

# Highly Reactive and Regenerable Fluorinating Agent for Oxidative Fluorination of Aromatics

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## Abstract:

A newly synthesized copper aluminum fluoride of nominal composition  $\text{CuAl}_2\text{F}_8$  exhibits excellent reactivity towards direct oxidative fluorination of aromatic compounds, as well as fluoro-dechlorination of chloroaromatics. The spent  $\text{CuAl}_2\text{F}_8$  reagent can be regenerated by treatment with  $\text{O}_2$  and HF, and the fluorination process has been demonstrated to retain high conversions through 20 reaction cycles. The main advantages of this new process are safety, minimal waste, and potentially low cost.

## Introduction

Fluorinated aromatic compounds are valuable synthetic intermediates for the preparation of pharmaceutical drugs, agrochemicals, and polymers.<sup>1</sup> However, for all practical purposes, the only way that fluorine is currently incorporated into a benzene ring commercially is the Balz–Schiemann reaction and related processes involving diazonium ion chemistry<sup>2,3</sup> or under special circumstances by halogen exchange of aromatic chlorine by fluorine.<sup>4</sup> The diazonium processes exhibit poor atom economy and generate considerable waste. In the current study, we have sought to identify and explore new, low-cost, and environmentally benign processes for replacing aromatic hydrogen with fluorine.

There are already a number of fluorinating agents known that will either electrophilically or oxidatively replace aromatic hydrogen with fluorine,<sup>5–8</sup> although few of them are effective in converting relatively unreactive benzene to fluorobenzene. These include reagents such as  $\text{XeF}_2$ ,<sup>6,9,10</sup>  $\text{CF}_3\text{OF}$ ,<sup>7,11</sup>  $\text{CH}_3\text{CO}_2\text{F}$ ,<sup>7,12</sup>

$\text{CsSO}_4\text{F}$ ,<sup>7,13</sup> various  $\text{N-F}$ ,<sup>8,14,15</sup> and  $\text{N}^+-\text{F}$  compounds,<sup>8,16,17</sup> as well as elemental  $\text{F}_2$  itself.<sup>5</sup> However, with most of these compounds requiring  $\text{F}_2$  for synthesis, they are all relatively expensive, generally highly toxic, and often dangerous to use, thus effectively precluding their use in commercial manufacture of fluoroaromatics.

Alternatively, fluorides of transition metals have been examined as fluorinating agents. Organic compounds, including aromatic systems, have been oxidatively fluorinated using metal fluorides such as  $\text{CoF}_3$ ,  $\text{KCoF}_4$ ,  $\text{AgF}_2$ ,  $\text{CeF}_4$ , and  $\text{MnF}_3$ .<sup>18–21</sup> Unfortunately such reagents have not been found to be useful for introducing only one or two fluorines into benzene or other aromatics, generally acting to exhaustively fluorinate compounds, with the result that saturated polyfluoro or perfluoro compounds are usually obtained. Moreover, they require expensive elemental  $\text{F}_2$  to prepare or regenerate. Therefore, the discovery of a transition metal fluoride reagent that is powerful enough to fluorinate but not so reactive as to destroy an aromatic system and that can be regenerated without the need for  $\text{F}_2$  is a noteworthy event.

In general, the relative fluorinating activities of transition metal fluorides are directly related to their respective redox potentials. For example, the fluorides of metal ions that have  $E^\circ > 1$  comprise the potent group of fluorinating agents mentioned above that give rise to exhaustive fluorination. In contrast, fluorides of the metal ions with  $E^\circ < 0$ , such as  $\text{ZnF}_2$ ,  $\text{MgF}_2$ , and  $\text{AlF}_3$ , are inert towards aromatic hydrocarbons. On the other hand, fluorides of metal ions with  $1 > E^\circ > 0$ , such as  $\text{CuF}_2$ ,  $\text{AgF}$ ,  $\text{HgF}_2$ , and  $\text{Hg}_2\text{F}_2$ , can act as mild fluorinating agents. In principle, all of these fluorides can be reoxidized and the fluorides regenerated by sequential or simultaneous treatment with  $\text{O}_2$  and HF. Among these reagents, copper(II) fluoride appeared to have the greatest potential with respect to fluorinating benzene, as was demonstrated recently by Subramanian and

