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Removal, Recovery, and Recycling of Triarylphosphonium-Supported Tin Reagents for Various Organic Transformations

Jean-Christophe Poupon, David Marcoux, Jean-Manuel Cloarec, and André B. Charette*

Département de Chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal (Québec), Canada H3C 3J7

andre.charette@umontreal.ca

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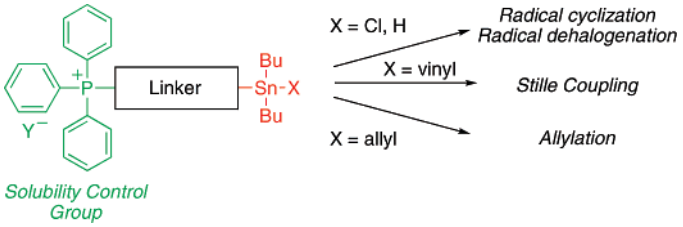
ABSTRACT



Phosphonium-supported tin reagents and catalysts were prepared and were shown to be effective in Stille couplings, radical dehalogenations, radical cyclizations, and carbonyl allylations. Not only could the tin residues be removed from the crude reaction mixture through a phase separation process but also they could be recovered and recycled.

Triorganotin derivatives are extremely versatile and useful reagents in organic synthesis and radical chemistry.[1] Nevertheless, these compounds are toxic[2] and sometimes malodorous, and tin byproducts are usually difficult to remove from the desired reaction products.[3] Furthermore, contamination from stannane residues is a major concern in the synthesis of pharmaceuticals and radiopharmaceuticals. Alternatives to tin reagents have been disclosed, but no reagent is as broadly applicable as the parent tin hydride reagents.[4] Recently, we have described the use of the tetraarylphosphonium unit as a solubility control group for triphenylphosphine and DEAD.[5,6] Because the molecular weight of the tributyltin subunit constitutes a little bit less than half of the total molecular weight of the phosphonium-supported tin reagent, it was not clear whether the solubility properties of the reagent would still be primarily dictated by the phosphonium group. The phosphonium reagents are typically very soluble in chlorinated solvents, and they can

(1) (a) Neumann, W. P. *Synthesis* **1987**, 665. (b) Curran, D. P. *Synthesis* **1988**, 417. (c) Curran, D. P. *Synthesis* **1988**, 489. (d) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001. (e) *Organotin Chemistry*, 2nd ed.; Davies, A. L., Ed.; Wiley-VCH: Weinheim, New York, 2004.

(2) Thoonen, S. H. L.; Deelman, B. J.; van Koten, G. *J. Organomet. Chem.* **2004**, *689*, 2145.

(3) Several approaches have been reported to remove tin hydride residues from reaction mixtures: (a) Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471. (b) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449. (c) Curran, D. P.; Chang, C. T. *J. Org. Chem.* **1989**, *54*, 3140. (d) Farina, V. *J. Org. Chem.* **1991**, *56*, 4985. (e) Crich, D.; Sun, S. X. *J. Org. Chem.* **1996**, *61*, 7200. (f) Renaud, P.; Lacote, E.; Quaranta, L. *Tetrahedron Lett.* **1998**, *39*, 2123. (g) Edelson, B. S.; Stoltz, B. M.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 6729. (h) Salomon, C. J.; Danelon, G. O.; Mascaretti, O. A. *J. Org. Chem.* **2000**, *65*, 9220.

(4) For a discussion of this issue, see: (a) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3073. (b) Studer, A.; Amrein, S. *Synthesis* **2002**, 835.

(5) (a) Poupon, J. C.; Boezio, A. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2006**, *45*, *1415*. (b) Zoute, L.; Lacombe, C.; Quirion, J. C.; Charette, A. B.; Jubault, P. *Tetrahedron Lett.* **2006**, *47*, 7931.

(6) For reviews on soluble supports: (a) Chen, J. N.; Yang, G. C.; Zhang, H. Q.; Chen, Z. X. *React. Funct. Polym.* **2006**, *66*, 1434. (b) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325. Bergbreiter, D. E. *Chem. Rev.* **2002**, *102*, 3345.

