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Cocatalysis by tetravalent tin compounds in phase-transfer catalyzed fluorination of alkyl halides and sulfonates

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Abstract—Phase-transfer catalyzed fluorination of alkyl halides or sulfonates is co-catalyzed efficiently by triorganotin halides. The cocatalytic action is due to continuous formation of lipophilic hypervalent triorganodifluorostannate anions, which act as fluorinating agents in the organic phase.

Many pharmaceuticals and plant protection agents contain fluorinated substituents,[1] thus methods for introduction of this halogen into organic molecules are of great interest.[2,3] An important way to achieve this goal is nucleophilic substitution of halogen or other nucleofugal groups with F^- anions.[2–4] This reaction, although widely used, encounters serious problems connected with the insolubility of KF, the common F^- source, in the majority of solvents and also the high basicity of F^- anions, and so β-elimination is often a significant side process. Phase-transfer catalysis, PTC, a general methodology for reactions using inorganic anions,[5] is of limited use for reactions of F^- anions. Due to their low lipophilicity and high energy of hydration, the ion-exchange equilibrium governing PTC processes, is very unfavorable for transfer of F^- into the organic phase and only liquid–solid systems can be used for such reactions. The high basicity of F^- often results in the decomposition of tetraalkyl ammonium cations of the PT catalyst.[6]

These problems can be solved by the use of cocatalysts: tetravalent tin compounds such as R_3SnF for PTC fluorination of alkyl halides. It is known that $Bu_4N^+F^-$ reacts with Ph_3SnF giving a stable, crystalline salt, $Bu_4N^+Ph_3SnF_2^-$ with a hypervalent pentacoordinated anion.[7] This compound can be used as a source of F^- anions in some reactions including fluorination of haloalkanes.[8] However, the high price and high molecular weight (630.5) preclude the use of this compound in practical synthesis. We have assumed that due to the ability of R_3SnF or R_3SnCl to react with F^- and produce lipophilic hypervalent anions, they can act as cocatalysts in the PTC fluorination of haloalkanes as shown in Scheme 1.

Indeed, triphenyltin fluoride and triphenyltin chloride (the chloride, converted under the reaction conditions into fluoride, is less expensive) both exhibit substantial cocatalytic action on the PTC fluorination of the model benzyl bromide, as is shown in experiments carried out

$$Q^+X^-_{org} + R_3SnX + K^+F^-_{solid} \longrightarrow Q^+R_3SnF^-_{2\ org} + K^+X^-_{solid} \quad a$$

$$R{-}X + Q^+R_3SnF^-_{2\ org} \longrightarrow R{-}F + Q^+X^-_{org} + R_3SnF \quad b$$

$$\text{or } Q^+R_3SnF^-_{2\ org} \longrightarrow Q^+F^-_{org} + R_3SnF \quad c$$

$$R{-}X + Q^+F^-_{org} \longrightarrow R{-}F + Q^+X^-_{org} \quad d$$

Scheme 1.

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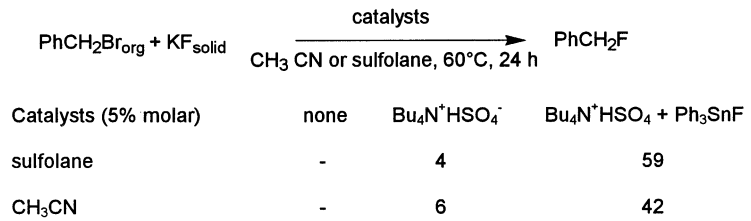
under arbitrarily chosen conditions assuring moderate conversions so that the effectiveness of various system can be compared (Scheme 2).

The process can proceed as a direct reaction of the haloalkanes with the complexed anion, Scheme 1b or via dissociation of the latter and subsequent reaction of the free F^- anions, Scheme 1c, d, which albeit in low concentration exhibit high activity. Although the thermal stability of $Bu_4N^+Ph_3SnF_2^-$ (mp 192–193°) and its ^{119}Sn and ^{19}F NMR spectra, in which signals of tetracoordinated Sn and free F^- anions are absent, suggest that dissociation does not occur, we have answered this question independently taking into account differences in the reactivity patterns of F^- and $Ph_3SnF_2^-$ anions.

