Fluorination

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Site-Selective Tertiary Alkyl–Fluorine Bond Formation from α-Bromoamides Using a Copper/CsF Catalyst System

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Abstract: *A copper-catalyzed site-selective fluorination of α-bromoamides possessing multiple reaction sites, such as primary and secondary alkyl–Br bonds, using inexpensive CsF is reported. Tertiary alkyl–F bonds, which are very difficult to synthesize, can be formed by this fluorination reaction with the aid of an amide group. Control experiments revealed that in situ generated CuF_2 is a key fluorinating reagent that reacts with the tertiary alkyl radicals generated by the reaction between an α-bromocarbonyl compound and a copper(I) salt.*

Nucleophilic fluorination reactions using fluorides are one of the most important methods of forming C–F bonds from carbon electrophiles, such as those with C–halogen bonds.[1] Although the synthesis of aryl fluorides has been studied extensively,[2] studies on the development of alkyl fluoride synthesis are rare.[3] The Finkelstein reaction is one of the conventional choices for synthesizing primary and secondary alkyl fluorides by nucleophilic substitution, in which an alkali fluoride[1] MF (M = Li, Na, K, Rb, Cs) reacts with alkyl bromide, iodide, or tosylate. However, this reaction is not attractive for the synthesis of fluorinated fine chemicals because a Finkelstein reaction involving an alkali fluoride is very sensitive to water, as the fluorides have a strong tendency to form hydrogen bonds with water molecules to decrease the nucleophilicity of the fluoride ions. Therefore, researchers have focused on the development of new nucleophilic and electrophilic fluorinating reagents, such as Selectfluor, NFSI, DAST, PyFluor, Phenofluor, Deoxo-Fluor, XtalFluor, and Fluolead.[4] These fluorinating reagents are very useful and reactive, but they are also much more expensive than alkali fluorides, and their cost might suppress further development in fluorination chemistry for industrial purposes.

Other problems facing researchers in fluorination chemistry include 1) site selectivity in the fluorination reaction of a substrate possessing more than two active reaction sites and 2) fluorination of tertiary alkyl groups with a cheap F source (Figure 1 a). Recent progress in this field has been achieved by Ritter and co-workers, who reported a very interesting site-selective deoxyfluorination of aliphatic alcohols using PhenoFluor as an electrophilic fluorinating reagent.[5] However, the site-selective fluorination of alkyl substrates possessing primary, secondary, and tertiary alkyl–X bonds (X = halogen, OH, boron, or another leaving group) remains a highly challenging issue in fluorination chemistry.[1,6–8] In this context, we aim to achieve the copper-catalyzed site-selective fluorination of tertiary alkyl bromides using CsF as a low-cost fluorinating reagent (Figure 1 b).

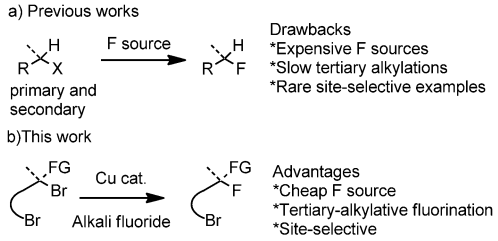
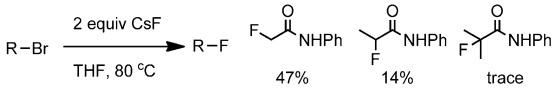


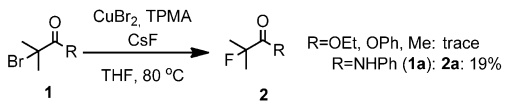
Figure 1. Previous reports and the current study.

The Finkelstein reaction is very useful for obtaining C–F bonds, but tertiary alkyl–F bond formation is very difficult. For example, primary and secondary alkyl–F bonds formed in the presence of CsF in yields of 47 and 14 %, respectively,[9] but tertiary alkyl–F bonds did not form (Scheme 1).



Scheme 1. Finkelstein reaction. THF = tetrahydrofuran.

Our first trial of the fluorination reaction employed α-bromoisobutyryl carbonyl compounds (**1**) as model compounds (Scheme 2). It is well known that the reaction of a copper salt with **1** gives alkyl radical species by atom transfer radical addition,[10] atom transfer radical polymerization,[11] and our previous tertiary alkylations of styrenes.[12] There have been a few examples of radical fluorination reactions,[13–15] but the site selectivity of radical fluorination reactions has not been examined. In the presence of copper(I)/tris(2-pyridylmethyl)amine (TPMA) or 1,10-phenanthroline (Phen) and CsF, the desired fluorinated product **2** was not obtained when using either an ester or a ketone, most likely because electron-deficient radicals are not reactive toward a fluorination source.[7a,13,14] However, the amide **1a** underwent the corresponding fluorination reaction to produce **2a** in 19 % yield. We speculated that an amide group affects the



Scheme 2. Fluorination of various carbonyl compounds.