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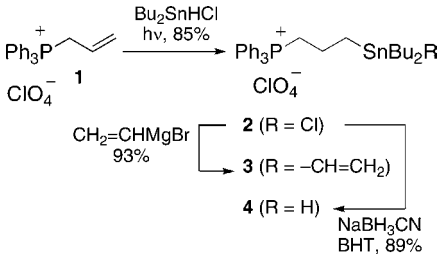
be precipitated out of solution by ether, hexane, or toluene addition. In this communication, we report that phosphonium salts can be used as effective solubility control groups for tin reagents involved in Stille coupling reactions, in carbonyl allylation reactions, and in radical-mediated processes such as the dehalogenation and cyclization reactions.[7−10] We also demonstrate that the tin byproducts can be removed by a simple phase separation upon ether or hexane addition and recycled if needed.

We first chose to test the more conveniently prepared triphenylalkylphosphonium-supported tin chloride salt **2** obtained in three steps from triphenylphosphine (allylation with allyl bromide, anion exchange, and hydrostannylation) (Scheme 1). Conversion of **2** into the vinyltin reagent **3** was

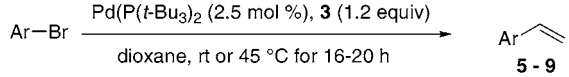
Scheme 1. Preparation of Phosphonium-Supported Tin Chloride

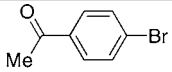
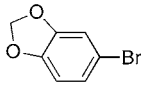
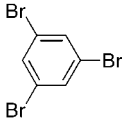
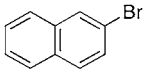
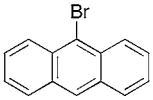


achieved upon treatment with vinylmagnesium bromide. Alternatively, $NaBH_3CN$ reduction of **2** in the presence of BHT led to the tin hydride reagent **4**. Although the solubility properties of the reagents bearing this scaffold are not as suitable as those of the parent substituted tetraarylphosphonium salts,[11] their ease of synthesis led us to further investigate them as reagents and catalysts for tin-mediated processes.

The Stille reaction[12] involving vinyltin reagent **3** using Fu's catalyst[13] was initially tested. Treatment of various aryl bromides with catalytic $Pd(P(t\text{-}Bu_3P))_2$ in 1,4-dioxane led to corresponding Stille coupling products in high yields (Table 1). The reactivity of this reagent was comparable to

Table 1. Stille Coupling with Phosphonium-Supported Vinyltin **3**



entry	aryl bromide	product	yield (%)[a]
1		**5**	85 (88)[b]
2		**6**	78[c]
3		**7**	86[c,d]
4		**8**	88 (88)[b]
5		**9**	91 (66)[b]

[a] Isolated yields. The yield in parentheses was obtained with tributylvinyltin. [b] rt for 16 h. [c] 45 °C for 20 h. [d] $Pd(P(t\text{-}Bu)_3)$ (7.5 mol %) and **3** (3.5 equiv) were used.

that of tributylvinylstannane under these conditions. The removal of the tin byproducts was achieved by evaporation of the reaction mixture, dissolution in dichloromethane followed by hexane addition, and filtration. Concentration of the filtrate under reduced pressure afforded the desired tin-free coupling product.[14,15] It should also be pointed out that the resulting tin bromide could be recovered and recycled into the vinyltin reagent upon treatment with vinylmagnesium bromide (90% overall yield).

The next reaction that was investigated was the tin hydride catalyzed dehalogenation reaction. The first reaction that was tested was the reduction of 1-bromoadamantane using 0.1 equiv of tin chloride **2** and $NaBH_4$ as the stoichiometric reagent (AIBN as the initiator).[16a] Although a successful dehalogenation was observed in high yield within 2 h in refluxing acetonitrile, the phosphonium-supported reagent **4** could not be recovered and recycled because it partly

(7) For pioneering work on removal of tin reagents, see: (a) Light, J.; Breslow, R. *Tetrahedron Lett.* **1990**, *31*, 2957. (b) Clive, D. L. J.; Yang, W. *J. Org. Chem.* **1995**, *60*, 2607.

