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Hydroxymethylation of Organic Halides. Evaluation of a Catalytic System Involving a Fluorous Tin Hydride Reagent for Radical Carbonylation

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Abstract: Hydroxymethylation of organic halides **2** using a catalytic amount of fluorous tin hydride **1**, CO, and $NaBH_3CN$ as a reducing agent, proceeded smoothly to give one-carbon homologated alcohols **5** in good yields. Three phase workup (water-dichloromethane-perfluorohexane) was conveniently performed for the separation of **1** and **5**. © 1997 Elsevier Science Ltd.

Recently introduced fluorous tin hydride reagents,[1] whose reactivity is comparable to ordinary triorganotin hydride reagents, are poised to have a large impact on organotin mediated radical chemistry. Reaction systems which employ fluorous tin hydride reagents are operationally simple, since the cumbersome removal of organotin hydrides can be circumvented by simple fluorous-organic biphase extraction techniques. The objective of this work is to determine whether a fluorous tin hydride can be successfully used for free-radical carbonylations.[2] For this purpose we chose to study the hydroxymethylation of organic halides[3] using a catalytic amount of a fluorous tin hydride, a reducing reagent, and carbon monoxide.

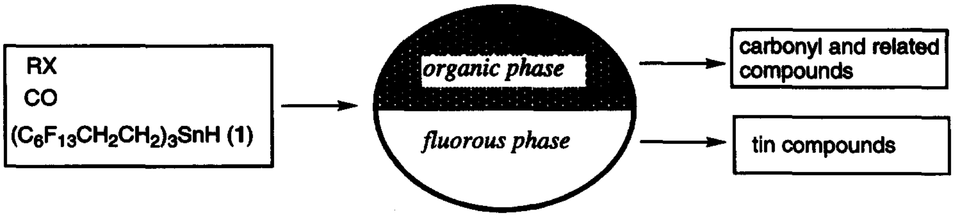


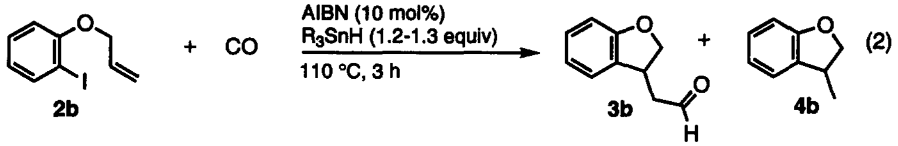
Chart 1

Tin hydride mediated radical carbonylation of organic halides[4] is dominated by several factors. Two reaction variables, CO pressure and tin hydride concentration, are frequently tuned taking into consideration the hydrogen donor ability of the tin hydride,[5] since the direct hydrogen abstraction by alkyl radicals is competing with carbonylation. We carried out the control experiments of the formylation of nonyl bromide (**2a**) to give decanal (**3a**) using tributyltin hydride and fluorous tin hydride **1** for comparison. Under identical reaction conditions, tributyltin hydride gave more formylation/reduction ratio than fluorous tin hydride (eq 1). This result strongly suggested that hydrogen donating ability of the fluorous tin hydride is higher than conventional tributyltin hydride, and higher CO pressure and/or higher dilution would be required for **1** to obtain results identical to tributyltin hydride. A similar tendency was observed for cyclization-formylation sequence of **2b** leading to **3b** (eq 2). This is quite reasonable in light of the recent kinetic study undertaken by Newcomb, Curran, and coworkers, who reported that the rate constant for primary alkyl radical trapping by the fluorous tin hydride **1** is about 2 times greater than that for tributyltin hydride at 20 °C.[6] Nevertheless, the greatly simplified liquid/liquid extraction workup is a great advantage of the fluorous system.

$$\underset{\mathbf{2a}}{n\text{-}C_9H_{19}Br} + CO \xrightarrow[80\ ^\circ C,\ 2\ h]{AIBN\ (10\ mol\%)\quad R_3SnH\ (1.2\text{-}1.3\ equiv)} \underset{\mathbf{3a}}{n\text{-}C_9H_{19}CHO} + \underset{\mathbf{4a}}{n\text{-}C_9H_{20}} \quad (1)$$

0.02 M	70 atm	Bu_3SnH/C_6H_6	84%	9%
0.02 M	80 atm	Bu_3SnH/BTF	87%	8%
0.02 M	70 atm	$(C_6F_{13}CH_2CH_2)_3SnH$/BTF	70%	21%
0.02 M	90 atm	$(C_6F_{13}CH_2CH_2)_3SnH$/BTF	82%	15%

(BTF: benzotrifluoride)

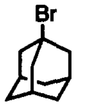
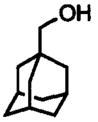
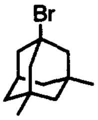
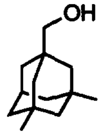
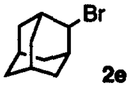
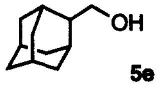
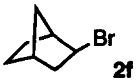
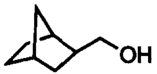
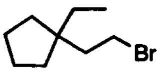
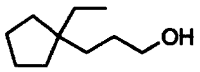
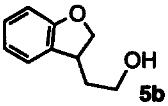


