# Deoxyfluorination using $CuF_2$

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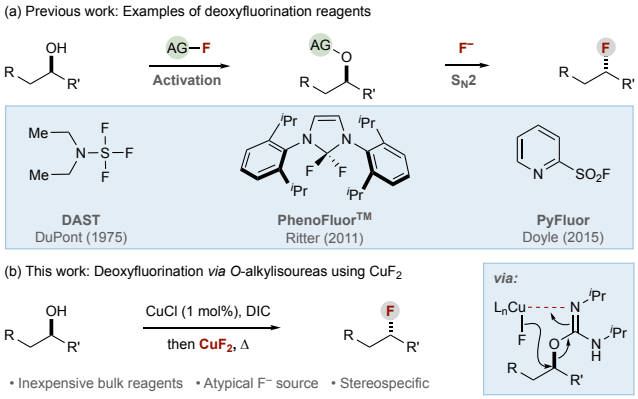
**ABSTRACT:** Deoxyfluorination is a primary method for the formation of C–F bonds. Bespoke reagents are commonly used due to issues associated with the low reactivity of metal fluorides. Here, we report the development of a simple strategy for deoxyfluorination using first-row transition metal fluorides that overcomes these limitations. Using $CuF_2$ as an exemplar, activation of an *O*-alkylisourea adduct formed *in situ* allows effective nucleophilic fluoride transfer to a range of primary and secondary alcohols. Spectroscopic investigations have been used to probe the origin of the enhanced reactivity of $CuF_2$. The utility of the process towards enabling $^{18}F$-radiolabeling is also presented.

The installation of C–F bonds is a fundamental approach towards the modulation of molecular properties within agrochemicals, pharmaceuticals, and materials.[1] Electronic effects imparted by fluorine have become integral within pharmaceutical and agrochemical development, *e.g.*, enhancing metabolic stability or for radiolabeling applications. In addition, the well-known non-covalent interactions introduced by C–F bonds (*e.g.*, the *gauche* effect),[2] provides conformational control in a variety of cyclic and acyclic systems and, in turn, exploration of molecular space through the variation in topology that this affords. Accordingly, methods for C–F bond formation are highly valuable and continue to be advanced.

Deoxyfluorination is one of the most widely used methods for conversion of alcohols to the corresponding fluorides, achieved by nucleophilic displacement of the activated alcohol by $F^-$ (Scheme 1a).[3] This suggests that cheap, readily available metal fluorides ($MF_n$) would be the ideal reagent for deoxyfluorination. However, the intrinsic properties of $MF_n$ have meant that their direct use in these processes is underdeveloped. These species are generally highly solvated, polymeric, hygroscopic, basic, have high lattice energies, and are often poorly soluble in organic solvents.[1d,3b,4] To circumvent these issues, a number of bespoke reagents have been developed for deoxyfluorination,[3,5] including diethylaminosulfur trifluoride (DAST),[5c] PhenoFluor™,[5k] and PyFluor,[5l] amongst others (Scheme 1a). These reagents offer the combined advantages of *in situ* activation of the alcohol with an activating group (AG), while simultaneously addressing the solubility and reactivity problems of fluoride by allowing use of more compatible (organic) media.

Overcoming the problems with the use of $MF_n$ salts remains a major challenge in this field. There are limited examples of the use of alkali metal fluorides (KF and CsF) for deoxyfluorination.[6] Recent seminal studies by Gouverneur demonstrated that KF and CsF can also be used for nucleophilic additions,[7a] including asymmetric ring opening of thionium and aziridinium ions.[7b,7c] Here, the poor reactivity of $F^-$ is overcome by the use of a chiral H-bonding phase transfer catalyst that facilitates $F^-$ transfer. However, the general challenges of $MF_n$ use in deoxyfluorination remain and, despite recent advances with alkali metal fluorides, readily available transition metal fluorides remain overlooked.[8] Here we show the development of a simple method for deoxyfluorination with typically unreactive transition metal (TM) fluorides, using $CuF_2$ as an example (Scheme 1b).




**Scheme 1.** (a) Deoxyfluorination using bespoke reagents. (b) This work. Deoxyfluorination using $CuF_2$. AG, activating group; DIC, *N*,*N*'-diisopropylcarbodiimide.

