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Stille Couplings with Fluorous Tin Reactants: Attractive Features for Preparative Organic Synthesis and Liquid-Phase Combinatorial Synthesis

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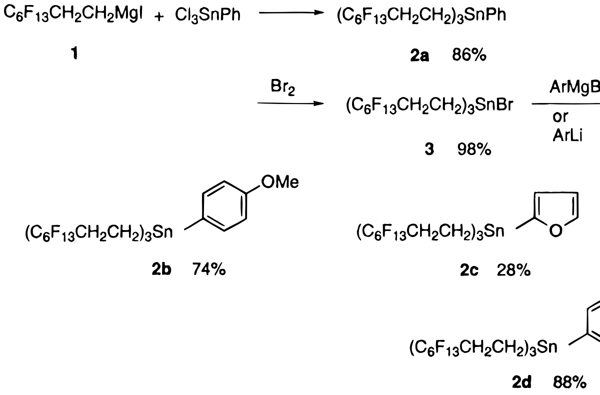
Horváth and Rabái recently introduced the concept of “fluorous biphasic reactions” by synthesizing a fluorous phosphine ligand $[P(CH_2CH_2C_6F_{13})_3]$ and showing that a rhodium complex of this ligand catalyzed hydroformylation reactions in a biphasic mixture of toluene and a liquid perfluoroalkane.[1] Simple separation of the two liquid phases sufficed to provide the organic products and the fluorous catalyst, which could be reused. We extended this concept by making a fluorous tin hydride reagent $[(C_6F_{13}CH_2CH_2)_3SnH]$ and conducting reactions in a homogeneous medium (usually benzotrifluoride, $C_6H_5CF_3$) followed by separation by two- or three-phase liquid−liquid extractions.[2] The tin compound from the fluorous liquid phase was recovered and recycled in very high yield. The fluorous strategy retains the attractive features of the organotin hydride reagent but mitigates its liabitites (toxicity, separation, disposal).

We selected the Stille reaction to probe the potential of the fluorous tin strategy for solving these problems in a different reaction class. The Stille reaction[3] is an important member of a family of transition metal-catalyzed cross-coupling reactions that is regularly used in modern organic synthesis, and it has recently been extended to solid phase combinatorial synthesis.[4] The characteristic feature of the Stille reaction is that one of the coupling partners is a trialkylorganotin compound (eq 1). The Stille reaction is popular because the tin reactants are relatively air and moisture stable, can be easily synthesized and purified, and tolerate a wide variety of both protected and unprotected functional groups. The alkyl on tin substituents are almost always methyl or butyl groups:[5] trimethyltin byproducts are easy to remove but toxic while tributyltin byproducts are less toxic but difficult to remove. Herein, we report that compounds of the general structure $ArSn(CH_2CH_2C_6F_{13})_3$ participate in representative Stille couplings to make biaryls and diarylmethanes, and that all the advantages of the fluorous strategy are exhibited. These are the first transformations with fluorous reactants,[6] and they illustrate new options for the emerging field of liquid-phase combinatorial synthesis.[7]

$$R^1\text{-}Sn(Alkyl)_3 \ + \ R^2\text{-}X \xrightarrow{Pd^0} R^1\text{-}R^2 \ + \ X\text{-}Sn(Alkyl)_3 \qquad (1)$$

R^1= sp, sp^2, allyl X = I, Br, Cl, OTf
Alkyl = Me, Bu

We have already described the preparation of fluorous tin reactant **2a**, which is an intermediate in our preparation of the fluorous tin hydride.[2a] The supporting information provides an improved procedure for the synthesis of **2a** by Grignard reaction of perfluorohexylethyl magnesium iodide (**1**) with phenyltrichlorotin (eq 2). This procedure has been used to prepare over 50 g of **2a**. Brominolysis of **2a** as previously described[2a] provided the tin bromide **3**, which served as the precursor for preparing the 4-methoxyphenyl (**2b**), 2-furyl (**2c**), and 2-pyridyl (**2d**) fluorous tin reactants by standard reactions with either aryllithium or Grignard reagents.



