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# New, Practical and Effective Sources of Fluoride Ion for Desilylation to Form Carbon Anions

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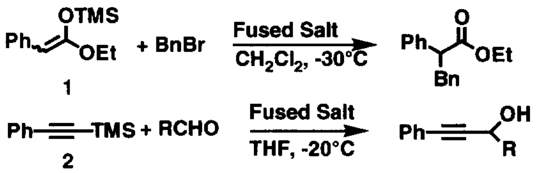
***Abstract:*** *Suspensions of powdered glassy solids prepared by fusion of 1 : 1 mixtures of CsF–CsOH and CsF–CsCl effectively catalyze the generation of enolates, acetylide and other anions from trimethylsilylated precursors.*

The fluoride ion-induced nucleophilic cleavage of trimethylsilyl derivatives of a variety of organic substrates is exceedingly useful for the deprotection of oxygen functions[1] and for the generation of carbon nucleophiles, e.g. enolates and other stabilized carbanions.[2] Tetra-*n*-butylammonium fluoride, the most commonly used fluoride ion source, is generally not satisfactory for carbanion generation because it cannot be freed of water without decomposition.[3,4] Indeed, an inexpensive soluble source of "naked" (i.e. weakly solvated) fluoride ion has been elusive.[4] Cesium fluoride, for example, does not dissolve in non-polar solvents, even in the presence of quaternary ammonium salts that are commonly used for phase-transfer type reactions. Although pure tetramethylammonium fluoride has been prepared, it also lacks solubility in non-polar solvents.[5] Extensive research on more complex structures as soluble, dry fluoride ion sources or equivalents has led to a number of novel reagents including: (1) the fluoride salt of the Schwesinger P2 cation,[6] (2) tetra-*n*-butylammonium difluorotriphenylstannate[7] and difluorotriphenylsilicate (TBAT),[8] and (3) tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF).[9] These reagents are not ideal because they are relatively expensive.[10]

In this report we describe the preparation and use of various cesium salt mixtures containing cesium fluoride as heterogeneous desilylating reagents. A series of mixtures were prepared by fusion of the components in a nickel crucible over a Bunsen burner flame using components such as cesium fluoride (mp 682 °C), cesium hydroxide (mp 272 °C), and cesium chloride (mp 645 °C) and including: (1) 10 : 1–, 1.3 : 1–, and 1 : 1–CsF–

**Scheme 1**



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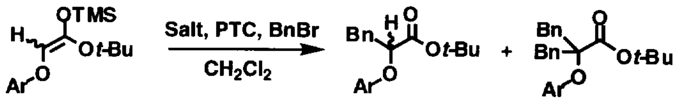
CsOH, (2) 1 : 1 : 1–CsF–CsOH–CsCl, and (3) 1 : 1–CsF–CsCl. The mixtures were obtained as glassy solids which could readily be ground to a fine powder using a mortar and pestle. The reactivity of these mixtures as desilylating agents was tested using a suspension of salt and either the trimethylsilyl ketene acetal of ethyl phenylacetate **1** or 1-trimethylsilyl-2-phenyl acetylene **2** as substrates (Scheme 1). All cesium hydroxide containing salts proved to be potent anhydrous desilylating agents, even as suspended solids, with 1 : 1–CsF–CsOH being the most reactive. 1 : 1–CsF–CsCl (mp 440 °C) displayed enhanced, but lower, reactivity.[11] The desilylation and benzylation of **1** proceeded at low temperature in dichloromethane even in the absence of a phase transfer catalyst (PTC). For additional reactions of aldehydes with **2** and other anion sources, THF proved to be the medium of choice giving increased reaction rates and higher yields. The most reactive salt mixture, 1 : 1–CsF–CsOH, was investigated further to determine the scope of its applicability with the results summarized in Table 1.[12,13]

The results demonstrate that in addition to enolates and acetylides, dithianyl, tributylstannyl and trifluoromethyl anions are readily generated using 1 : 1–CsF–CsOH. It should be noted that the products resulting from addition to aldehydes (entries 4-10) initially were isolated as mixtures of the product alcohols and the corresponding trimethylsilyl ethers, with the ether often being the major constituent. In most cases chromatography on silica gel resulted in silyl ether cleavage yielding pure alcohols; however, the cleavage of some silyl ethers required brief exposure to 1N HCl (see Table 1). This observation suggests that, in principle, only a catalytic amount of the mixed salt may be required to effect cleavage since fluoride ion is regenerated by reaction of the resulting alkoxide with TMSF. This was demonstrated experimentally by the finding that reactions went to completion even when a substoichiometric amount of salt was used (entries 5,7,8).

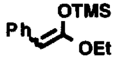
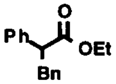
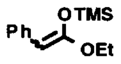
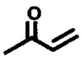
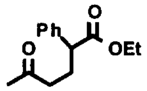
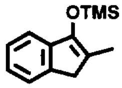
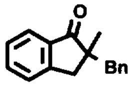
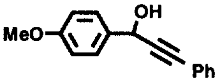
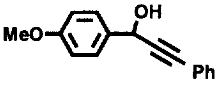
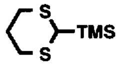
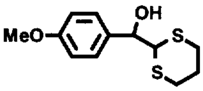
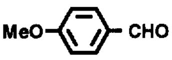
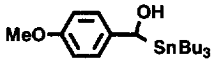
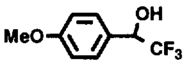
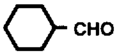
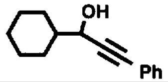
The high Brønsted basicity of 1 : 1–CsF–CsOH can sometimes present a problem as illustrated in Scheme 2. Deprotonation of the desired monoalkylated product and subsequent alkylation resulted in a predominance of the bis-alkylated product. In such cases 1 : 1–CsF–CsCl is very useful as an alternative fluoride source. Although it is less reactive as a desilylating reagent, enolate generation and alkylation still proceed at a reasonable rate while the undesired deprotonation-dialkylation reaction is largely suppressed.

