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Potassium carbonate–silica: a highly effective stationary phase for the chromatographic removal of organotin impurities†‡

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Organotin impurities in product mixtures can be reduced from stoichiometric levels to ~15 parts per million by column chromatography using 10% w/w anhydrous potassium carbonate–silica as a stationary phase.

Concerns over the toxicity of organotin reagents, products and byproducts, and difficulties associated with the purification of product mixtures containing organotin residues, often limit the appeal of organotin chemistry.[1] Thus, while it is generally easy to reduce organotin impurities to below 1% w/w, their removal to a parts per million level is necessary for biological screening and health-care applications.[2] To address this, many methods of organotin removal have been developed,[3] including water-soluble and solid-supported stannanes, catalytic procedures and alternative reagents based on metal and metalloid hydrides of lower toxicity.[4] Though many are highly effective, their adoption usually adds to the cost or complexity of an experimental procedure.

Our groups have previously reported two simple and inexpensive procedures for the removal of organotin impurities from product mixtures.[5,6] The first involved dilution of the concentrated product mixture with reagent grade ether, adding a slight excess of DBU then an ethereal solution of iodine until the iodine colour just persists. Elution through a plug of silica followed by standard flash column chromatography completed the purification. The second method required no pretreatment of product mixtures as, after concentration, the residue is simply eluted through a stationary phase composed of 10% finely ground potassium fluoride and 90% silica (w/w). In this way, levels of organotin impurities could be reduced from full equivalence to below 30 ppm.

The simplicity and effectiveness of the methods have ensured their widespread adoption,[7,8] though neither is without drawbacks. One practical issue with the KF/silica protocol relates to the hygroscopic nature of the salt. On prolonged standing, this leads to a loss of fluidity in the stationary phase which in turn reduces its efficacy for both compound separation and the removal of reactive organotin species. Herein we detail an improved procedure using K_2CO_3 as an additive, making the method cheaper and more practicable. Its effectiveness has been demonstrated in a range of common applications including the purification of tetraorganyltin and hexaorganylditin compounds from complex product mixtures. The latter observation broadens the method's scope and application considerably and offers a fresh insight into the action of the additive.

Our investigation began with an examination of stationary phases comprising silica mixed with various organic and inorganic fluorides. In our chosen test reaction, **1** → **2**,[9] none came close to matching the success achieved using the KF–silica combination,[6] with many performing worse than silica alone (Table 1). The results suggested that the basicity of potassium fluoride was a key factor, a hypothesis substantiated when a mixture of KOAc and silica proved highly effective for the removal of organotin impurities. Thus, in the reduction of aryl bromide **1** to arene **2** with 2 equiv. tributyltin hydride and TBAF (Scheme 1), chromatographic purification using a stationary phase of 10% KOAc and 90% silica (w/w) reduced organotin impurity levels from 2 full equivalents to 76 ppm. The result was then eclipsed by a combination of K_2CO_3 and silica, which repeatedly reduced levels of organotin impurity to below 15 ppm in this system.

We have applied the method in Bu_3SnH-mediated reductions of aryl halides and acid chlorides,[9,10] Stille coupling[11] and tin-mediated radical cyclisation reactions (Scheme 1).[12,13] In each case, ^1H NMR analysis of the purified products showed them to be free of organotin impurities (see ESI‡), including situations in which a low-yielding product had to be separated from a complex product mixture containing substantial organotin residues.

Treatment of amide **9** under standard Bu_3SnH-mediated radical cyclisation conditions proved informative as cyclisation to the arene occurred with concomitant hydrostannylation of the terminal alkyne.[13] Importantly, the resulting vinylstannane

Table 1 The effectiveness of various additives for the chromatographic removal of tin residues

Additives	Levels of tin impurity observed in **2**[a]
Potassium fluoride	28 ppm
Potassium chloride	2–5 mol%
Sodium fluoride	> 10 mol%
Calcium fluoride	> 10 mol%
Ammonium fluoride	> 10 mol%
Rochelle salt	> 10 mol%
Potassium acetate	110 ppm
Sodium acetate	76 ppm
Sodium carbonate	> 10 mol%
Potassium carbonate	13 ppm

[a] Tin analyses were determined independently and in duplicate at the GSK laboratories in Stevenage, UK.

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† Dedicated to Professor G. Pattenden on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available: Experimental details and ^1H NMR spectra. See DOI: 10.1039/c0cc01328e