(8) For solid supported tin reagents: (a) Neumann, W. P.; Peterseim, M. *React. Polym.* **1993**, *20*, 189. (b) Gerigk, U.; Gerlach, M.; Neumann, W. P.; Vieler, R.; Weintritt, V. *Synthesis* **1990**, 448. (c) Kuhn, H.; Neumann, W. P. *Synlett* **1994**, 123. (d) Gerlach, M.; Jordens, F.; Kuhn, H.; Neumann, W. P.; Peterseim, M. *J. Org. Chem.* **1991**, *56*, 5971. (e) Neumann, W. P.; Peterseim, M. *Synlett* **1992**, 801. (f) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Murphy, F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2534. (g) Hernan, A. G.; Kilburn, J. D. *Tetrahedron Lett.* **2004**, *45*, 831. (h) Hernan, A. G.; Guillot, V.; Kuvshinov, A.; Kilburn, J. D. *Tetrahedron Lett.* **2003**, *44*, 8601. (i) Chrétien, J. M.; Zammattio, F.; Le Grognec, E.; Paris, M.; Cahingt, B.; Montavon, G.; Quintard, J. P. *J. Org. Chem.* **2005**, *70*, 2870. (j) Chrétien, J. M.; Zammattio, F.; Gauthier, D.; Le Grognec, E.; Paris, M.; Quintard, J. P. *Chem.−Eur. J.* **2006**, *12*, 6816. (k) Chrétien, J. M.; Mallinger, A.; Zammattio, F.; Le Grognec, E.; Paris, M.; Montavon, G.; Quintard, J. P. *Tetrahedron Lett.* **2007**, *48*, 1781. (l) Chemin, A.; Deleuze, H.; Maillard, B. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 137.

(9) (a) Enholm, E. J.; Gallagher, M. E.; Moran, K. M.; Lombardi, J. S.; Schulte, J. P. *Org. Lett.* **1999**, *1*, 689. (b) Enholm, E. J.; Schulte, J. P. *Org. Lett.* **1999**, *1*, 1275.

(10) Curran, D. P.; Hadida, S.; Kim, S. Y.; Luo, Z. Y. *J. Am. Chem. Soc.* **1999**, *121*, 6607.

(11) Typically, the tetraarylphosphonium-supported reagents precipitate well out of a CH_2Cl_2 solution upon ether addition (ca. ≤5:1 v/v). With reagent **2** and **3**, hexanes had to be used in significant amounts (ca. 9:1 v/v).

(12) (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React. (N.Y.)* **1997**, *50*, 1. (b) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704.

(13) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

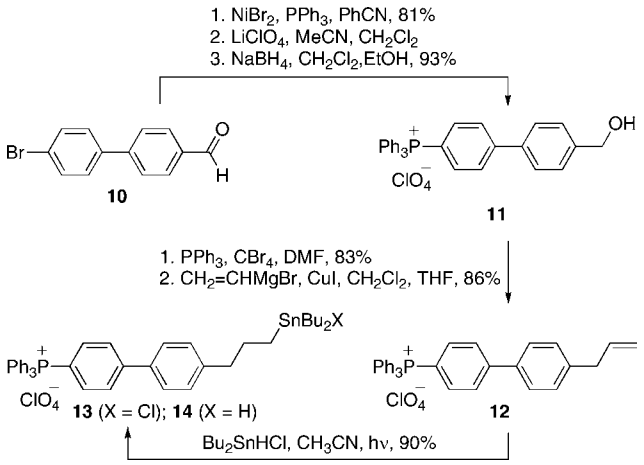
(14) Analysis by ICP-AES of the product indicated that the concentration in residual tin of the final product was 13 ppm (crude) and <5 ppm (after flash chromatography).

(15) See Supporting Information for typical crude NMR spectra and further experimental details.

(16) (a) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554. (b) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303.

decomposed into a phosphine−borane complex and cleaved tin hydride. However, it should be pointed out that **4** could be prepared in 89% yield when the chloride **2** was treated with sodium cyanoborohydride[16b] in the presence of the radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (BHT).[17] In light of these results, a more robust tetraarylphosphonium-supported tin reagent that would be effective in the tin-catalyzed dehalogenation reactions was synthesized (Scheme 2). Horner reaction[18] of bromoaldehyde **10**, anion exchange,