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Manzer.<sup>22</sup> However, only modest yields of fluorobenzene were obtained when benzene was exposed to pure CuF<sub>2</sub> in the gas phase at 500 °C.<sup>23</sup>

In subsequent work on the use of CuF<sub>2</sub>, which was a continuation of the work reported by Subramanian and Manzer, the fluorination of aromatics was examined using a physical mixture of commercial fluorides, CuF<sub>2</sub> with AlF<sub>3</sub>, MgF<sub>2</sub>, or CaF<sub>2</sub>. Although significantly increased yields were observed (~48%),<sup>24</sup> regeneration, in particular *multiple* regeneration of the spent reagents, could not be effectively accomplished. Both oxidation of Cu to CuO at 350 °C and conversion of the oxide to CuF<sub>2</sub> by treatment by anhydrous HF at 400 °C are known, and such processes are dependent upon particle size.<sup>25</sup>

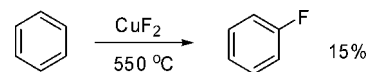
Typically commercial metal fluorides have a tendency to form regular crystallites as a result of their high lattice energies. Therefore, upon thermal treatment, metal fluoride surface areas are on the order of 10–60 m<sup>2</sup>/g, comparable to aluminum fluorides. The fluorination ability of CuF<sub>2</sub> depends significantly upon its surface area and the resistance of Cu to sintering under high temperature reaction conditions. Normally commercial metal fluorides are treated at high temperature and possess thermally stabilized structures. Also, mechanical mixing of commercial fluorides coupled with high temperature treatment may lead to loss of fluorine content. In contrast, one can consider the Tanabe model<sup>26</sup> for binary metal fluoride systems, where acid generation is caused by an excess of a positive or negative charge in the model structure of a binary fluoride. According to this model, when a divalent metal ion (guest) is doped with a trivalent metal ion (host), Brønsted acidic centers will be formed. Brønsted acid sites can play a key role in fluorination reactions.<sup>27</sup> The current project had as its goal the preparation of a binary fluoride system comprising CuF<sub>2</sub> and AlF<sub>3</sub>.

## Results and Discussion

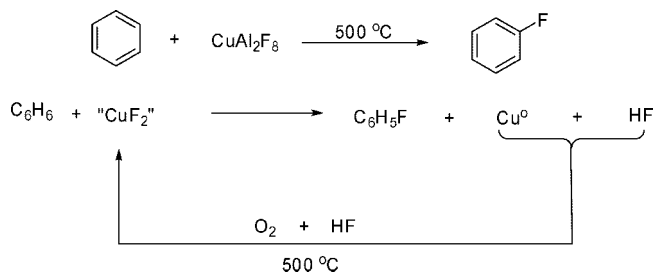
As a result of this study, we would like to report the discovery of a metal fluoride reagent of the nominal composition CuAl<sub>2</sub>F<sub>8</sub> that has proved very effective for carrying out direct, gas-phase, oxidative fluorination of benzene and other aromatics and which is highly regenerable. Using this CuAl<sub>2</sub>F<sub>8</sub> reagent, conversions of benzene as high as 70% have been obtained, and multiple recycling of the reagent, in situ, using O<sub>2</sub> and AHF has been demonstrated. Process details and scope of the reaction are discussed below.

There are few experimental or theoretical data in the literature that might provide insight into the possible mechanism of this oxidative fluorination process. Because we detect HF as a coproduct in the benzene/CuF<sub>2</sub> reaction, we presume the stoichiometry of the reaction to be as shown. Cu(I) is known to bind to benzene to form  $\pi$ -complexes that dissociate in the gas phase, exhibiting about a 50 kcal/mol BDE.<sup>28</sup> In complexes

