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KF–Silica as a stationary phase for the chromatographic removal of tin residues from organic compounds†

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Through the simple expedient of using a mixture of KF and silica as the stationary phase in column chromatography, levels of organotin impurities from tributyltin hydride mediated reductions have been reduced from stoichiometric levels to ~ 30 ppm.

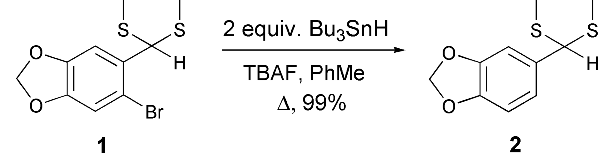
Organotin reagents have found widespread use in organic synthesis with radical processes mediated by tributyltin hydride and the Stille cross-coupling reaction being particularly significant in recent years.[1–3] However, such procedures have been beset by the perennial problem of removing organotin by-products from product mixtures. While it is generally easy to reduce levels sufficiently to pass the purity criteria of micro-analysis,[4] the high toxicity of organotin compounds necessitates removal to the parts per million level for health-care applications.[5]

Numerous strategies have been employed in an attempt to overcome the purification problems. In the sphere of radical chemistry, for example, catalytic variants have been developed wherein 10 mol% tributyltin hydride is used in conjunction with a non-toxic reducing agent to make clean-up more manageable.[6] Organotin hydrides that are more readily extracted from product mixtures have also been prepared and used,[7,8] with much attention having been paid to solid supported stannanes.[9] Others have sought to develop alternative mediators for radical reactions,[10] such as tris(trimethylsilyl)silane and tributylgermanium hydride,[11,12] though a cheap replacement giving the scope of applications offered by tin based reagents has yet to be identified.

Thus, removing organotin impurities from product mixtures remains an important goal.[13–16] In this communication we report a simple and inexpensive chromatographic procedure that has proven to be remarkably effective for the removal of organotin impurities.[17] The method employs a mixture of finely ground potassium fluoride and flash silica as a stationary phase for chromatographic purification of product mixtures containing organotin impurities.

Using the hydrodehalogenation of aryl halide **1** with the tributyltin hydride–TBAF reagent combination as a representative procedure (Scheme 1),[18] chromatographic purification of the concentrated product mixture using silica alone gave **2** contaminated with *ca*. 50 mol% of organotin impurities (as evidenced by characteristic signals for the butyl residues between δ_H 1.8 and 0.9 ppm in the ^{1}H NMR spectrum, Fig. 1a). Tin contamination was reduced significantly when the concentrated product mixture was first partitioned between acetonitrile and pentane.[13] Nonetheless, chromatographic purification of the acetonitrile extract using silica as the stationary phase gave **2** with a level of organotin impurity estimated to be in excess of 25 mol% (Fig. 1b). Our previously favoured method, pioneered by Leibner and Jacobus, involved prolonged stirring of the reaction mixture with aqueous potassium fluoride.[14] Applying this work-up procedure, together with column chromatography using silica, furnished **2** contaminated with ~5 mol% tin impurities (Fig. 1c). A second chromatographic purification gave a sample passing the 'micro-analytical purity' test, though some organotin contamination was still evident in the ^{1}H NMR spectrum.

In stark contrast to the aforementioned methods, simply concentrating the reaction mixture and eluting it with dichloromethane through a stationary phase comprising 10% w/w of finely ground KF and 90% w/w silica gave **2** in a high state of purity. Indeed, it was impossible to assess the level of organotin impurity



Scheme 1

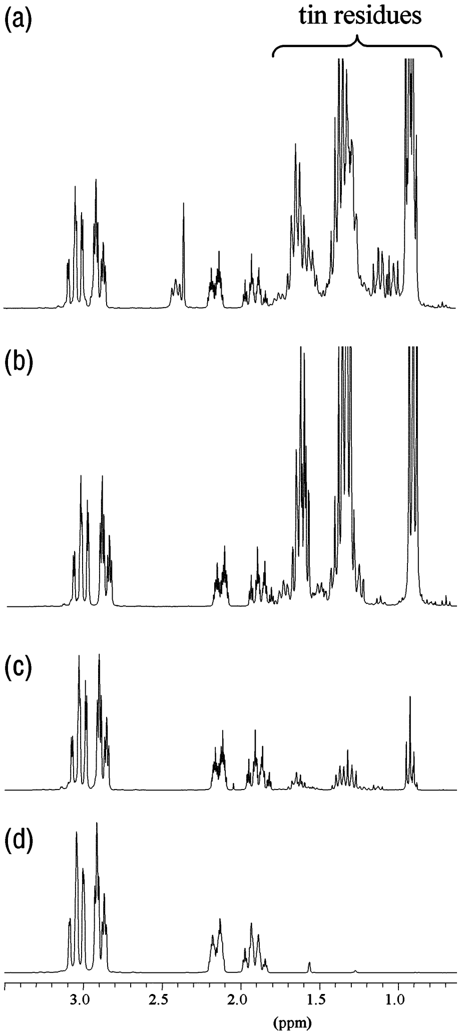


Fig. 1 ^{1}H NMR spectra of **2** following various work-up procedures: (a) after silica column, (b) after CH_3CN/pentane partition and silica column, (c) after aq. KF work-up and silica column, and (d) after KF/silica column.

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† Electronic supplementary information (ESI) available: uncropped images of the spectra presented in Figs. 1a–d. See http://www.rsc.org/suppdata/cc/b4/b406041e/

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by ^{1}H NMR (Fig. 1d). An independent elemental analysis for tin, conducted in duplicate, confirmed that the level of tin impurity had been reduced to below 30 parts per million.

This method of purification has been employed by us for a range of reductions and radical cyclisations mediated by tributyltin hydride. In each case it has proven to be highly effective for the removal of trialkyltin residues. By circumventing the need for an aqueous KF extraction (or pre-treatment of the reaction mixture with DBU),[15] the time taken to complete each experiment is significantly reduced. Management of the waste stream is also simplified as the organotin impurities are no longer split between an aqueous phase and the chromatographic stationary phase.

In summary, we have found that a stationary phase comprising 10% w/w of finely ground KF and 90% w/w silica is highly effective for the removal of organotin impurities from tributyltin hydride mediated reductions and radical cyclisation procedures. Impurity profiles of below 30 parts per million in tin have been achieved using this simple expedient, offering an inexpensive solution to a persistent problem.

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