Scheme 2. Synthesis of Phosphonium-Supported Tin Chloride **13**



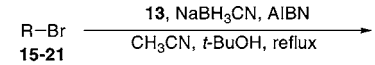
and reduction led to benzyl alcohol **11**. A subsequent treatment of the resulting bromide with vinyl Grignard led to alkene **12** that underwent hydrostannylation to produce the desired tin chloride reagent **13**. The chemical shift for the stannane reagent **13** (^{119}Sn NMR ($CDCl_3$) δ 143.9) was relatively close to that observed for the parent tributyltin chloride (^{119}Sn NMR ($CDCl_3$) δ 156.5) indicating that this reagent should simulate the parent compound quite well. Furthermore, its loading (1.2 mmol/g) is comparable to polymer supported (0.5−1.5 mmol/g),[7b,7e,9b] fluorous (0.8 mmol/g),[9] and inorganic (0.8 mmol/g) tin reagents.[19]

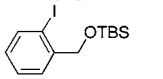
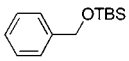
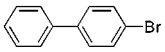
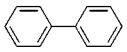
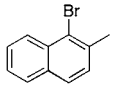
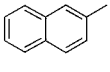
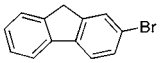
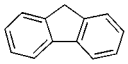
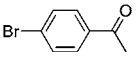
Chloride **13** could be converted to the relatively unstable phosphonium-supported tin hydride **14** upon treatment with $NaBH_3CN$ in the presence of BHT. ^{1}H NMR analysis indicated the presence of a Sn−H resonance at 4.64 δ ppm.

The reduction of halides using tin chloride **13** proceeded very well under Stork's conditions[16b] (Table 2). Several aryl and alkyl bromides were converted to the reduced product in very high yields. After a standard workup, the crude product was dissolved in CH_2Cl_2 and the residual tin hydride **14** was precipitated upon hexane addition (5-volume relative to CH_2Cl_2). Filtration of the mixture and concentration of the solution led to a tin-free product.[20] In the case of the

(17) The half-life of **4** is ca. 1 day in CD_2Cl_2 containing traces of BHT.
(18) Horner, L.; Mummenthey, G.; Moses, H.; Beck, P. *Chem. Ber.* **1966**, *99*, 2782.
(19) Fu, Q. J.; Steele, A. M.; Tsang, S. C. *Green Chem.* **2001**, *3*, 71.
(20) Analysis by ICP-AES of the crude product indicated that the concentration in residual tin of the final product was 5 ppm (crude).

Table 2. Reduction of Halides with Phosphonium-Supported Tin Hydrides



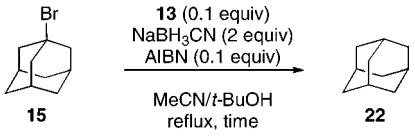
entry	substrate		product		yield (%)[a]
1		**15**		**22**	98[b]
2	*n*-$C_{18}H_{37}$–Br	**16**	*n*-$C_{18}H_{38}$	**23**	97[b]
3		**17**		**24**	93[b]
4		**18**		**25**	81[c]
5		**19**		**26**	94[c]
6		**20**		**27**	90[c]
7		**21**		**28**	90[d]

[a] Isolated yield after flash chromatography. [b] **13** (0.1 equiv), AIBN (0.1 equiv), 3 h. [c] **13** (0.25 equiv), AIBN (0.1 equiv), 8 h. [d] **4** (1.2 equiv), AIBN (0.1 equiv), 6 h.

less reactive aryl bromide **21**, a stoichiometric amount of tin hydride **4** led to the reduced product in excellent yield (Table 2, entry 7). The phosphonium-supported tin hydride reagent **14** could be recovered by dissolving the filtered solid in CH_2Cl_2. ^{119}Sn NMR analysis showed that the recovered solid was very clean as it only displayed signals corresponding to the tin hydride reagent.

This observation led us to explore the possibility of recycling it and reusing it in the dehalogenation reaction of bromoadamantane (Table 3).

Table 3. Recycling of Phosphonium-Supported Tin Hydride **14**



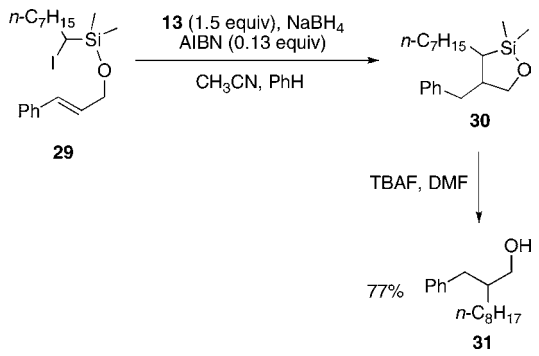
run	time (h)	yield (%)[a]
1	3	98
2[b]	3	90
3[b]	3	96
4[b]	3	92
5[b]	4.5	94
6[b]	4.5	90

[a] Determined by GC using decane as the internal standard. [b] Recovered tin hydride reagent **14** from the previous entry was used for this entry.