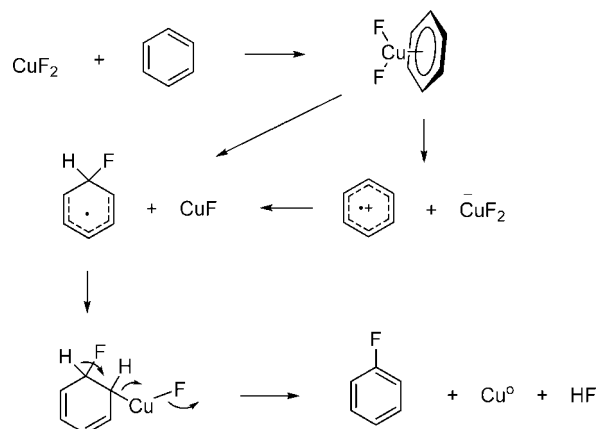
### Scheme 1. First gas-phase reaction of CuF<sub>2</sub> with benzene



### Scheme 2. New process of oxidative fluorination of benzene



### Scheme 3. Possible mechanism of oxidative fluorination of benzene by CuF<sub>2</sub>



with electron-rich benzene derivatives, such as *N,N*-dimethylaniline, such dissociation occurs with electron transfer to form Cu<sup>0</sup> plus the aromatic radical cation.<sup>29</sup> Although there have been no similar published calculations (or experiments) related to Cu(II)  $\pi$ -complexes with benzene, one can be confident that such  $\pi$ -complexes exist (with fluoride-bound Cu(II), the complex could be <sup>2</sup> $\eta$  rather than <sup>6</sup> $\eta$ ),<sup>30</sup> and because of the larger oxidation potential of Cu(II), it is possible that dissociation of this complex would occur with electron transfer to form the benzene radical cation. Thus we could propose an overall mechanism similar to that depicted in Scheme 3. There are, of course, mechanisms other than the simple “oxidative fluorination process” of Scheme 3, but until evidence is acquired relevant to this issue, this mechanism should suffice as a working hypothesis.

**Preparation of the Cu-Al Fluoride Reagents.** Four solids of different composition were prepared by using CuF<sub>2</sub>/AlF<sub>3</sub> molar ratios of 1:1, 1:1.5, 1:2, and 1:2.5. Appropriate amounts of Al(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O and Cu(NO<sub>3</sub>)<sub>2</sub>·xH<sub>2</sub>O were dissolved in ethanol. The mixture was then added dropwise to a stirred 48% hydrofluoric acid solution. After stirring for 2 h, the precipitate was filtered, washed with a small amount of distilled water/ethanol, dried at 120 °C overnight (16 h), and calcined at 450 °C for 6 h under Ar flow.

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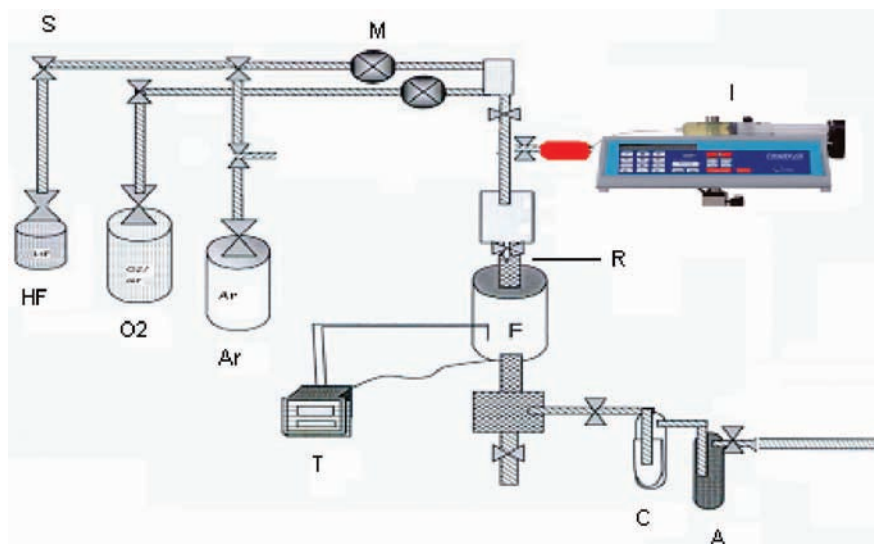


Figure 1. Schematic diagram of reaction/recycle setup.

