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Copper-Mediated Nucleophilic Fluorination for Preparing Alkyl Fluorides

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Introduction

The introduction of fluorine into an organic molecule is a reaction of great interest in both industrial and academic researches [1–5]. Despite the significant achievements made in the synthesis of aryl fluorides, there are only a limited number of examples of alkyl fluoride synthesis. These include nucleophilic [6] or electrophilic [7] substitution reactions or radical fluorination [8, 9]. Among them, the nucleophilic substitution of alkyl sulfonates and halides with fluoride ions appeared as a powerful strategy to generate alkyl fluorides [10, 11], but remains challenging. The difficulty arises from the weak nucleophilicity in protic solvent or the low solubility in aprotic solvents of fluoride ions (such as KF or CsF). To overcome these difficulties, a variety of metal fluorides such as KF/18-crown-6 [12], "spray-dried" KF [13], polymer-supported fluoride [14] and calcium fluoride supported on alkali metal fluoride [15], and tetraalkylammonium fluorides [16] were employed as reagents which are not solvated tightly by bulky cations or solvent molecules that facilitate efficient conversion. Despite these advances for the synthesis of simple alkyl fluorides, significant limitations remain with respect to elimination of alkyl halides, the formation of alkyl sulfonates to alkenes, and the hydroxylation to alcohols, which result from the use of basic and nucleophilic "naked" fluoride [16].

Therefore, there is a continued strong demand for efficient and selective syntheses of alkyl fluorides. In recent years, transition-metal-mediated nucleophilic fluorination has been recognized as an increasingly viable tool for the preparation of functionalized alkyl fluorides under mild reaction conditions [17–19]. Among them, methods that use copper-mediated nucleophilic fluorination have drawn much attention. The low cost, low toxicity, and easy availability of copper salts have made them an attractive target as catalysts for performing fluorination reactions.

Copper(I) Fluoride Complex-Mediated Nucleophilic Fluorination

In 2013, Weng and co-workers reported the diimine-ligated copper(I) fluoride complex-mediated nucleophilic fluorination [20]. Complexes $(Me_2phen)_2Cu(FHF)$ (**1**) and (*t*-Bu_2Phen)Cu(F) (**2**) (Me_2phen, neocuproine; *t*-Bu_2Phen, 2,9-Di-*tert*-butyl-l,l0-phenanthroline) were prepared from the reaction of CuO*t*-Bu with the

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phenanthroline ligand and $(HF)_3{\cdot}NEt_3$ in THF at rt (Scheme 1).

The ionic complex **1** contained one cationic tetrahedral copper center and one anionic $[HF_2]^-$, in which the fluorine atoms were not directly bonded with the Cu(I) center (Fig. 1). Complex **2** possessed a trigonal planar geometry and one fluoride coordinated to the copper atom.

A comparison of fluorinating reagent in fluorination of 3-phenylpropyl bromide was summarized in Table 1. When complex **1** was used as reagent for fluorination in CH_3CN at 110 °C for 15 h, the yield of (3-fluoropropyl)benzene was excellent (entry 1), while complex **2**, KF, and Bu_4NF gave the desired products in low yields (entries 2–4). The $(HF)_3{\cdot}NEt_3$ alone was found to be completely ineffective under this reaction condition (entry 5).

By using $(Me_2phen)_2Cu(FHF)$ (**1**) as reagent, a variety of alkyl fluorides were obtained through fluorination of alkyl bromides and benzyl bromides (Table 2). The reaction tolerated a number of functional groups, such as phenoxide, benzyl ether, thioether, amide, nitrile, hydroxyl, and ester groups. Complex substrate, such as vitamin E derivative, was also fluorinated by **1** in up to excellent yield.

Unactivated secondary alkyl bromides could also be employed in this reaction, and a wide range of substitution patterns were tolerated with good yields (Table 3).

It was demonstrated that reaction of 6-bromohexan-1-ol with **1** in the presence of a radical scavenger, cyclohexa-1,4-diene (CHD), afforded 6-fluorohexan-1-ol in 65% yield (Scheme 2). Moreover, fluorination of 6-bromo-1-hexene with **1** furnished 6-fluoro-1-hexene as the only product in 99% yield. The lack of any influence on the reactivity with the addition of radical scavenger and the absence of cyclization product provided evidence against a radical intermediate.