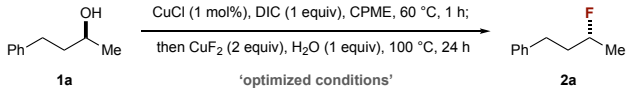
Our approach was based on the proposal that a group used for activation of an alcohol, typical of deoxyfluorination,[3,5] could be used as a coordinating group for $MF_n$. Variation of the activating group would provide a Lewis basic site that could, in principle, be tuned for coordination to a specific metal. This approach may assist in overcoming solubility and hydration issues by providing a vector for chelate-directed $F^-$ transfer, potentially offsetting the issues with $F^-$ reactivity when used in an intermolecular process.

An initial screen of TM fluorides and alcohol activating groups revealed $CuF_2$ and DIC-derived *O*-alkylisourea as a promising system for the deoxyfluorination of benchmark substrate **1a** (Table 1; see SI for full details). Optimization delivered a system where Cu(I)-catalyzed formation of *O*-alkylisourea[9] followed by deoxyfluorination using $CuF_2$ at 100 ºC gave **2a** in 78% isolated yield and with clean $S_N2$ (entry 1).[10-12]

Several optimization points are worth noting (for full optimization, see Supporting Information): (1) The reaction required formation of the *O*-alkylisourea prior to addition of $CuF_2$. Significantly reduced efficiency was observed in experiments where all reagents were combined from the outset (entry 2). (2) The addition of $H_2O$ to anhydrous $CuF_2$ was essential. Removal of $H_2O$ or use of the known (commercial) dihydrate was less effective (entries 4 and 5; *vide infra*). (3) Alternative activating groups were less effective – acetate, tosylate, methyl xanthate, trichloroacetimidate were largely ineffective (entries 6-10). (4) The urea byproduct was found to inhibit the reaction, suggesting an absence of advantageous

urea•$F^-$ H-bonding (entry 10).[7] The inhibitory effect may be related to interference with substrate-Cu(II) ligation by formation of Cu(II)•urea complexes;[13] (5) It was possible to use an exogenous fluoride (KF) with stoichiometric $Cu(OTf)_2$ (entry 11), providing utility within Positron Emission Tomography (PET) radiolabeling (*vide infra*). This process does not operate in the absence of $Cu(OTf)_2$; however, attempts to render this process catalytic in $Cu(OTf)_2$ were unsuccessful, possibly due to Cu(II) inhibition as noted above.

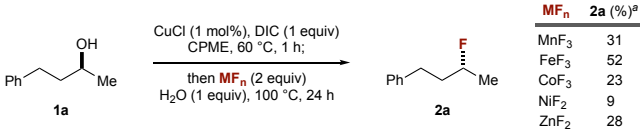
**Table 1.** Reaction development.




| Entry | Deviation from 'optimized conditions' | Yield (%)[a] |
|---|---|---|
| 1 | None | 78[b] (94% *es*)[c] |
| 2 | All reagents present from start | 21 (19)[d] |
| 3 | Second stage temperature = 80 ºC | 34 |
| 4 | No water | 22 |
| 5 | $CuF_2$•$2H_2O$ | 27 |
| 6 | Activating group = acetate | 0 |
| 7 | Activating group = tosylate | 16 |
| 8 | Activating group = methyl xanthate | 0 |
| 9 | Activating group = trichloroacetimidate | 32 |
| 10 | *N*,*N*'-diisopropylurea (1 equiv) additive | 38 |
| 11 | $Cu(OTf)_2$ (1 equiv), KF (2 equiv), 18-crown-6 (2 equiv), 110 ºC, 1 h | 57 |

Reactions performed on 1 mmol scale. [a] Determined by $^1$H NMR using an internal standard. [b] Isolated yield. [c] Determined by HPLC using a chiral stationary phase. [d] 100 ºC from start. CPME, cyclopentyl methyl ether.

