## Mild Copper-Catalyzed Fluorination of Alkyl Triflates with Potassium Fluoride\*\*

#### Hester Dang, Melrose Mailig, and Gojko Lalic\*

Abstract: A chemoselective catalytic fluorination of alkyl triflates is described using potassium fluoride as a fluoride source. Excellent yields of the desired alkyl fluorides are obtained after one hour at 45°C using 2 mol% of the copper catalyst. With 10 mol% of the catalyst, full conversion can be achieved in less than 10 minutes at 45°C, and thus makes this procedure potentially suited for the preparation of <sup>18</sup>F-labeled PET probes. As a result of the mild reaction conditions, only the substitution products are observed with no evidence of common side reactions, such as elimination. Reported is a preliminary study of the reaction scope, which demonstrates that the fluorination can be performed in the presence of a wide range of functional groups. Evidence suggests an unusual role of the [IPrCuOTf] catalyst as a phase-transfer catalyst and points to [IPrCuF] as the active fluorinating reagent (IPr = 1,3bis(2,6-diisopropylphenyl)imidazol-2-ylidene).

he importance of organofluorine compounds in medicinal chemistry<sup>[1]</sup> and as positron emission tomography (PET) probes<sup>[2]</sup> has made the development of new fluorination reactions a major focus of research in the field of transitionmetal catalysis.<sup>[3]</sup> As a result, a number of methods for the synthesis of aryl<sup>[4]</sup> and allyl fluorides have been developed.<sup>[5]</sup> In contrast, catalytic methods for the synthesis of aliphatic fluorides are relatively underdeveloped.<sup>[6,7]</sup> In fact, the most general method for the synthesis of this class of compounds remains the nucleophilic substitution of alkyl electrophiles. Because of the low solubility of fluorides in aprotic solvents and poor nucleophilicity in protic ones, this reaction is usually performed in aprotic solvents in the presence of additives which increase the solubility of the fluoride source. Numerous stoichiometric additives have been used to promote the phase transfer, including tBuOH,<sup>[8]</sup> ionic liquids,<sup>[9]</sup> crown ethers,<sup>[10]</sup> and tetrabutyl ammonium salts.<sup>[11]</sup> Early studies of tetrabutyl ammonium salts indicated that catalyst poisoning with common anions, such as bromides and iodides, is the major obstacle for the development of catalytic phase-transfer agents for nucleophilic fluorination.<sup>[11,12]</sup>

In addition to the fundamental challenge of developing an additive that can catalytically facilitate phase transfer of fluoride ions, there is also a practical need for a catalyst which would promote the reaction at lower temperature and with a greater selectivity. The most commonly used phase-transfer agent, crown ether Kryptofix-222,<sup>[10]</sup> allows fast fluorination of alkyl electrophiles with KF as a fluoride source, and makes it uniquely suited for the synthesis of PET probes.<sup>[10,13]</sup> Unfortunately, the high reactivity is observed only at high temperatures (often > 110 °C). Furthermore, harsh reaction conditions, together with the basicity of the fluoride anion<sup>[14]</sup> lead to significant side reactions, such as elimination, even with simple primary alkyl electrophiles.<sup>[15]</sup> Herein, we describe a new approach to a nucleophilic fluorination reaction using transition-metal complexes as phase-transfer catalysts and transition-metal fluorides as fluorinating reagents [Eq. (1)].

$$R - X + KF_{(s)} \xrightarrow{phase-transfer catalyst} R - F + KX_{(s)} (1)$$

Nucleophilic properties of late-transition-metal fluorides, and their stoichiometric reactions with various electrophiles have been known since the early reports by the groups of Bergman and Richmond.<sup>[16]</sup> However, two problems have prevented the development of practical fluorination reactions based on these early findings. One problem is that in most cases fluorination of alkyl electrophiles with metal fluorides occurs only at high temperature and usually leads to the formation of a significant amount of elimination products. For example, a significant amount of elimination products has recently been observed in reactions of alkyl electrophiles with a copper fluoride diamino complex, performed for over 15 h at 110°C in MeCN.<sup>[17]</sup> The second problem is that the formation of metal fluoride complexes is difficult to accomplish under catalytic conditions. Again, a good example is the formation of copper fluoride diamino complex, which was accomplished by protonation of a copper alkoxide precursor using  $(HF)_3 \cdot NEt_3$  as a fluoride source.