(2)

Stille reactions were conducted under the standard set of conditions shown in eq 3. These conditions were selected on the basis of a number of trial experiments with phenyl tin reactant **1a**. These experiments showed that lithium chloride was a beneficial additive for couplings with both triflates and halides. Equal parts of DMF/THF and DMF/$C_6H_5CF_3$ both provided homogeneous mixtures (as judged by the naked eye) and reasonable reaction rates (<22 h) at 80 °C. The DMF/THF mixture (1/1) was selected for the standard experiments.

$$\underset{\substack{1.2\ \text{equiv}\\ \mathbf{2a\text{-}d}}}{Ar^1\text{-}Sn(CH_2CH_2C_6F_{13})_3} \ + \ \underset{\substack{1\ \text{equiv}\\ \mathbf{4a\text{-}e}}}{R^2\text{-}X} \xrightarrow[\substack{LiCl\\ DMF/THF\ (1/1)\\ 80\ ^\circ C,\ 22\ h}]{2\text{mol\%}\ PdCl_2(PPh_3)_2} \underset{\substack{\text{major}\\ \mathbf{5}}}{Ar^1\text{-}R^2} \ + \ \underset{\substack{\text{minor}\\ \mathbf{6}}}{Ar^1\text{-}Ar^1} \ + \ \underset{\mathbf{7}}{Cl\text{-}Sn(CH_2CH_2C_6F_{13})_3} \qquad (3)$$

A mixture of 1.2 equiv of tin reagent (**2a**−**d**), 1 equiv of halide or triflate (**4a**−**e**, 0.2 mmol), 2 mol % $PdCl_2(PPh_3)_2$, and 3 equiv of LiCl in 1/1 DMF/THF (1 mL) was heated at 80 °C. Reactions were conducted in individual vessels in groups of five (one tin reagent with all five

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(1) (a) Horváth, I. T.; Rabái, J. *Science* **1994**, *266*, 72. (b) Horváth, I. T.; Rabái, J., U.S. Patent no. 5,463,082, 1995. (c) Hughes, R. P.; Trujillo, H. A. *Organometallics* **1996**, *15*, 286. (d) DiMagno, S. G.; Dussault, P. H.; Schultz, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 5312.

(2) (a) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531. (b) Curran, D. P. *Chemtracts-Org. Chem.* **1996**, *9*, 75.

(3) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Mitchell, T. N. *Synthesis* **1992**, 803. (c) Farina, V.; Roth, G. P. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: Greenwich, 1995; Vol. 5.

(4) (a) Deshpande, M. S. *Tetrahedron Lett.* **1994**, *35*, 5613. (b) Forman, F. W.; Sucholeiki, I. *J. Org. Chem.* **1995**, *60*, 523. (c) Plunkett, M. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 3306.

(5) Important exceptions. (a) Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556. (b) Brown, J. M.; Pearson, M.; Jastrzebski, J. T. B. H.; van Koten, G. *J. Chem. Soc., Chem. Commun.* **1992**, 1440.

(6) For the purposes of combinatorial synthesis, a “reactant” provides a variable piece to the product library.

(7) (a) Carell, T.; Wintner, E. A.; Sutherland, A. J.; Rebek, J., Jr.; Dunayevskiy, Y. M.; Vouros, P. *Chem. Biol.* **1995**, *2*, 171. (b) Han, H.; Wolfe, M. M.; Brenner, S. D.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419. (c) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539. (d) Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 2567. (e) Boger, D. L.; Tarby, C. M.; Myers, P. L.; Caporale, L. H. *J. Am. Chem. Soc.* **1996**, *118*, 2109.

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Table 1. Yields of Cross-Coupled Products 5[a]

substrate	tin reactant		
	2a (% yield)	**2b** (% yield)	**2c** (% yield)
C_6H_5I	90[b,c]	97 (10)	45[f]
p-$CH_3COC_6H_4Br$	90 (7)	87 (6)	72
p-$NO_2C_6H_4Br$	94 (9)[c]	98 (8)	93
p-$NO_2C_6H_4OTf$	82 (9)[d]	86 (8)[e]	83[e]
$PhCH_2Br$	77 (5)	98 (7)	32[f]

[a] Yields (%) of symmetrical biaryl **6** in parentheses. [b] **5** and **6** are the same (biphenyl). [c] Solvent was THF. [d] Solvent was DMF. [e] About 10% of *p*-nitrophenol was also isolated. [f] Volatile product.

partners). After 22 h, each mixture was evaporated to remove some of the solvent and then partitioned in a three-phase extraction between water (top), dichloromethane (middle), and FC-72[8] (bottom). Evaporation of the FC-72 phase provided the tin chloride **7** (($(C_6F_{13}CH_2CH_2)_3SnCl$, 80−90%),[9] which was routinely recycled (see below). Evaporation of the organic phase provided a crude organic product that was further purified by preparative TLC to provide the major cross-coupled biaryl or diarylmethane **5** along with small amounts of the symmetrical biaryl **6** derived from the tin reactant (this is a common byproduct in Stille couplings[3]).