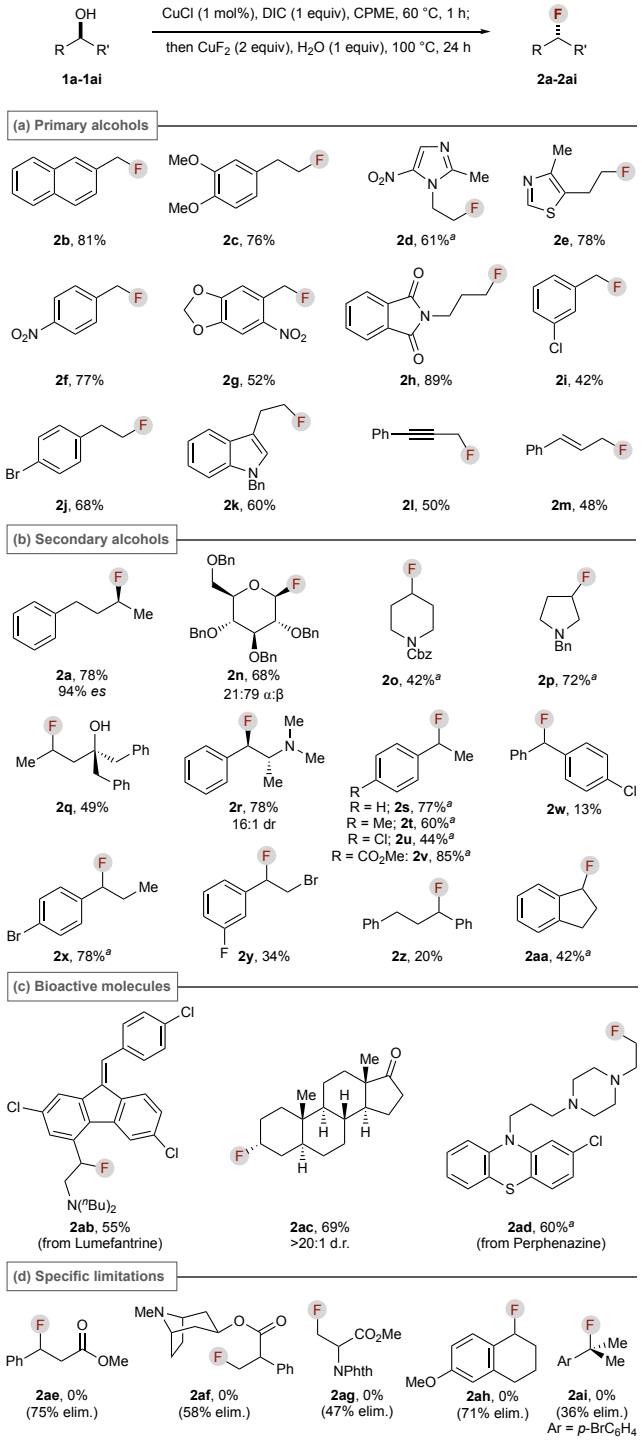
Finally, while $CuF_2$ was selected as an exemplar system, the same process allows deoxyfluorination to proceed using a range of other first row TM fluorides (*e.g.*, Scheme 2). These unoptimized results suggest the method is a viable general approach for developing deoxyfluorination protocols using these atypical fluoride sources (see SI for full details).




| $MF_n$ | 2a (%)[a] |
|---|---|
| $MnF_3$ | 31 |
| $FeF_3$ | 52 |
| $CoF_3$ | 23 |
| $NiF_2$ | 9 |
| $ZnF_2$ | 28 |

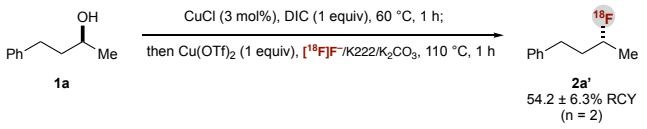
**Scheme 2.** Use of other $MF_n$ under $CuF_2$ 'optimized conditions'. Reactions performed on 1 mmol scale. [a] Determined by $^1$H NMR using an internal standard.