We chose to address both problems using [IPrCuF] (see Table 1 for structure of IPr ligand) as a fluorinating reagent. [IPrCuF] is soluble in organic solvents,<sup>[18]</sup> and we reasoned that the sigma-donating ability of NHC ligands will contribute to the nucleophilicity of the copper fluoride. Based on the idea outlined in Equation (1) we explored the ability of various [IPrCu] complexes to form [IPrCuF] in a reaction with KF, and in such a way effectively function as a phasetransfer catalyst. Not surprisingly, we found that with most copper precursors an insignificant amount of [IPrCuF] was formed in common organic solvents. However, [IPrCuOTf]

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(Tf = trifluoromethanesulfonyl) reacts with KF in dichloromethane to give 12 % of [IPrCuF] after several hours at 45 °C. Subsequently, an extensive solvent screen revealed that 1,4dioxane is uniquely effective as a solvent for this reaction, and allows formation of [IPrCuF] in 88% yield in less than 10 minutes at 45 °C [Equation (2)].

[IPrCuOTf] + KF <u>45 °C, 10 min</u> [IPrCuF] (2) <u>88% yield</u>

Based on this discovery, we were able to develop a catalytic fluorination of alkyl triflates using [IPrCuOTf] as a phase-transfer catalyst. Under the standard reaction conditions, in the presence of just 2 mol% of the [IPrCuOTf] catalyst, the alkyl fluoride **2** is formed in excellent yield after less than an hour at 45 °C (Table 1). Importantly, we did not



[a] KF was dried for 5 min prior to use (see the Supporting Information for details). [b] GC yields are reported. [c] The electrophile remained unchanged. [d] 95% yield after 3 h with 10 mol% catalyst. [e] After 12 h. THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

observe the formation of even a trace amount of the elimination product or any other byproducts. We believe that the low basicity of a [IPrCuF], relatively low reaction temperature, and the low solubility of KF in 1,4-dioxane, are responsible for the absence of side reactions.

Table 1 summarizes the observations we made during the development of the reaction. A simple control experiment confirms that the copper catalyst is necessary for the formation of the alkyl fluoride (entry 1). Similarly, the use of alkyl triflates as electrophiles was necessary, and other common electrophiles could not be used in the reaction. Several NHC copper complexes also catalyzed the reaction,

albeit at a lower rate than that of [IPrCuOTf] (entries 4 and 5). In agreement with our initial observations about the formation of [IPrCuF], we also observed that very little product is formed in other common organic solvents (entries 6–8) We also found that while drying KF for 5 minutes is sufficient, KF which has not been dried could not be successfully used in the reaction (entry 9). Finally, a catalyst loading of just 0.2 mol% is sufficient to accomplish full conversion of the alkyl triflate within 16 hours. In contrast, with 10 mol% of the catalyst complete conversion is achieved in less than 10 minutes at 45°C.

By using the fluorination reaction described in Table 1, we explored the fluorination of a wide range of primary alcohols using the two-step procedure shown in Table 2. Although the





[a] Yield of the isolated alkyl fluoride is based on the alkyl triflate. Yields within parentheses are based on the alcohol. [b] Reaction was completed in 10 min using 10 mol% of the catalyst. [c] Used 10 mol% of [IMeCuCl] as a catalyst, at 100 °C. [d] Yield determined by NMR spectroscopy because of the volatility of the product.

fluorination of alcohols requires two steps, we found that the overall transformation is efficient. The reaction is compatible with esters, nitriles, protected alcohols, nitroarenes, iodoarenes, alkenes, ethers, imides, and alkyl bromides and tosylates. This level of chemoselectivity has not been documented in other methods for the synthesis of alkyl fluorides. The

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fluorination can also be accomplished in the presence of a stereocenter bearing an acidic proton, as demonstrated by the synthesis of a single enantiomer of 13. Interestingly, we found that the stereocenter in 13 epimerizes in the presence of TBAF (see the Supporting Information). The products 3, 4, and **16**, are particularly interesting, as their <sup>18</sup>F analogues are common prosthetic groups<sup>[19]</sup> used in convergent synthesis<sup>[20]</sup> of PET probes. These <sup>18</sup>F-labeled electrophiles are often used in the synthesis of radiolabeled tertiary alkyl amines<sup>[21]</sup> and other complex probes for which nucleophilic precursors are easier to prepare.<sup>[13a]</sup> We have also prepared 18 from the corresponding triflate in excellent yield after 10 minutes with 10 mol% of the catalyst. The only reported synthesis of the <sup>18</sup>F-labeled cholesterol-derived probe 20 was previously accomplished in 4% yield, by nucleophilic fluorination of the tosylate precursor performed at 165°C for 10 minutes.<sup>[22]</sup> We have also discovered that secondary alkyl triflates can be converted into secondary alkyl fluorides (Table 1, compound 18) in excellent yield and without formation of the elimination product. The use of a copper catalyst supported by a smaller NHC ligand was essential for the success of this reaction.