Yields for the cross-coupled products are shown in Table 1 for tin reactants **2a**−**c**. These reactants gave very clean crude products. Isolated yields of **5** were generally high (>80%), except for a few cases with the furyl tin reactant where the products are somewhat volatile. For **2a,b** the isolated yields of the symmetrical biaryl **6** (biphenyl from **2a** and 4-methoxybiphenyl from **2b**) ranged from 5 to 10%. We believe that comparable amounts of bifuryl were formed from **2c**, but isolated yields (not shown) were much lower because this compound is volatile and unstable. The five crude products from the pyridyl tin reactant **2d** were not very clean, so these reaction mixtures were not fully purified.[10]

A preparative reaction was conducted with 400 mg of 1-bromo-4-nitrobenzene (2 mmol) and 2.97 g of phenyltin reactant **2a** (2.4 mmol) in 10 mL of 1/1 DMF/THF at 80 °C for 22 h. Both the halide and **2a** were consumed according to TLC analysis. After azeotropic evaporation with toluene at 75 °C (to remove some of the solvent), a three-phase extraction was conducted as above. The dichloromethane phase was then washed three more times with water and FC-72 (together) to remove DMF and fluorous products. The crude organic product was purified by flash chromatography to provide 337 mg (85%) of 4-nitrobiphenyl and 17 mg (5%) of biphenyl. The crude fluorous tin chloride (99% yield) from the FC-72 phase was treated with phenylmagnesium bromide to provide 2.85 g (96% overall) of the original tin reactant **2a** after purification by passing through a short column of neutral alumina.

These Stille reactions provide the first examples of transformations with fluorous reactants.[6] The ease of separation and reuse of the tin reactants are attractive features for preparative organic synthesis. The success of the Stille reaction coupled with the prior radical and ionic reactions of the analogous tin hydride[2a] suggests that rendering other tin reagents fluorous could be a general strategy to make the vast repertoire of organotin chemistry more practical and more environmentally friendly.

Although the number of parallel transformations that we report is small by today's combinatorial standards, these results have important implications for liquid-phase combinatorial synthesis. As more and more fluorous tin reactants become available, one can contemplate conducting increasing numbers of automated parallel Stille couplings (and other reactions) in the liquid phase. More generally, the use of fluorous reactants is a feature of a larger strategy for liquid phase combinatorial synthesis in which a synthesis is planned so that the phase of the products is different from the phase(s) of the other components of the mixture.[2b] The types of acid/base purifications recently reported by the group from Scripps and CombiChem[7d] constitute a complementary component of this strategy, as does the use of polymer-bound reagents.[11]

An oft-cited advantage of solid-phase synthesis over traditional liquid-phase synthesis is that the organic reactant can be used in excess. In these liquid-phase reactions, the fluorous reactant can also be used in excess and removed at the end by extraction;[12] however, in the case of the fluorous liquid-phase Stille reaction, this is neither necessary nor advantageous. The use of excess fluorous tin reactants does not increase the yield of the (desired) cross-coupled product **5**, but it does increase the yield of the (undesired) homocoupled product **6**. Indeed, even though the potential to use excess fluorous reactant exists in this strategy, the use of homogenous liquid phase reactions will frequently render this unnecessary. With respect to a solid-phase strategy for Stille couplings, the 15 examples that we report do not bear a common functional group, so the repetition of these experiments in a solid-phase approach would require the development of a suitable linking strategy. However, the solid-phase approach has a clear advantage over the fluorous approach at this point: a solid-phase synthesis would probably not require chromatographic separation of the cross-coupled product **5** from the symmetrically coupled byproduct **6**.[4] This is a general problem with the strategy reported herein: when a byproduct from the reactant is formed with concomitant detachment of the fluorous group, it will not routinely be possible to separate this product from the desired product by extraction. Strategic solutions to this general problem are in hand, and these will be reported in the near future.

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Supporting Information Available: Details on the preparation and characterization of all tin reactants, representative small- and preparative-scale experimental procedures, and copies of the ^{1}H and ^{119}Sn NMR spectra of all tin reactants (18 pages).

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(8) FC-72 is a commercially available (3M) flurocarbon liquid consisting of mostly of isomers of C_6F_{14} (bp 56 °C).

(9) Most of the residual 10−20% remained in the organic phase. If desired, this can be removed by washing with FC-72, as shown in the preparative procedure.

(10) Significant amounts of cross-coupled products (estimated 25−50%) were produced with 4-nitrophenyl triflate and bromide and with iodobenzene; however, yields of pure products were not determined. These results parallel results with normal 2-pyridyltin reagents. See: Gronowitz, S; Björk, P.; Malm, J.; Hörnfeldt, A.-B. *J. Organomet. Chem.* **1993**, *460*, 127.

(11) (a) Bergbreiter, D. E. *Chemtech* **1987**, *17*, 686. (b) Bergbreiter, D. E. *ACS Symp. Ser.* **1986**, *308*, 17.

(12) Simple extractions demonstrate that **2a** and **7** readily partition into the fluorous phase. We estimate that the partition coefficients between FC-72 and either CH_2Cl_2 or toluene are ≥97/3.