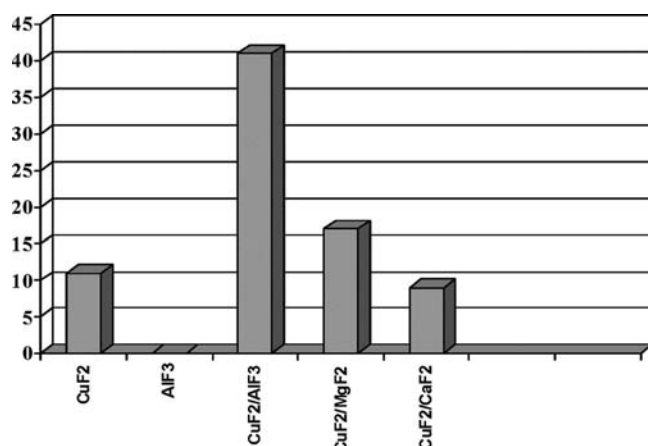


Figure 2. Conversion of benzene to fluorobenzene using different metal fluorides. The y-axis is the yield of fluorobenzene (%).

Table 1. Effect of Cu to Al ratio upon benzene conversion<sup>a</sup>

CuF <sub>2</sub> /AlF <sub>3</sub> ratio	conversion of benzene (%)	
	initial activity	recycled activity
1:1	28	9
1:1.5	53	14
1:2	57	42
1:2.5	36	30

<sup>a</sup> Conditions: 2.5 g of reagent, 500 °C, 0.5 mL of benzene.

**Typical Fluorination and Recycle Experimental Conditions.** The fluorination activities of these materials were evaluated in a fixed bed reactor in the gas phase (Figure 1). About 2.5 g of reagent was loaded into a hastalloy reactor tube (8 mm o.d.) in a dry box between two plugs of silver wool. The reactor was placed in an electrically heated furnace, and the reagent was pretreated under a flow of argon gas (40 mL/min) for 4 h at 500 °C. Benzene was introduced into the reactor using a syringe pump (flow rate, 15 mL/min; volume, 0.5 mL) along with the carrier gas (Ar, 25 mL/min) at 450–500 °C. The product mixture coming out of the reactor was condensed in a cold trap kept at 0 °C for 30 min for each pass of benzene, and the outlet from this trap was connected to an alkali trap to

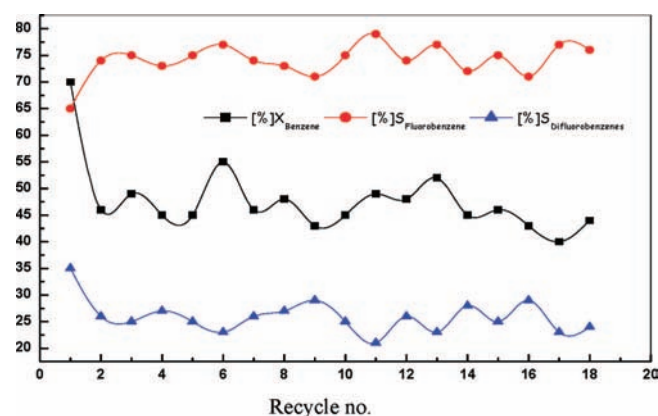


Figure 3. Performance of copper aluminum fluoride in time on stream analysis; 2.5 g of CuAlF<sub>8</sub> is reacted with 0.3 mL of benzene in each experiment. Ar flow was 30 mL.