0.01 M	85 atm	Bu_3SnH/C_6H_6	71%	25%
0.01 M	85 atm	$(C_6F_{13}CH_2CH_2)_3SnH$/BTF	51%	41%

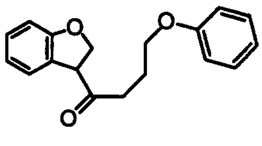
Next we carried out a catalytic procedure for the conversion of organic bromides into the corresponding hydroxymethyl compounds using a catalytic amount of fluorous tin hydride **1** and $NaBH_3CN$[7] as a reducing agent in a 1/1 mixture of BTF (benzotrifluoride)[8] and *tert*-butyl alcohol (Table 1). Thus, the treatment of 1-bromoadamantane (**2c**) with 3 mol% of **1** with 1.2 mol equiv of $NaBH_3CN$ and 10 mol% of AIBN under 80 atm of CO pressure at 90 °C for 3 h provided 81% of 1-hydroxymethyladamantane (**5c**) (entry 1). The simple three phase workup procedure which was used for catalytic "Giese type" addition[1] is applicable to this hydroxymethylation: after evaporation of the solvent, the product mixture was partitioned into three phases (water-dichloromethane-perfluorohexane), with **5c** contained within the dichloromethane layer. Removal of dichloromethane and the subsequent short silica gel chromatography gave pure hydroxymethyl product **5c**. Similarly, hydroxymethylation of secondary substrate, 2-bromoadamantane (**2e**), gave 2-hydroxymethyladamantane (**5e**) in 77% isolated yield (entry 3). The catalytic cycle for this hydroxymethylation is given in Figure 1. Hydroxymethylation of primary alkyl bromides was less efficient, despite the fact that stoichiometric formylation gave good yields of aldehydes. This is partly due to competing direct reduction of the bromides by $NaBH_3CN$[9] and partly because of the rather high hydrogen donating ability of fluorous tin hydride. For comparison, the result of tributyltin hydride is given in entry 6. Cyclization-hydroxymethylation sequence of **2b** using a catalytic system was not feasible, since the acyl radical generated by cyclization/carbonylation sequence adds to the C-C double bond of the starting substrate giving an undesirable dimerization product **6** (entry 8).[10] The low concentration of the fluorous tin hydride permits this unusual addition reaction. At this stage, the stoichiometric radical formylation/in situ reduction sequence is recommended for hydroxymethylation of this substrate. Irrespective of the process employed (catalytic or stoichiometric), three phase separation can be carried out conveniently and the fluorous tin hydride is recovered from the perfluorohexane portion.

Table 1. Catalytic Hydroxymethylation of Organic Halides with Fluorous Tin Hydride 1

$$\underset{\mathbf{2}\ (0.5\ \mathrm{M})}{\mathrm{RX}} + \mathrm{CO} + \underset{(1.2\ \mathrm{mol\ equiv})}{\mathrm{NaBH_3CN}} \xrightarrow[\mathrm{BTF}/t\text{-}\mathrm{BuOH}]{\mathbf{1}\ (2\text{-}5\ \mathrm{mol\%}),\ \mathrm{AIBN}\ (10\ \mathrm{mol\%})} \underset{\mathbf{5}}{\mathrm{RCH_2OH}}$$

entry	2	conditions	5	yield (%)[a]
1	 **2c**	1 (3 mol%) 80 atm, 90 °C, 3 h	 **5c**	81%
2	 **2d**	1 (2 mol%) 80 atm, 90 °C, 3 h	 **5d**	79%
3	 **2e**	1 (3 mol%) 80 atm, 90 °C, 3 h	 **5e**	77%
4[b]	 **2f**	1 (5 mol%) 95 atm, 90 °C, 4 h	 **5f**	58% *endo/exo* =1/9[c]
5	$n\text{-}C_{12}H_{25}Br$ **2g**	1 (2 mol%) 80 atm, 90 °C, 3 h	$n\text{-}C_{13}H_{27}OH$ **5g**	42%
6	**2g**	Bu_3SnH (5 mol%)[d] 80 atm, 90 °C, 3 h	**5g**	60%
7[b]	 **2h**	1 (5 mol%) 95 atm, 90 °C, 4 h	 **5h**	52%
8[e]	**2b**	1 (3 mol%) 80 atm, 90 °C, 3 h	 **5b**	25%

[a] Isolated yields. [b] [RBr] = 0.5 M. $NaBH_3CN$ (2.8 mol equiv). AIBN (20 mol%). [c] Determined by ^1H NMR. [d] Bu_3SnCl was used. Conducted in C_6H_6/*t*-BuOH. [e] Byproducts: **4b** (32%), **6** (10%).



6

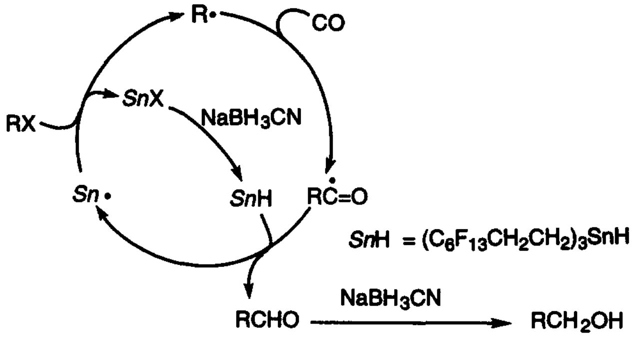


Figure 1

In summary, we have shown that fluorous tin hydride **1** can be used for free-radical carbonylation. Catalytic hydroxymethylation, in combination with $NaBH_3CN$ as a reducing agent, can be carried out and three phase workup (water-dichloromethane-perfluorohexane) is convenient for the separation of tin hydride and products. A somewhat higher hydrogen donating ability of fluorous tin hydride **1** in comparison with conventional tributyltin hydride was suggested in this study, which is in accord with the recent kinetic study. The reason for this increased reactivity is not clear at this stage and variation of the reducing power would be a necessity for developing a wide range of fluorous tin hydride reagents.

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9. Indeed, separate experiment of the reaction of 1-bromododecane to $NaBH_3CN$/t-BuOH at 80 °C gave dodecane in 10-20% yield.
10. Cf.: For easy separation of conventional tributyltin hydride via in situ reduction, see: Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200-7201.

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