Further experiments on the stereochemistry of the reaction with an enantiopure secondary tosylate were also investigated. Reaction of (2*S*,4*R*)-1-tert-butyl 2-methyl 4-(tosyloxy) pyrrolidine-1,2-dicarboxylate, prepared from the corresponding chiral secondary alcohol, with **1** gave the desired product (2*S*,4*S*)-1-tert-butyl 2-methyl 4-fluoropyrrolidine-1,2-dicarboxylate in 85% yield with complete inversion of configuration (Scheme 3). Based on these observations, the authors suggested that the fluorination occurs through an S_N2-type displacement of the bromide leaving group with the copper fluoride reagent.

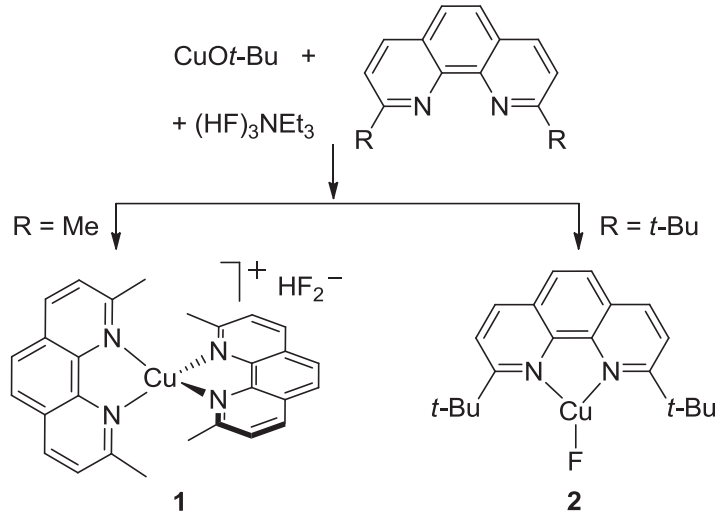
Copper-Catalyzed Fluorination of Alkyl Triflates

In 2014, Lalic and co-workers reported the synthesis of alkyl fluorides from alkyl triflates by a copper-catalyzed fluorination with KF as a fluoride source [21]. The authors performed the fluorination by using a copper catalyst [IPrCuOTf] at 45 °C in dioxane. A number of alkyl triflate derivatives were used as substrates, and the corresponding monofluorinated products were obtained with yields ranging from 81% to 98% (Table 4).

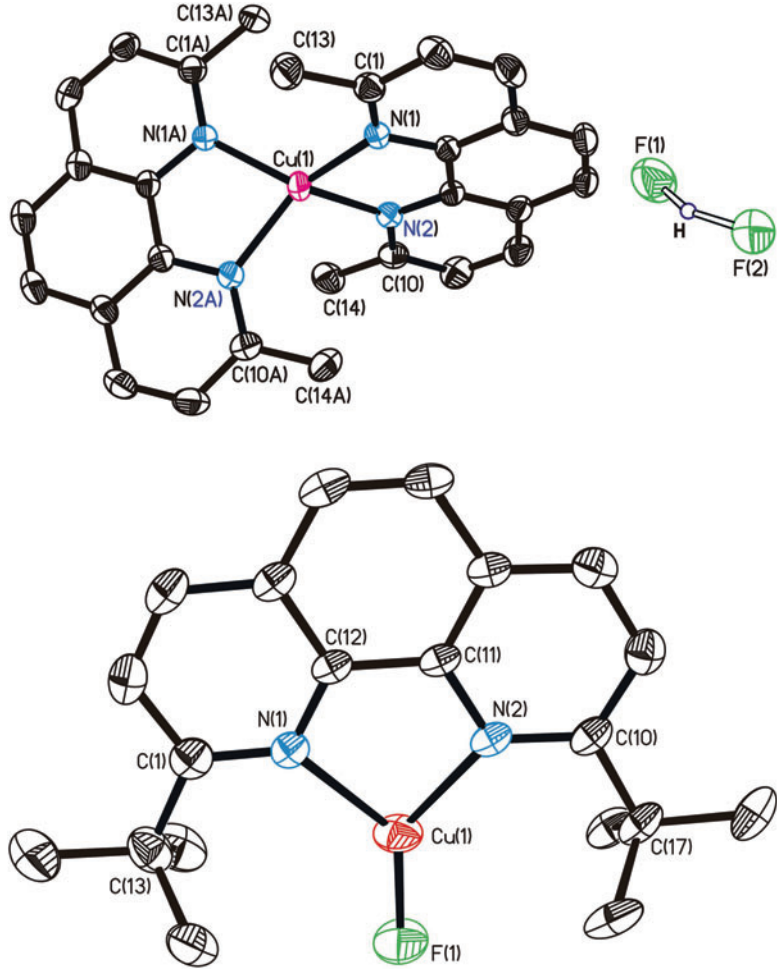
Based on the experimental results, a copper-catalyzed fluorination of alkyl triflates was proposed (Scheme 4). Initially, reaction of [IPrCuOTf] with KF would form [IPrCuF]. Subsequently, fluorination of alkyl triflate by the resulting [IPrCuF] furnished the desired alkyl fluoride and regenerated [IPrCuOTf]. In the presence of KF, the copper species acted as phase-transfer catalyst which provided a soluble and nucleophilic source of fluoride for fluorination.