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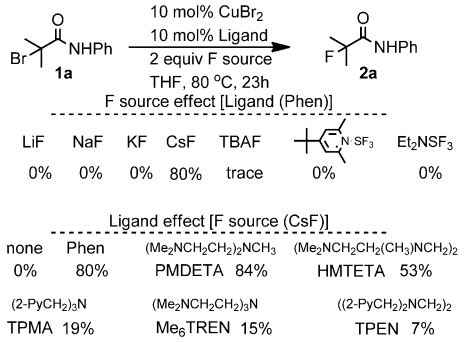
fluorination step with an active fluorination species, such as CuF_2. Recently, Loh reported copper-catalyzed amide-directed trifluoromethylation with Togni's reagent.[16] By controlling the acidity of the amide moiety as a directing group, they obtained stereoselective C–CF_3 bonds. Similarly, we expect that the nitrogen atom of the amide group plays an important role in our fluorination reaction.

Based on our preliminary results, optimization studies were conducted using the combination of 2-bromo-2-methyl-*N*-phenylpropanamide (**1a**; 1 equiv) and a fluorination reagent (1 equiv) in the presence of $CuBr_2$ (10 mol%) and Phen (10 mol%) in THF under nitrogen atmosphere (Scheme 3). We suspected that the Finkelstein reaction

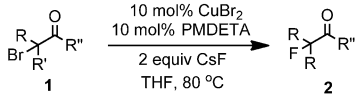


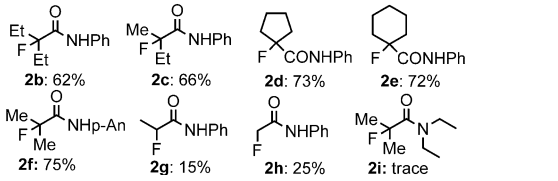
Scheme 3. Optimization. Conducted at 80 °C for 23 h in THF with 10 mol% Cu salt, 10 mol% ligand, F source (2 equiv), and **1a** (1 equiv). Yields are those of the isolated products.

would proceed under our reaction conditions. We observed that the addition of the copper catalyst was crucial for obtaining the desired fluorinated compound **2a** and the addition of 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT) suppressed the reaction. This result is one bit of evidence showing that the current fluorination reaction involves a radical reaction rather than a nucleophilic reaction. The choice of the fluorination reagent is very important, and use of the alkali fluoride CsF resulted in an 80% yield of **2a**. Other alkali fluorides, including LiF, NaF, and KF, were not effective, most likely because of their solubility. We also examined various nucleophilic and electrophilic organic fluorination reagents, such as tetra-*n*-butylammonium fluoride (TBAF), but the reactions were sluggish. $CuBr_2$ was used in this optimization, but other copper salts, including various copper(I) and copper(II) salts, were not effective. Although a copper(I) species is required to obtain an alkyl radical intermediate,[10–12] copper(II) may give a copper(I) and copper(III) species.[17] In this reaction, a nitrogen ligand is also important for obtaining **2**. Our investigation of reactions with or without nitrogen ligands revealed that *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDETA), which possesses three nitrogen atoms, provided the highest yields.

Before attempting site-selective fluorination of alkyl bromides containing two or more reactive bonds, we the examined monobrominated substrates **1** to assess their basic reactivities under our optimized reaction conditions (Table 1). The sterically hindered substrates, which led to

Table 1: Fluorination of **1** under optimized reaction conditions.[a]