Gratifyingly, the tin reagent **14** could be recovered and recycled up to six times without much lost in its effectiveness (Table 3). These results are comparable to the best recyclable polymer-supported organotin[7l] and fluorous[10] organotin reagents.

Tin chloride **13** was also used in a radical-mediated cyclization of iodide **29** (Scheme 3). Treatment of the

Scheme 3. Radical Cyclization Using Stoichiometric Tin Chloride **13**



phosphonium-supported tin chloride **13** with $NaBH_4$ generated a stoichiometric amount of the corresponding tin hydride that reacted with iodide **29** in the presence of AIBN to generate silyl ether **30** as a mixture of diastereomers. The tin byproducts were quantitatively removed by a filtration following the dilution of the reaction mixture with ether/hexanes.

NMR analysis of crude **30** did not show the presence of any tin residues. This material was directly submitted to the protodesilylation reaction to generate **31** in 77% yield.

The last application of phosphonium-supported tin-mediated reactions that was studied is the Lewis acid mediated allylation of aldehydes with allyltin reagents.[21,22] Both reagents **32** and **33** (Figure 1) were prepared in 88 and 90% yield upon treating the corresponding tin chlorides **2** and **13** with allylmagnesium bromide (Et_2O/CH_2Cl_2, −78 °C).

3-Phenylpropionaldehyde (**34**) was treated with both reagents in the presence of BF_3-OEt_2 to produce the desired homoallylic alcohol in excellent yields (Scheme 4).

Because the products of these allylation reactions were the corresponding tin alkoxides, an aqueous workup had to be performed prior to the phase separation process. The crude product obtained after workup was therefore dissolved in

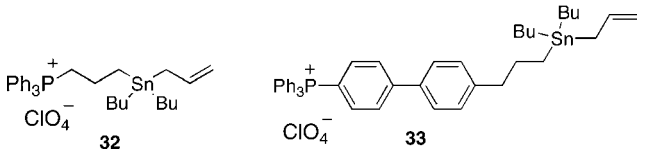
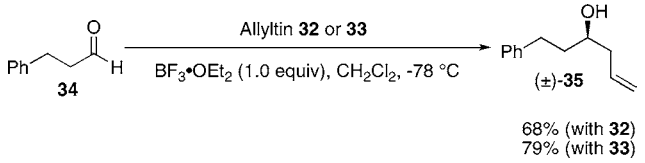


Figure 1. Phosphonium-supported allyltin reagents.

CH_2Cl_2, and the tin residues were precipitated upon ether addition. Filtration and concentration of the filtrate under reduced pressure led to a tin-free product.[23] Although its synthesis is slightly longer, **33** was a more conveniently handled solid that precipitated well upon diethyl ether addition.

Scheme 4. Allylation with Phosphonium-Supported Allyltin **32** and **33**



In conclusion, we have demonstrated that phosphonium-supported tin reagents provide a general solution for the removal of tin residues upon product isolation in various processes. Further work in this area is in progress and will be reported in due course.

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Supporting Information Available: General experimental procedures. Characterization spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701447Q

(21) (a) Naruta, Y.; Ushida, S.; Maruyama, K. *Chem. Lett.* **1979**, 919. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(22) For supported allyltin reagents, see: (a) Ref 8a. (b) Ref 7j. (c) Cossy, J.; Rasamison, C.; Pardo, D. G.; Marshall, J. A. *Synlett* **2001**, 629. (d) Cossy, J.; Rasamison, C.; Pardo, D. G. *J. Org. Chem.* **2001**, *66*, 7195. (e) Gastaldi, S.; Stien, D. *Tetrahedron Lett.* **2002**, *43*, 4309. (f) Stien, D.; Gastaldi, S. *J. Org. Chem.* **2004**, *69*, 4464.

(23) Analysis by ICP-AES of the crude product indicated that the concentration in residual tin of the final product was 7 ppm.