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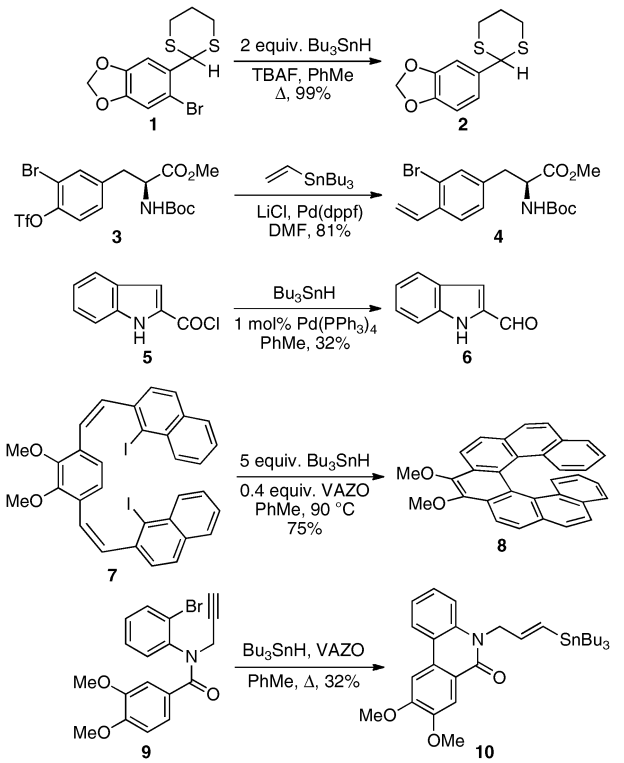


Scheme 1 Applications of the method in halide reduction, Stille coupling, Bu_3SnH-mediated radical cyclisation and hydrostannylation reactions.[9–13]

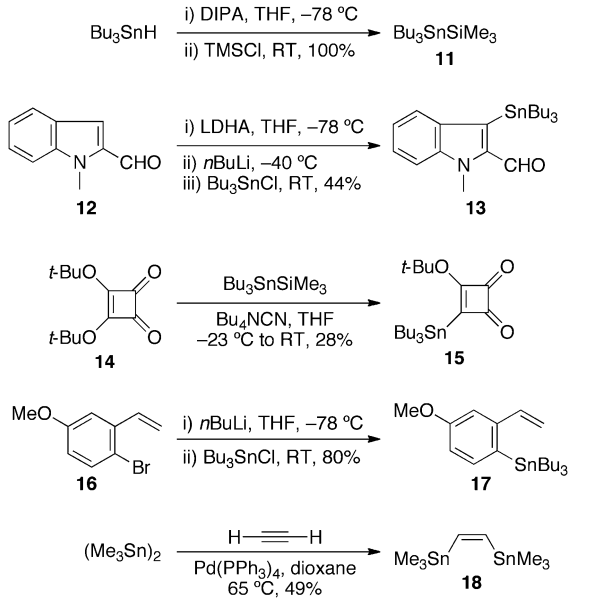
10 was amenable to chromatographic purification using K_2CO_3–silica as the stationary phase, with residual organotin compounds being eluted close to the solvent front or retained by the stationary phase. To probe this further, a series of commercial organotin reagents was subjected to chromatographic purification using the new methodology (Table 2). The study confirmed that tributyltin hydride, tetraorganyltin and hexaorganylditin compounds eluted without significant loss in mass balance while reactive tributyltin halides and tributyltin oxide were retained by the stationary phase (along with carboxylic acids and phenols).

The effectiveness of the method for the purification of organyltin compounds has been demonstrated further through application.[14–17] It has proved especially valuable with products

Table 2 The behaviour of various organotin reagents on the 10% w/w anhydrous K_2CO_3–silica stationary phase

Reagent	Outcome	% Recovery
Bu_3SnH	Eluted	100%[a]
Bu_3SnCl	Retained	0
Bu_3SnI	Retained	0
Bu_3SnOTf	Retained	0
$(Bu_3Sn)_2O$	Retained	0
$AllylSnBu_3$	Eluted	97%
$VinylSnBu_3$	Eluted	98%
$PhSnBu_3$	Eluted	97%
$(Bu_3Sn)_2$	Eluted	97%[a]

[a] Recorded on pre-purified samples. Applying the method to 'aged' reagents gave poorer mass recovery and purified samples. Full details are provided in the ESI.‡



Scheme 2 Applications involving the preparation of organyltin compounds.

that are prone to protodestannylation on silica (*e.g.* **17**[18] and **18**[17]) and in the separation of low-yield components from complex product mixtures containing high levels of organotin residues.[19]

In summary, a stationary phase composed of 10% powdered anhydrous K_2CO_3 and silica is remarkably effective for the removal of organotin impurities from product mixtures, reducing these from stoichiometric levels to ~15 ppm. The K_2CO_3–silica mixture may be stored for many months without significant loss in fluidity or activity. Purifications are best carried out on concentrated product mixtures, eliminating the need for an aqueous work-up and treatment of the associated waste-stream. The method is compatible with tetraorganyltin and hexaorganylditin compounds (Table 2 and Scheme 2), which pass through the stationary phase as distinct bands at rates similar to those observed using silica alone. Separation of these from other organic components relies on polarity differences, while reactive organotin halides and oxides are captured by the stationary phase.

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18 Compound **17** underwent rapid protodestannylation during TLC analysis and in contact with silica, but was obtained in good yield and excellent purity using the K_2CO_3 method (see ESI‡).

19 For example, compound **15** was isolated from a complex product mixture containing both starting materials and product, which were all isolated cleanly, in addition to further unidentified side-products.

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