Copper-Catalyzed Fluorination of α-Bromoamides

In 2016, Nishikata and co-workers developed a copper-catalyzed site-selective fluorination of α-bromoamides using CsF as an active fluorinating reagent [22]. The reaction was optimized with $CuBr_2$ as the catalyst and *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDETA) as nitrogen ligand. It was demonstrated that the fluorination of tertiary alkyl substrates containing more than one reactive site produced the corresponding tertiary alkyl fluorides in good yields (Table 5). However, the use of substrates

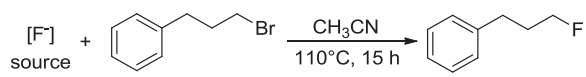


Copper-Mediated Nucleophilic Fluorination for Preparing Alkyl Fluorides, Scheme 1 Synthesis of copper (I) fluoride complexes **1** and **2**



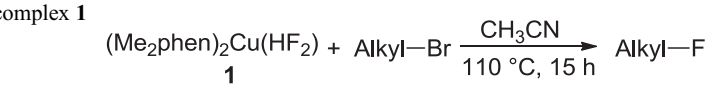
Copper-Mediated Nucleophilic Fluorination for Preparing Alkyl Fluorides, Fig. 1 Crystal structures of **1** (*top*) and **2** (*bottom*)

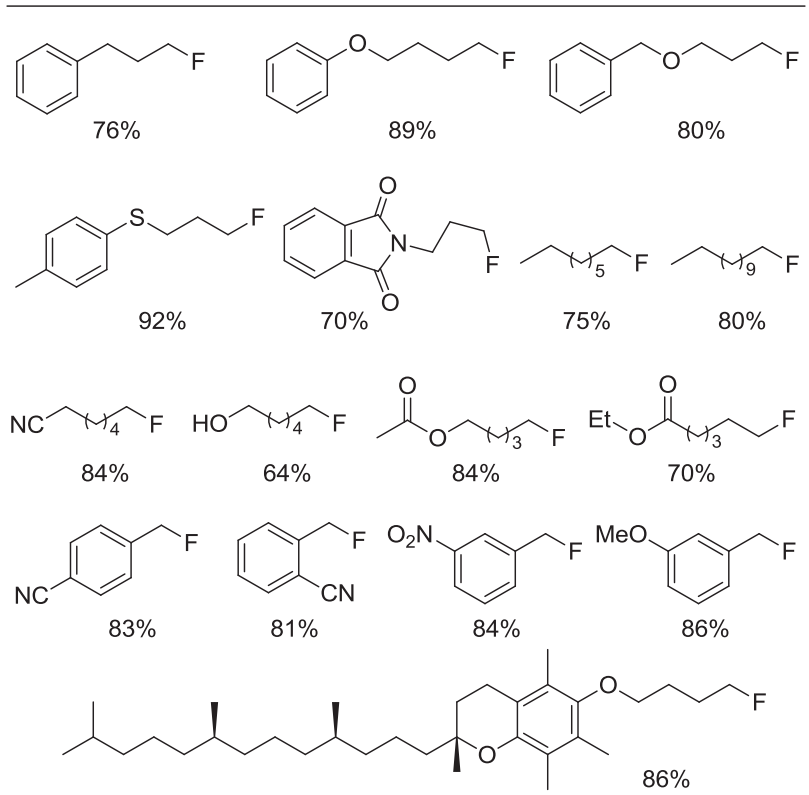
Copper-Mediated Nucleophilic Fluorination for Preparing Alkyl Fluorides, Table 1 Comparison of fluorinating reagent in fluorination of 3-phenylpropyl bromide