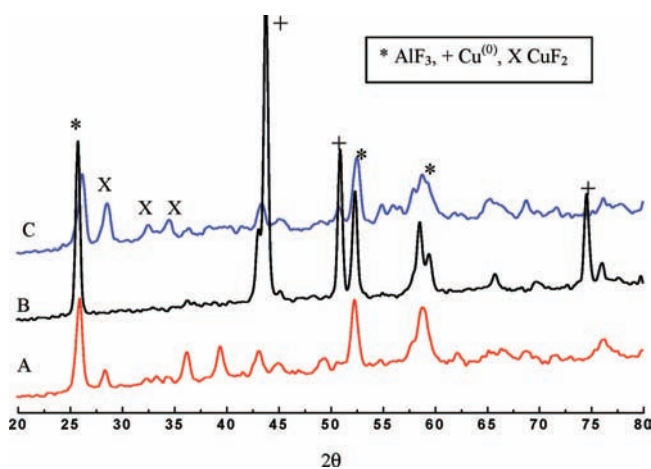
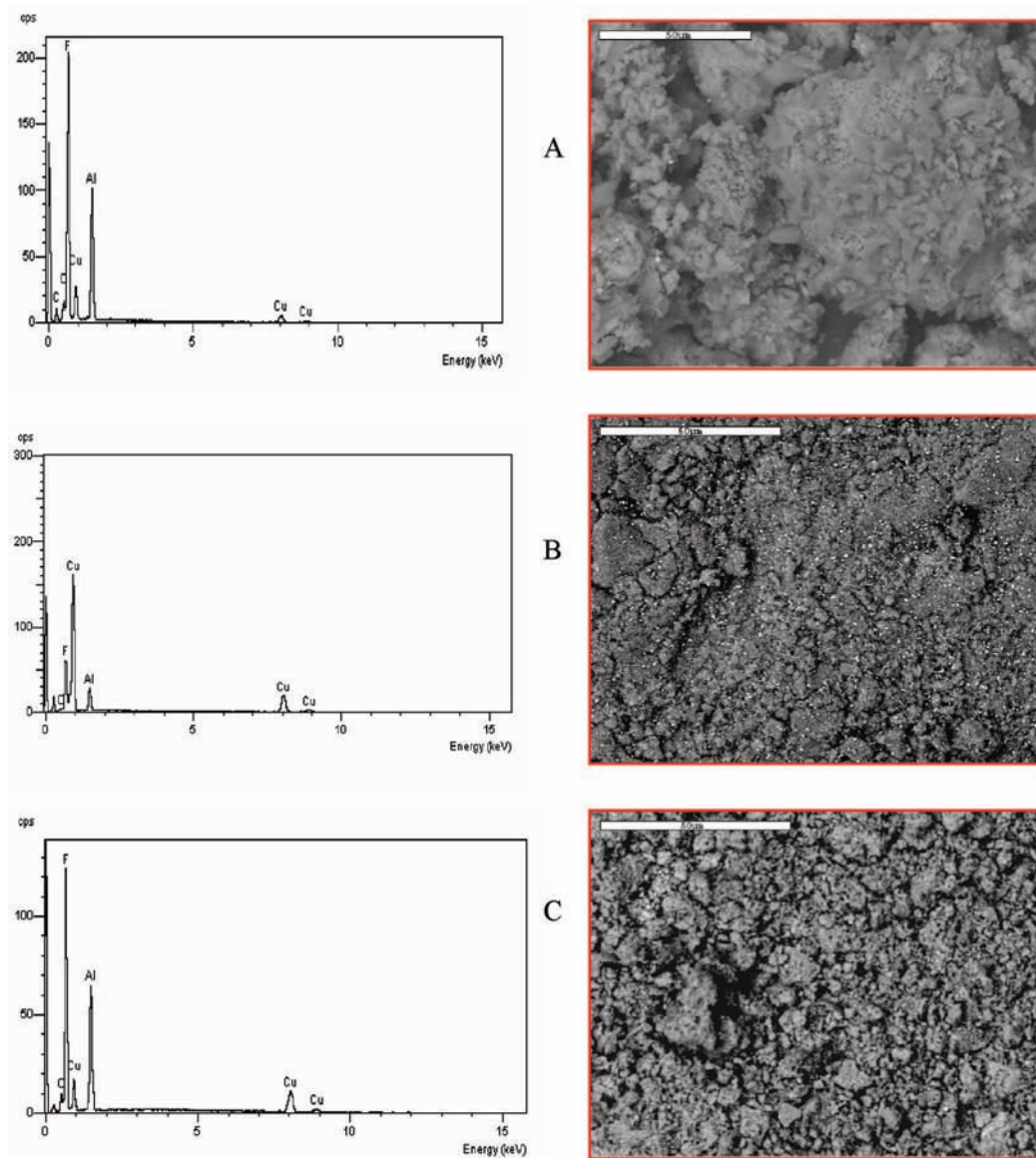









