm and was often under 25 ppm, despite the possible cleavage of every Sn–C bond by Br_2 or ICl . Otherwise, the *para* orientating effect of the stannyl amide moiety is high.

Another example using supported organotins with a highly reactive Sn–N bond was recently developed for the synthesis of 5-substituted 1*H* tetrazoles. In this case, thanks to the high oxophilicity of silicon, the reaction can be achieved in a catalytic mode through an *in situ* generated polymer-supported tin azide reacting on a nitrile. Better results were obtained with the smaller dimethyltin methoxide reagent thanks to the influence of the steric bulk both on the cycloaddition reaction and on the Sn–O/Si–N exchange reaction (Scheme 125).⁴³³

Scheme 125. In Situ Generation of a Supported Tin Azide and Its Use in the Preparation of Tetrazoles

Once more, thanks to the supported reagent used in a catalytic mode, the remaining contamination by organotins can be reduced to nearly the ppm level.

7. CONCLUSION

This Review reporting on the different methods used to minimize the presence of organotin residues in the products of reactions involving organotin reagents exposed two main types of strategies with different goals.

When the purpose is to facilitate the purification of the products by a preliminary elimination of the organotin residues as a precipitate or by partitioning between two liquid phases, the suggested strategies aim to be efficient at a preparative scale to obtain pure products within the sensitivity limits of ^1H NMR. It means that such preparative methods have to be simple and cheap to obtain key precursors that should be used in the early part of a multistep synthesis sequence. In this case, the ability of the method to minimize the presence of tin at the trace level in the products (lower than 20 ppm for instance) does not need to be considered as a priority, and therefore an easy workup combined with a moderate cost will be the key criteria to select the most appropriate of the methodologies reviewed above. Therefore, methods using precipitation of organotins as fluorides or partition methods using hexane/acetonitrile will be the most interesting ones when compatible with the nature of the desired products. Among the numerous other methods, the organic chemist will have to pay attention to their functional groups' compatibility when too harsh experimental conditions have to be used, or to their nondestructive one for liquid chromatography methods. In this last category, Harrowven's method appears highly efficient for tin halides elimination because of its ability to reach very low levels of tin contaminants in the products.

Otherwise, for modified soluble organotin reagents like stannatranes or organotins with pendant side chains inducing specific properties (as for instance PFC or PEG chains), their interest has to be considered in terms of compromise between their cost, their improved reactivity (for instance, higher reactivity of stannatranes due to the tin atom coordination expansion), and their ability to limit the tin concentration in the targeted products.

For reactions achieved in ionic liquids, water, or other "unusual" media, some advantages can be observed as for instance the possible use of mono-organotin trihalides as reagents affording after reaction nearly nontoxic inorganic species, but the cost of the solvents required to extract the desired products has to be considered prior claiming these methods as "green ones".

On the other hand, when the objective is to obtain reaction products with control of the tin concentration at the trace level (about 10 ppm) when organotin reagents are involved at the end of a multistep synthesis, the strategy is quite different. To obtain very low contamination by tin residues, the methods considered have to be formally nonpolluting ones, meaning for instance that the reagents will be anchored onto an insoluble matrix to have a complete elimination of nonreacted tin reagent and tin byproducts at the end of the reaction. In practice, the situation is slightly different because of the possible degradation of the grafted matrixes (abrasion in the case of insoluble polymer, for example) or of side-decomposition reactions, which can bring a few ppm of organotins into the products. In these series, use of fluorinated organotins in fluororous phases or grafting organotin reagents onto ionic liquids, phosphonium

salts, or polymers has been proved to be a convincingly efficient strategy to afford the expected results with tin contaminations often lower than 10 ppm. In the case of polymer-supported reagents, the more insoluble is the matrix, the more efficient is the prevention of the tin contamination, as pointed out by studies involving poorly or highly cross-linked organic polymers. Furthermore, in the case of polystyrene-type polymers, the use of a two-carbon spacer should be avoided due to its ability to release soluble organotins through a β -elimination. In practice, once more, the organic chemist will have to find the appropriate compromise between efficiency and price to obtain the desired products with very low pollution levels compatible with biological applications.

Therefore, in this case, the recyclability of the supported or modified organotin reagents has to be seriously considered. While possible from tributyltin fluoride or tetrabutyltin after their separation as byproducts, in practice, recycling is scarcely planned for the regeneration of inexpensive reagents. The situation is completely different when sophisticated reagents are involved because an efficient recycling along the runs can allow a cheap strategy even starting from an expensive reagent. Accordingly, when grafted organotin reagents were used, the recyclability of the supported organotin residues into organotin reagents, when it can be efficiently achieved, opens new perspectives in synthetic sustainable chemistry, and the ideal situation is encountered when the supported reagent can be used in a catalytic mode and regenerated *in situ*.

In summary, a lot of strategies have been developed to facilitate the workup of reactions involving organotins. The results obtained proved that pollution and safety issues related to the toxicity of the organotin compounds can be circumvented, allowing the use of organotin reagents in every step of an organic synthesis with the benefits of the flexibility and versatility of this type of reagents. This point has to be especially emphasized in the case of catalytic reactions, because in such a situation organotin reagents can offer the most appropriate route to reach the target molecules. In such a context, the organotin reagents that have been sometimes banned unfairly, not always on rational bases, should recover a new importance in organic synthesis much more in line with their remarkable synthetic potential.