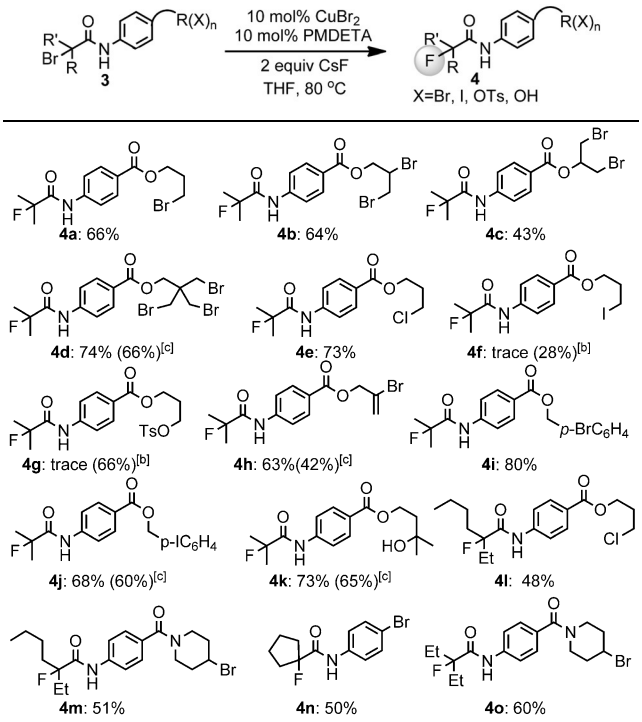


[a] Conducted at 80 °C for 23 h in THF with 10 mol% $CuBr_2$, 10 mol% PMDETA, CsF (2 equiv), and **1** (1 equiv). Yields are those of isolated products.

2b–**e**, underwent smooth fluorination in good yields, whereas the less hindered substrates, which led to **2g** and **2h,** provided low yields because primary and secondary alkyl radicals are less stable than tertiary alkyl radicals. In this case, **2g** and **2h** are considered to form by an S_N2 reaction.[9] The *p*-anisyl-substituted substrate gave **2f** in good yield, thus illustrating that substrates with tertiary alkyl–Br bonds and N-aryl-substituted amides reacted smoothly with CsF in the presence of a copper catalyst. In contrast, N-alkyl-substituted tertiary amides, such as the substrate leading to **2i**, were not reactive.

We next evaluated functional-group compatibilities for current fluorination using the α-bromoamides **3**, which possess either a primary or secondary alkyl–X or aryl–X bonds (X = Cl, Br, I, OH, OTs) as a model compound (Table 2).[18] The reactivities of alkyl halides in the fluorination reaction generally followed the order primary carbon center > secondary carbon center ≫ tertiary carbon center, according to the S_N2 reaction rule. In particular, nonfunctionalized primary and secondary alkyl halides and tosylates are good substrates for S_N2 nucleophilic fluorination reactions.[3,6] Therefore, selective fluorination of tertiary alkyl substrates containing more than one reactive site is challenging. However, our reaction system discriminated between different reactive alkyl–X bonds and produced the corresponding single-fluorinated product **4** in good yields. In the fluorination of alkyl halides, alkene formation by an E2 reaction is problematic,[6d] but no alkenes were formed under our reaction conditions. In each reaction, the selectivity was perfect. The only challenge was the generation of the proto-debromination products of **3**, as they hindered the separation of **4**. For example, substrates possessing primary or secondary alkyl halide moieties (**3a**–**e**) underwent fluorination only at the tertiary alkyl–Br to produce the desired products (**4a**–**e**) in moderate to good yields. Although C(sp^2)–Br and C(sp^2)–I bonds are also good reaction sites for catalytic fluorination,[2,19] the substrates **3h**–**j** underwent fluorination without loss of the C(sp^2)–Br and C(sp^2)–I bonds (**4h**–**j**). The substrate **3k**, which possesses a tertiary alkyl–OH, is a good substrate for electrophilic fluorination,[5] and the OH group did not affect the reaction. The limitation of our reaction system was observed in the reactions of **3f** and **3g**, which possess iodide and tosyl group moieties, respectively. Both the fluorination of the tertiary alkyl–Br bond and the bromina-

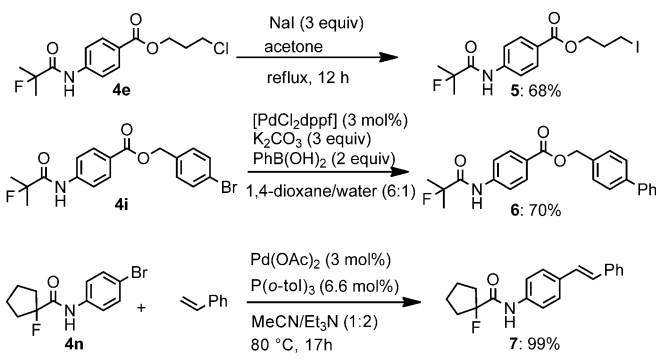
Table 2: Site-selective fluorination tests with model compounds **3**.[a]



[a] Conducted at 80 °C for 23 h in THF with 10 mol% $CuBr_2$, 10 mol% PMDETA, CsF (2 equiv), and **1** (1 equiv). Yields were determined by ^{1}H NMR spectroscopy and GPC. [b] Yield of fluorobrominated product. [c] Yield of product isolated after flash column chromatography.