Entry	[F⁻] Source	^{19}F Yield (%)
1	Complex **1**	92
2	Complex **2**	21
3	KF	6
4	Bu_4NF	27
5	$(HF)_3{\cdot}NEt_3$	0

Copper-Mediated Nucleophilic Fluorination for Preparing Alkyl Fluorides, Table 2 Fluorination of alkyl bromides by complex **1**

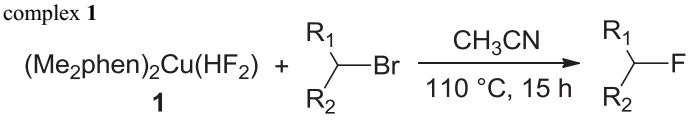


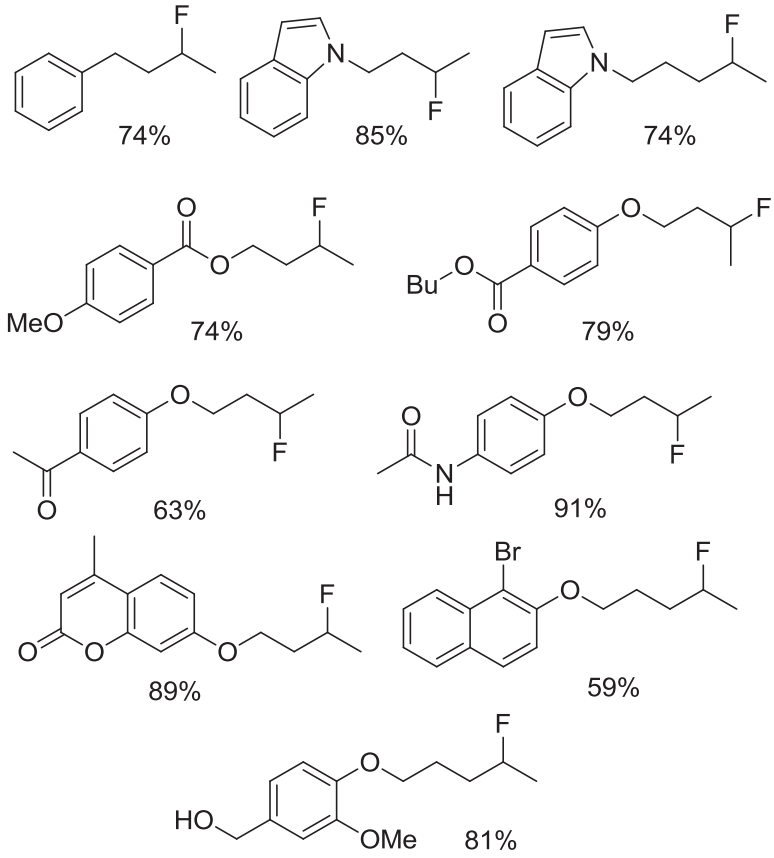


having iodide and tosyl group moieties forms the fluorobrominated products.

The authors presented a plausible mechanism for the copper-catalyzed site-selective fluorination of α-bromoamides involving a radical reaction (Scheme 5). Initially, the copper salt abstracted a bromide atom from α-bromoamide, and the alkyl radical species **A** was therefore generated. The

Copper-Mediated Nucleophilic Fluorination for Preparing Alkyl Fluorides, Table 3 Fluorination of secondary alkyl bromides by complex **1**

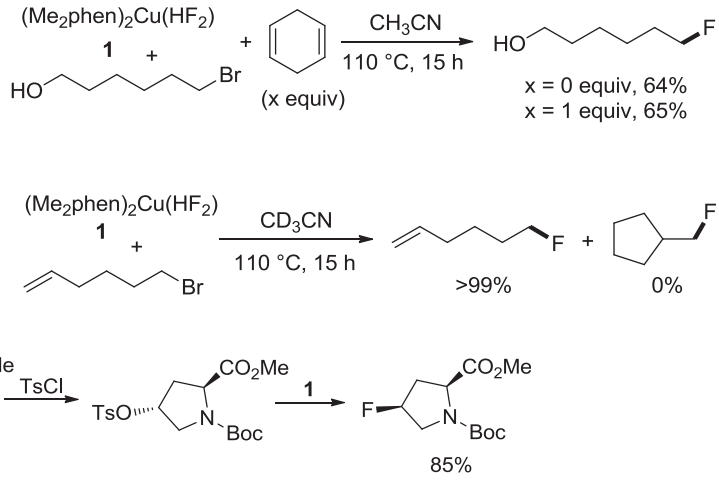




reaction of **A** with CuF_2, which was generated from the reaction of CuXBr and CsF, led to the intermediate **B**. Finally, **B** underwent reductive elimination to give the desired alkyl fluorides.