It is important to note that the only products observed in the reactions reported in Table 2 were alkyl fluorides, and that we found no signs of elimination or other side reactions as commonly observed in reactions performed using other fluorination procedures. This observation was true even for substrates which are particularly prone to elimination, such as those used to prepare fluorides **17** and **19**.

After the exploration of the reaction scope we turned our attention to the mechanism of the reaction and the role that the copper catalyst plays in the fluorination reaction. Considering the low solubility of KF in organic solvents,<sup>[23]</sup> and the initial finding that [IPrCuF] can be formed from KF and [IPrCuOTf], we speculated that the fluorination reaction involves the formation of [IPrCuF] from [IPrCuOTf] and KF, followed by the fluorination of alkyl triflate by the [IPrCuF] (Scheme 1).<sup>[17]</sup> According to this proposal, the copper catalyst



*Scheme 1.* Proposed mechanism of the catalytic fluorination.

functions as a phase-transfer catalyst which provides a soluble and nucleophilic source of fluoride from the rather insoluble KF. Considering that we have already demonstrated the feasibility of the formation of [IPrCuF] under the reaction conditions [Equation (2)] we explored its reactivity in the presence of alkyl triflates. We found that in a stoichiometric reaction, alkyl fluoride is formed quantitatively in less than 10 minutes at 45 °C [Equation (3)], which confirms the

$$[IPrCuF] + \underbrace{1,4-dioxane}_{45 °C, 5 min} \underbrace{45 °C, 5 min}_{94\% yield} F (3)$$

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feasibility of the proposed catalytic cycle. Using the deuterium-labeled substrate **22**, we found that the reaction proceeds with inversion of configuration [Equation (4)].<sup>[24]</sup>



Consistent with the mechanism shown in Scheme 1 is also the observation that the rate of the reaction depends on the rate at which the reaction mixture is stirred.<sup>[25]</sup> Without stirring of the reaction mixture, only a trace amount of the fluorination product is formed after 12 minutes. With vigorous stirring (1500 rpm), about 40% of the product is formed after the same period of time. The difference in the rates of fluorination is also noticeable for stir rates of 250 and 1500 rpm. While it remains unclear whether the formation of [IPrCuF] occurs on the surface of solid KF or in solution, these experiments indicate that the phase transfer is a part of the rate law and contributes to the overall rate of the reaction.

In conclusion, we have developed an efficient coppercatalyzed fluorination of alkyl triflates with KF as a fluoride source. With as little as 10 mol% of the cooper catalyst the reaction can be accomplished within 10 minutes at 45 °C. The fluorination reaction is compatible with a wide range of functional groups including alkyl tosylates and alkyl bromides. Finally, we have described the preliminary study of the reaction mechanism which provides insight into the role of the copper catalyst and shows that transition-metal complexes can be used as efficient phase-transfer catalysts.

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- [24] See the Supporting Information for details of stereochemistry assignment. Attempts to prepare enantioenriched version of the product 18 did not allow us to rigorously establish the stereochemistry of the fluorination reaction.
- [25] See the Supporting Information for details.

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Mild Copper-Catalyzed Fluorination of Alkyl Triflates with Potassium Fluoride

[IPrCuOTf] (2 mol %) R-OTf + KF<sub>(s)</sub> R-F 1,4-dioxane, 45 °C 1 h

excellent yields of the desired alkyl fluo-

a fluoride source in the presence of the

copper catalyst [IPrCuOTf]. This proce-

rides by using potassium fluoride as

>80% yield (20 examples)

dure is potentially suited for the preparation of <sup>18</sup>F-labeled PET probes. IPr = 1,3bis (2,6-diisopropylphenyl) imidazol-2-ylidene, Tf=trifluoromethanesulfonyl.

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