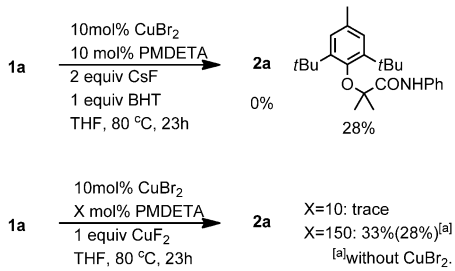
tion of C–I and C–OTs bonds with in situ generated CsBr proceeded to form the fluorobrominated product in 28 and 66% yields, respectively. We next examined multibrominated substrates possessing various carbon functionalities on the carbonyl α-position (**3l–o**). As demonstrated in the reaction described above, sterically hindered substrates with tertiary alkyl–Br bonds also selectively allowed the fluorination reaction to afford the corresponding products (**4l–o**) in moderate to good yields.

The obtained fluorinated products **4**, possessing various active functional groups, were easily converted into a wide range of derivatives using conventional organic reactions (Scheme 4). The compound **4e** reacted with NaI to produce **5** in 68% yield, whereas **4i** and **4n**, possessing C(sp^2)–Br bonds, underwent Suzuki and Heck coupling reactions to produce the corresponding arylated and 1-alkenylated products, respectively (**6** and **7**). These results show that our fluorination reaction is a powerful technique for synthesizing fluorinated building blocks.



Scheme 4. Utilities of the fluorinated building blocks. DMF = *N*,*N*-dimethylformamide, dppf = 1,1′-bis-(diphenylphosphino)ferrocene.

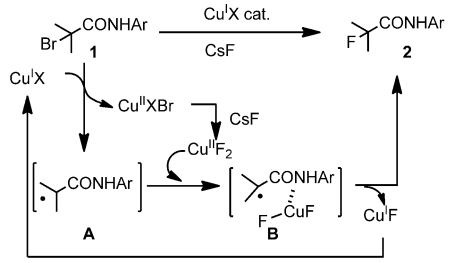
We next conducted the following control experiments (Scheme 5: 1) A radical capture test with BHT: The fluorination reaction was inhibited by the addition of BHT, and indicated that this reaction may involve a radical species.



Scheme 5. Control experiments. [a] Yields were determined by ^{1}H NMR analysis.

Indeed, we detected alkylated BHT species in the reaction of **1a** with BHT. 2) Copper fluoride effect: A stoichiometric amount of CuF_2 was used instead of CsF as the fluorination reagent in the fluorination reaction of **1a**. The product **2a** was not obtained when 10 mol% PMDETA was used, but it was obtained in 33% yield when 150 mol% PMDETA was used. Excess PMDETA is required to generate an active catalyst, namely, the copper(I)/PMDETA complex, which is very important for generating alkyl radicals from **1a**.[10,11] When 10 mol% PMDETA was used, no reaction occurred because most of the PMDETA ligated to the copper(II) species rather than to the copper(I) species. The fluorination reaction of **1a** with CuF_2 also occurred in the absence of $CuBr_2$ catalyst (28%). Although copper(I) species are required to generate alkyl radical species from **1a**, CuF_2 may generate active copper(I) species with concomitant formation of copper(III).[17] The reaction of α-bromoester in the presence of a stoichiometric amount of CuF_2 and the reaction with the tertiary amide **1** (Table 1; **2i**) did not give the desired product, likely reflecting that the amide group may act as a directing group. The importance of the amide NH is also supported by the reaction leading to **2i**. Since it is difficult to coordinate the tertiary amide group to copper species, NH is required.[16]

From the above results, the catalytic cycle of our copper-catalyzed fluorination reaction includes, at least, 1) a radical generation step and 2) a fluorination step involving the alkyl radical species generated from **1** and CuF_2 (Scheme 6). In the first step, the reaction of a copper salt with **1** gives the alkyl radical species **A**. The resulting alkyl radical species react with CuF_2, which is generated from the reaction of CuXBr and CsF, with the aid of an amide group (**B**). Then, the desired product **2** is obtained with concomitant formation of a copper(I) species to complete the catalytic cycle. This cycle would be a new copper-catalyzed site-selective radical fluorination reaction.



Scheme 6. Proposed mechanism.

In summary, we have developed the first copper-catalyzed site-selective fluorination of α-bromocarbonyl compounds with the aid of amide coordination to synthesize functionalized 3°tertiary alkyl fluorides in the presence of inexpensive CsF as a fluorination reagent. Moreover, control experiments revealed that this catalytic cycle includes radical species and CuF_2 as an active fluorinating reagent. Because the obtained products have C–halogen bonds which can be easily converted into other functional groups by couplings and nucleophilic reactions, the present fluorination methodology is very attractive for synthesizing fluorinated building blocks.

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