The generality of the optimized $CuF_2$ process was assessed by deoxyfluorination of a range of alcohol substrates (Scheme 3). Primary alcohols were broadly accommodated in good yield (Scheme 3a). A variety of common functional groups were tolerated in the presence including aryl halides, heterocycles, and amine protecting groups. The reaction was selective for $S_N2$ *vs.* potential $S_N2$' in systems where this is possible (**2l**, **2m**). Similarly, the reaction was broadly tolerant of functionalized secondary alcohols (Scheme 3b). In addition, the reaction demonstrated clean $S_N2$ with high stereospecificity observed across several substrate types, including simple alcohols (**2a**, 94% *es*) and aminoalcohols (**2r**, 16:1 dr), with good diastreoselection also displayed for exemplar sugar substrate **2n** (21:79 α:β). In addition, the reaction was selective for displacement of the *O*-alkylisourea *vs.* labile alkyl bromides (**2y**), consistent with the experimental design. Substrates more inclined to $S_N1$ pathways delivered product but in low yield (**2w**). Specific substrates were noted to undergo efficient fluorination but were prone to elimination on silica, leading to diminished isolated yield (*e.g.*, **2z**, **2aa**). The process was assessed on more complex substrates including marketed drugs, delivering the expected fluoride products in good yield (Scheme 3c). Finally, specific limitations (Scheme 3d) were observed with substrates liable to elimination (**2ae**-**2ai**).




**Scheme 3.** Example scope of the deoxyfluorination process. Isolated yields unless noted. [a] Determined by NMR using an internal standard.

As noted in Table 1 (entry 11), the deoxyfluorination can be achieved using $Cu(OTf)_2$ + KF. This enables application to PET radiolabeling by use of [$^{18}$F]fluoride. With minimal optimization (increased CuCl catalyst loading), the $^{18}$F-labelled benchmark product **2a'** was prepared in 54.2 ± 6.3% (n = 2) radiochemical yield (RCY; Scheme 4).




**Scheme 4.** Installation of $^{18}F$.

Efforts to understand the operation of the process were difficult based on the heterogeneity of the system and the stoichiometry of Cu(II), precluding *in situ* monitoring or meaningful NMR investigations. However, engagement of the *O*-alkylisourea intermediate by Cu(II) was demonstrated by EPR (see SI for full details).

In terms of the engagement/activation of $CuF_2$, we were intrigued by the results which showed a critical dependence on $H_2O$: addition of 1 equiv $H_2O$ to anhydrous $CuF_2$ was essential, with both an anhydrous reaction and use of the dihydrate significantly less effective (Table 1: entry 1 *vs.* entries 4 and 5). Accordingly, we sought to interrogate the nature of any possible active copper species generated using a combination of EPR, solid-state NMR, and powder XRD. It was not possible to directly study anhydrous $CuF_2$ + $H_2O$ due to heterogeneity within the sample; however, "aged" anhydrous $CuF_2$ (stored on benchtop under air) offered similar performance to anhydrous $CuF_2$ + 1 equiv $H_2O$. We therefore used instead the aged sample for analysis. EPR proved uninformative as a result of the lack of resolution of the hyperfine coupling (See SI). Greater insight was obtained through solid-state NMR and powder XRD. The $^1H$ MAS NMR spectra of each of the three copper samples (Figure 1) displayed distinct differences between the anhydrous and dihydrate samples. For the anhydrous sample, a featureless and low intensity signal attributing to surface hydration was obtained. In contrast, the dihydrate shows an intense signal with an isotropic shift of 45 ppm and a large paramagnetic shift anisotropy ($\Omega$ = 302 ppm, $\kappa$ = 0.0) which can be attributed to the Cu-bound $H_2O$. The $^1H$ MAS NMR spectrum of the aged sample is essentially a superposition of the spectra of the two pure phases, suggesting either a unique phase somewhere between anhydrous and dihydrate or mixture of phases.

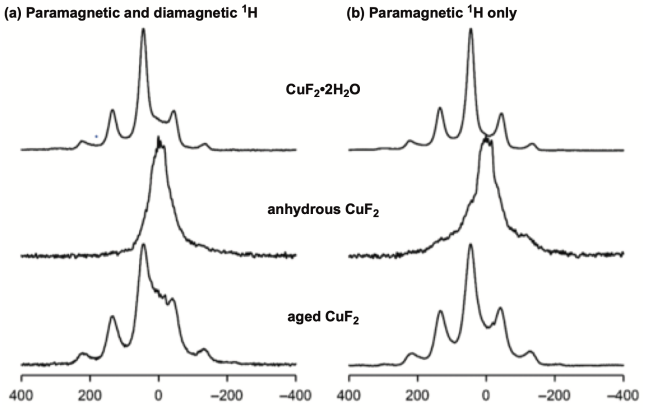



**Figure 1.** (a) $^1H$ (14. 1 T, 55 kHz MAS) NMR spectra of the three samples with a $T_1$ relaxation filter chosen to show (a) paramagnetic and diamagnetic H and (b) paramagnetic H.