Conclusion and Future Directions

In summary, the section described above illustrated the copper-mediated nucleophilic fluorination for synthesizing alkyl fluorides. Different

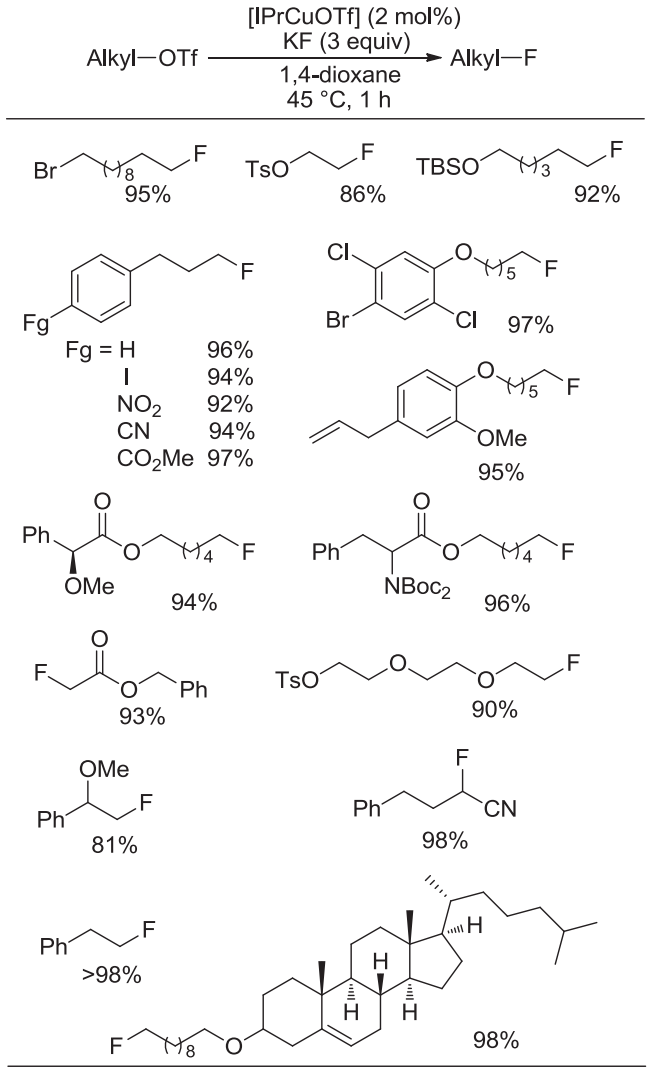


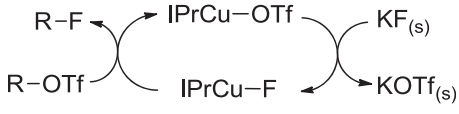
Copper-Mediated Nucleophilic Fluorination for Preparing Alkyl Fluorides, Scheme 2 Radical trapping experiments

Copper-Mediated Nucleophilic Fluorination for Preparing Alkyl Fluorides, Scheme 3 Inversion of configuration experiments

types of alkyl bromides, α-bromoamides, and alkyl triflates have been successfully applied to such transformations, providing a facile and economic access to a variety of alkyl fluoride compounds. Although impressive results have been achieved in this field, more research advances regarding new catalyst development, the use of inexpensive metal fluoride as fluorine source, and detailed mechanistic investigations are still very important in order to address the remaining challenges. The expected progress will enable copper-mediated nucleophilic fluorination to be a more general and viable methodology for preparing alkyl fluorides in the near future.