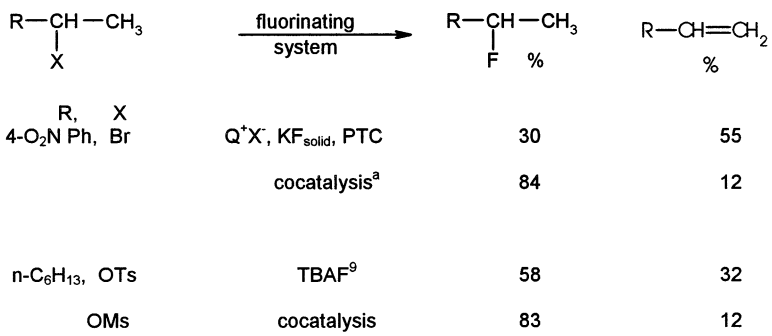
The reactions of *sec*-alkyl halides, mesylates or tosylates with the highly basic F^- anions proceed to a substantial extent as β-elimination reactions, whereas this undesired process should be less pronounced in the reactions of the much less basic $Ph_3SnF_2^-$ anions. Indeed the data in Scheme 3 indicate that the typical fluorination of 2-octyl tosylate and 1-(*p*-nitrophenyl)ethyl bromide with F^- anions is accompanied by substantial β-elimination, whereas the reaction cocatalyzed with Ph_3SnF gave mostly the expected *sec*-alkyl fluorides (Scheme 3).

The cocatalytic action of R_3SnF embraces two major steps: formation of the complex anion and its further reaction with alkylating agents, thus the effects of different R groups on both of these steps should affect the observed cocatalytic activity of R_3SnF. The activity of $R_3SnF_2^-$ as an F^- donor should be higher for electron donating substituents, they should, however, deactivate R_3SnF as a Lewis acid in the reaction with KF giving $R_3SnF_2^-$. Values of the relative rate constants of the reaction of $PhCH_2Br$ with $Bu_4N^+R_3SnF_2^-$ prepared separately are given in Scheme 4 and confirm the expected effect of R on the reactivity of $R_3SnF_2^-$.

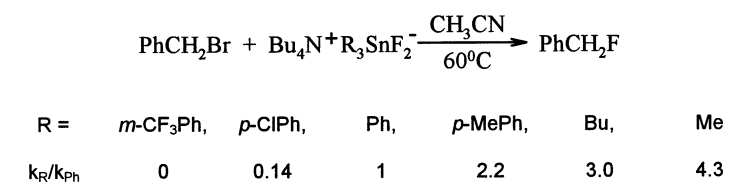
Direct measurement of the rate of formation of $R_3SnF_2^-$ as a function of R in R_3SnF in the heterogeneous reaction with solid KF cannot give reliable data. The observation that the cocatalytic activities of various R_3SnF under identical arbitrarily chosen conditions do not parallel the activities of the corresponding $R_3SnF_2^-$ in the reaction with $PhCH_2Br$ indicates that the overall cocatalytic effectiveness is a superposition of opposite effects.



Scheme 2.



Scheme 3. (a) Conditions as described for a typical experiment.[10]



Scheme 4.

The cocatalysis in PTC fluorination of alkyl halides and sulfonates is of general application, but it is particularly efficient, when, in the reaction with conventional fluorinating agents, β-elimination is a problem.

In preparative (but without optimization) experiments, high conversions and good yields of fluoroalkanes are obtained; for instance $PhCH_2F \sim 100\%$ GLC (72% isolated); $PhCOCH_2F$-94% GLC, (64% isolated); 4-$O_2NPhCHFCH_3$-84% GLC (80% isolated).[10]

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10. Freshly dried KF (8.78 g, 0.15 mol), Ph_3SnF (1.11 g, 3 mmol), $Bu_4N^+HSO_4^-$ (1.02 g, 3 mmol) and 1-(*p*-nitrophenyl)ethyl mesylate (7.38 g, 30 mmol) were stirred in acetonitrile (21 ml) at 85°C for 10 h. The reaction mixture was diluted with diethyl ether (35 ml) and treated with water (120 ml). The precipitated catalyst was removed, washed with ether (5×20 ml) and the ether extract dried. The product 1-(*p*-nitrophenylethyl fluoride, was purified by column chromatography. Yield 4.07 g (80%). ^1H and ^{19}F NMR spectra confirmed the structure and were in agreement with lit. data.[11]
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