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Notes

The authors declare no competing financial interest.

Biographies



Erwan Le Grogne was born in Lorient (France) in 1972. He undergraduate from the University of Nantes in 1996 and received his Ph.D. in 2000 under the supervision of Prof. Rinaldo Poli at the University of Burgundy (Dijon, France). After a postdoctoral stay at Shell Chemical in Amsterdam (The Netherlands) in the homogeneous catalysis department as a Marie Curie fellow, he was appointed CNRS Researcher at the University of Nantes in 2001 and worked in collaboration with Prof. Jean-Paul Quintard. His current interests concern the development of sustainable synthetic methods in organic chemistry, heterogeneous and homogeneous catalysis, polymer-supported chemistry, and asymmetric synthesis.



Jean-Mathieu Chrétien completed his Ph.D. in 2005 at the University of Nantes (France) under the supervision of Prof. Jean-Paul Quintard and Dr. Françoise Zammattio working on the development of polymer-supported organotin reagents for application in organic synthesis. He then joined the groups of Jeremy D. Kilburn and Philip N. Bartlett at the University of Southampton (UK) as a Post-Doctoral Research Fellow and worked on the development of modified carbon electrodes for biosensor applications from 2006 to 2010. In 2010, he moved back to the University of Nantes (France) to work again in the field of polymer-supported organotin reagents under the supervision of Dr. Erwan Le Grogne. After graduating from the Centre for International Intellectual Property Studies in Strasbourg (France) in 2011, he is currently working as a patent engineer.



Françoise Zammattio obtained her Ph.D. at the University of Nantes (France) in 1990 under the supervision of Prof. Jean Daniel Brion in the area of heterocyclic synthesis. After postdoctoral studies at the University of Cambridge (UK) under the direction of Prof. Ian Fleming, she joined the group of Dr. Jean Villiéras (1992–2000) and then the group of Prof. Jean-Paul Quintard at the University of Nantes (France) as Lecturer in chemistry. Current research focused on the development of new procedures for the synthesis of heterocycles and new supported organometallic reagents for use in organic synthesis.



Prof. Jean-Paul Quintard received his Ph.D. degree in 1974 from the University of Bordeaux, for a work on hydrostannylation reactions achieved under the supervision of Prof. M. Pereyre. He started his career as Assistant Professor in 1970 and spent a postdoctoral period with Prof. A. G. Davies at University College of London working on ESR spectroscopy (1977) before coming back to University of Bordeaux to develop research on stannylanions and use of organotin reagents in organic synthesis in collaboration with Prof. M. Pereyre. The book *Tin in Organic Synthesis* (Butterworths, 1987, by M. Pereyre, J.-P. Quintard, and A. Rahm) was one of the more meaningful contributions from this period and was concomitant with his promotion as Full Professor at the University of Nantes (1986). In Nantes, for teaching duties, he was the head of the branch Fine Organic Chemistry for 23 years before being nominated Emeritus Professor in 2012. During this period, his fields of interest in research were devoted to the use of organotin reagents in organic synthesis focusing on chemo-, regio-, and enantioselective reactions. His main contributions concern the preparation and use of unpoled vinyltins and allyltins with fixed configurations, the enantioselective synthesis of stannylated precursors of chiral α -alkoxyalkyllithium and α -amino-alkyllithium reagents, and the preparation and use of organotin reagents grafted on insoluble polymers to prevent contamination of the prepared organic products by organotin residues.

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ABBREVIATIONS

AIBN	2,2'-Azobisisobutyronitrile
BTF	Benzotrifluoride (trifluoromethylbenzene)
BVPB	1,4-bis (4-vinylphenoxy) but-2-ene
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diiisobutylaluminum hydride
DMAP	4-(N,N-dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DVB	Divinylbenzene
FC72	Perfluorohexane
FG	Functional group
FSPE	Fluorous Solid-Phase Extraction
G	Poly(ethylene glycol)
HC	Hydrocarbons
HIPE	High Internal Phase Emulsion
ICP-MS	Inductively coupled plasma mass spectrometry
LD ₅₀	Lethal Dose, 50%
MABG	Meta astatobenzylguanidine
MAS	Magic angle spinning
MBOH	3-Methyl-but-3-en-1-ol
MIBG	Meta iodobenzylguanidine
MPBIM	1,1-(methylenedi-1,4-phenylene) bis maleimide
NCS	N-Chlorosuccinimide
NMP	N-Methylpyrrolidone
NOK	β-Sisterol methoxy polyethyleneglycol succinate
P	Cross-linked polystyrene
PE	Polyethylene
PEG	Polyethylene glycol
PET	Positron emission tomography
PF	Polyfluorene
PFC	Perfluorocarbons
PMHS	Polymethylhydrosiloxane
PMI	N-Phenylmaleimide
PN	Polynorbornene
Ps	Polystyrene (non-crossed linked)
TFA	Trifluoroacetic acid
TPGS-750-M	Polyethanol-α-tocopherylsuccinate
TSTU	N,N,N',N'-Tetramethyl-O-(N-succinimidyl)-uronium tetrafluoroborate

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