Powder XRD patterns of the aged sample with both the anhydrous and dihydrate sample displayed similarities but, importantly, there are regions of significant difference. Similar to observations from $^1H$ MAS NMR, this suggests the aged sample is either a single unique phase or a mixture of phases.

In this regard, it is known that heating $CuF_2$•$2H_2O$ to the threshold temperature of 132 ºC will produce a Cu(OH)F•$CuF_2$ species with the release of HF and $H_2O$ (eqn 1).[14]

(eqn 1) $2\ CuF_2 \bullet 2H_2O \xrightarrow{132\ ^\circ C} Cu(OH)F \bullet CuF_2 + HF + 3\ H_2O$

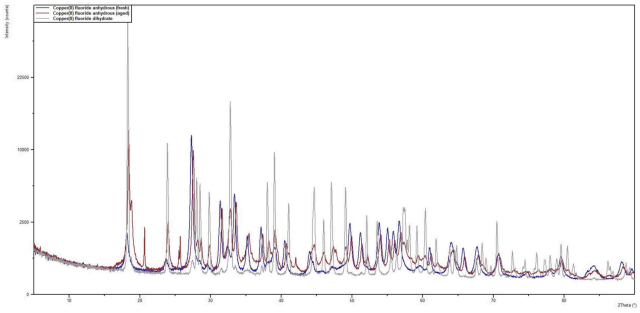


**Figure 2.** Powder XRD data showing overlay of anhydrous $CuF_2$ (a), laboratory 'in air' aged $CuF_2$ (b), and $CuF_2$•$2H_2O$ (c) samples.

It is therefore plausible that HF could be produced in small quantities in the present system, which posed the question as to whether the observed reactivity could perhaps be due to formation of HF *in situ*. A series of control reactions were therefore conducted to explore the possibility of $CuF_2$ acting as a masked HF source. Formation of the *O*-alkylisourea of **1a** using DIC as standard (Table 1, entry 1) and treatment with $Et_3N$•3HF at 100 ºC delivered the fluorinated product **2a** in 47% conversion (see SI), which, while notably lower than our optimized conditions, could suggest some involvement of HF. However, 100 ºC is insufficient to induce the formation of HF from $CuF_2$ (eqn 1).[14] In addition, no issues of acid-induced starting material or product decomposition were observed in the scope: for example, no hydration of olefins/alkynes (**2l**, **2m**), no elimination issues with diols (**2q**), and no issues over benzyl deprotection (**2n**, **2p**). Elimination issues were largely associated with substrates capable of $E_1$ or $E_1cB$, consistent with the presence of reactive $F^-$, as exemplified in Scheme 3d. It should be noted that NBoc amines did undergo deprotection, although this was also observed under thermal conditions in the absence of $CuF_2$ in control experiments (see SI). Practical observations for lack of HF generation was also obtained by a notable absence of etched glassware.[15] Attempts to use scavengers to establish HF involvement were inconclusive: addition of organic bases did not impair the reaction (neither did amine substrates **1d**, **1e**, **1p**, **1ab**, **1ad**, Scheme 3); silylated molecules were deprotected, but this cannot be separated from standard $F^-$ reactivity; and, powdered glass did diminish efficiency but this could not be separated from poor reactivity as a result of exacerbating heterogeneity.[15] Ultimately, while the generation of HF cannot be ruled out conclusively, the totality of the current data suggests that, if present, this contribution appears to be minimal.

In summary, a simple method for deoxyfluorination using first-row transition metal fluorides has been developed and exemplified using $CuF_2$. The process is based on a proposed chelate-driven fluoride transfer that effectively overcomes the reactivity issues associated with these fluoride sources. Control experiments and spectroscopic data suggest Cu(II) activation of an *O*-alkylisourea with fluoride transfer from a hydrated Cu(II)F species. The process can also be leveraged to allow $^{18}F$ installation.

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