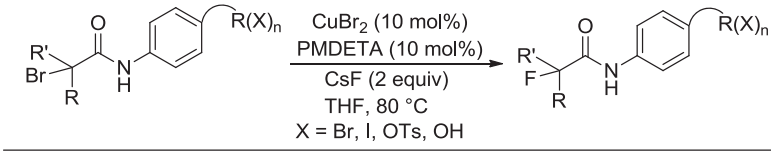
Copper-Mediated Nucleophilic Fluorination for Preparing Alkyl Fluorides, Table 4 Copper-catalyzed fluorination of alkyl triflates

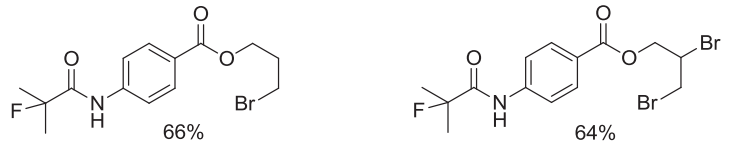


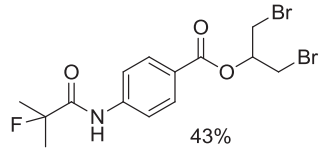


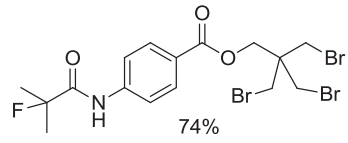
Copper-Mediated Nucleophilic Fluorination for Preparing Alkyl Fluorides, Scheme 4 Proposed mechanism for copper-catalyzed fluorination of alkyl triflates

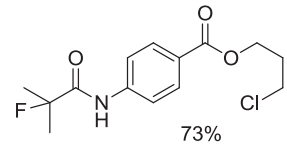
Copper-Mediated Nucleophilic Fluorination for Preparing Alkyl Fluorides, Table 5 Copper-catalyzed site-selective fluorination of α-bromoamides

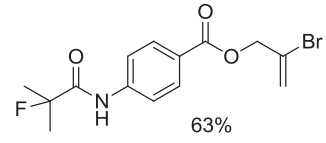


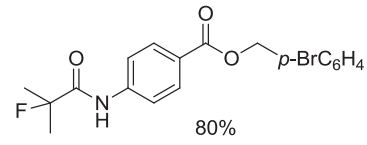


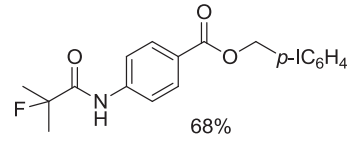


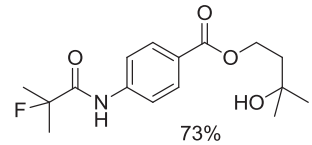


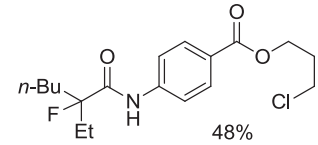


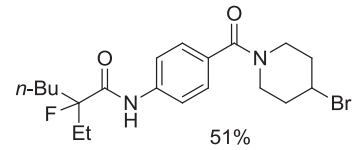


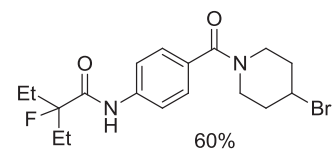


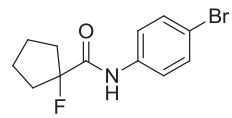


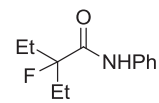


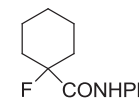


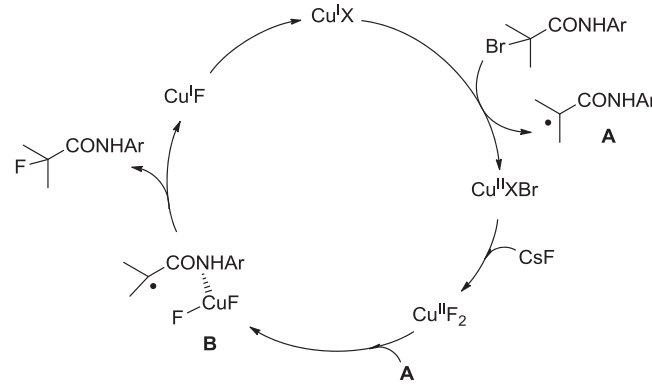












Copper-Mediated Nucleophilic Fluorination for Preparing Alkyl Fluorides, Scheme 5 Proposed mechanism for copper-catalyzed site-selective fluorination of α-bromoamides

Cross-References

- ▶ Electrochemical Fluorination for Preparation of Alkyl Fluorides
- ▶ Fluorination of Alkenes and Alkynes for Preparing Alkyl Fluorides
- ▶ N-Fluoropyridinium Salts Radical Fluorination for Preparing Alkyl Fluorides

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