**Scheme 2**



1:1–CsF–CsOH, -75 °C, 48 h: 1 : 1.3
1:1–CsF–CsCl, -55 °C, 48 h: 4 : 1

**Table 1. Reactions with suspensions of 1 : 1–CsF–CsOH.[a]**

| *Entry* | *Silane* | *Electrophile* | *Temp./Time* | *Product* | *Yield* |
|---|---|---|---|---|---|
| 1. |  | benzyl bromide | -30 °C, 3 h |  | 91% |
| 2. |  |  | -60 °C, 8 h |  | 65% |
| 3. |  | benzyl bromide | -78 °C, 24 h |  | 91% |
| 4. | Ph—≡—TMS |  | -20 °C, 6 h |  | 90% |
| 5. | Ph—≡—TMS |  | -20 °C, 8 h |  | 74% |
| 6. |  |  | 0 °C, 2 h[b] |  | 85% |
| 7. | $TMSSnBu_3$ |  | -40 °C, 3.5 h[b] |  | 79% |
| 8. | $TMSCF_3$ |  | 0 °C, 20 h |  | 86% |
| 9. |  |  | Several | - | 0% |
| 10. | Ph—≡—TMS |  | -20 °C, 8 h[b] |  | 85% |

(a) Entries 1-3: 1:1–CsF-CsOH (10 eq. $F^-$), electrophile (5 eq.), solvent: $CH_2Cl_2$, substrate concentration: 0.21 M. Entries 4,6,9,10: 1:1–CsF-CsOH (1.6 eq. $F^-$), electrophile (1.6 eq.), solvent: THF, substrate concentration: 0.76 M. Entries 5,7,8: 1:1–CsF-CsOH (0.25 eq. $F^-$), electrophile (1.6 eq.), solvent: THF, substrate concentration: 0.76 M.

(b) Brief exposure to 1N HCl was needed for complete TMS ether hydrolysis.

The mixed salts 1 : 1–CsF-CsOH and 1 : 1–CsF-CsCl are easily made, inexpensive and highly effective sources of fluoride ion in the generation of anions by desilylation of various organotrimethylsilane derivatives, with clear advantages over TASF, TBAT and similar[7-9] reagents. An additional virtue of these cesium salt mixtures is the ease of product isolation, involving simply filtration of the reaction mixture through a filter aid such as Celite and removal of solvent. Our results underscore the potentially much broader use of reactive glassy salt mixtures for other heterogeneous synthetic processes.[14]

**References and Notes:**

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9. (a) Middleton, W. J. U.S. Patent 3,940,402, 1976. (b) Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223. (TASF= tris(diethylamino)sulfonium difluorotrimethylsilicate).
10. For price comparison: CsF: \$0.66/g (Alfa); CsOH•$H_2O$: \$0.93/g (Aldrich); CsCl: \$0.46/g (Alfa); tris(dimethylamino)sulfonium difluorotrimethylsilicate: \$24.8/g (Aldrich).
11. Anhydrous CsOH alone displayed very low activity.
12. General procedure for the preparation of fused CsF–CsX salts: The salt mixture (total weight 10-15 g) were mixed in a dry, $N_2$ flushed nickel crucible. The crucible was then heated with a Bunsen burner until a clear melt had been obtained. The fused salt was allowed to cool while the crucible was flushed with $N_2$. When the salt had cooled to RT the crucible was placed in an $N_2$-filled glovebag and the salt is transferred to an oven-dried porcelain mortar and ground to a fine powder. The salt is transferred to a vial and stored in a dessicator over $P_2O_5$. The salts are generally quite hygroscopic. When used for reactions they were quickly weighed into $N_2$-filled vial and transferred to the reaction vessel where a light flamedrying was applied to remove adventitious water. The following modification applies to the preparation of CsF–CsOH salts: CsOH•$H_2O$ was melted in the crucible and heated all water had been driven off. CsF was then added gradually while the mixture was stirred with a spatula. During this process light heating was applied in such a way that gas evolution was kept to a minimum. Excessive heat causes extensive gas evolution presumably due to decomposition (CsOH + CsF → $Cs_2O$ + $H_2O$ and HF).
13. Typical procedure: 1-Trimethylsilyl-2-phenylacetylene (75 μL, 0.38 mmol) was added to 1 : 1–CsF–CsOH (181 mg, 0.6 mmol $F^-$) suspended in 0.5 mL THF at -20 °C. *p*-Anisaldehyde (68 μL, 0.6 mmol) was added and the reaction mixture was stirred rapidly under $N_2$ at -20 °C for 6 h. The salt was removed by filtration through Celite, which was subsequently washed with anhydrous ether. The solvent was evaporated *in vacuo* and the residue was purified by chromatography on silica gel eluting with ethyl acetate–hexane (1:8) yielding 81 mg of phenylethynyl-*p*-anisylmethanol. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.55 (d, $J$ = 8.7 Hz, 2H), 7.49-7.45 (m, 2H), 7.34-7.31 (m, 3H), 6.93 (d, $J$ = 8.7 Hz, 2H), 5.65 (s, 1H), 3.83 (s, 3H) ppm.

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