Figure 4. XRD patterns of copper aluminum fluoride: (A) calcined at 500 °C; (B) reacted with benzene after 18 cycles; (C) recycled with HF and O<sub>2</sub> for 4 h after 20 cycles.

neutralize the biproduct HF. The composition of the product mixture was determined by gas chromatography and <sup>1</sup>H and <sup>19</sup>F NMR. Fluorobenzene was the only product at 450 °C, whereas small amounts of other products such as 1,3- and 1,2-difluorobenzene were also obtained at 500 °C. Once the reagent was expended (i.e., conversion of benzene fell to zero), the



**Figure 5.** SEM/EDS patterns of copper aluminum fluoride: (A) calcined at 500 °C; (B) reacted with benzene after 18 cycles; (C) recycled with HF and O<sub>2</sub> for 4 h after 20 cycles.

**Table 2.** Yield comparison for different Cu reagents

Catalyst 2.5g, 500°C 0.5ml aromatic compound	% Yields of products						
	Reaction with Benzene		Reaction with monofluorobenzene			Reaction with Pyridine	
							
CuF <sub>2</sub>	11	0	7	3	3	8	0
CuF <sub>2</sub> +AlF <sub>3</sub>	40	1	14	9	7	9	3
Cu Al <sub>2</sub> F <sub>8</sub>	47	10	34	17	8	32	11

carrier gas was switched off, and the reactor was connected to a flow of gaseous anhydrous hydrogen fluoride (8 mL/min) and oxygen (10 mL/min) for 2.5 h. Then the reactor was flushed

with argon for 0.5 h, and the reaction cycle (fluorination of benzene) was repeated *without loss of activity* in the fluorination process.

**Table 3.** Yields of fluorotoluenes from chlorotoluenes

reactant <sup>a</sup>	yield of products (%)		
	<i>o</i> -fluorotoluene	<i>m</i> -fluorotoluene	<i>p</i> -fluorotoluene
<i>o</i> -chlorotoluene	60	7	4
<i>m</i> -chlorotoluene	0	61	2
<i>p</i> -chlorotoluene	5	10	71

<sup>a</sup> Conditions: 0.5 mL of reactant, 2.5 g of catalyst, at 500 °C.

Using this same procedure, a series of supported and unsupported CuF<sub>2</sub> systems were evaluated with respect to the fluorination of benzene. Pure copper(II) fluoride gave only low conversion (11%) to fluorobenzene, whereas among the supported, physically mixed systems, CuF<sub>2</sub>/AlF<sub>3</sub> was the most effective towards fluorination as compared to MgF<sub>2</sub>, CaF<sub>2</sub>, and AgF, giving rise to 41% conversion at 500 °C (Figure 2). All such metal fluorides were commercial samples (Aldrich). Among the coprecipitated binary fluoride systems, CuF<sub>2</sub>/AlF<sub>3</sub> at a ratio of 1:2 was found to exhibit optimal fluorinating ability in the fluorination of benzene (Table 1).

Regarding benzene fluorination, AlF<sub>3</sub> was found to be totally inactive, which indicates that it acts only as a support to disperse CuF<sub>2</sub>. Comparing the coprecipitated reagent of nominal composition CuAl<sub>2</sub>F<sub>8</sub> with the CuF<sub>2</sub>/AlF<sub>3</sub> mixture, the binary fluoride exhibits greater reactivity (56%) compared to that of the physically mixed, commercial CuF<sub>2</sub> and AlF<sub>3</sub> under identical conditions (Table 1). We believe that the observed high activity of the binary fluoride might be due to the CuF<sub>2</sub> being highly dispersed within the AlF<sub>3</sub> support. At the present time, we cannot be certain whether the fluorinating reagent constitutes a separate CuAl<sub>2</sub>F<sub>8</sub> phase or whether the synthesis conditions simply provide a good basis for forming a very amorphous, finely distributed CuF<sub>2</sub> reagent.

Fluorination of aromatics using inorganic metal fluorides in the gas phase is a “solid–gas” reaction. Normally in solid–gas reactions, once the surface CuF<sub>2</sub> has become reduced to Cu(0), sintering of copper can begin to occur at the high temperature of reaction. As a result of the process of coprecipitating CuF<sub>2</sub> with AlF<sub>3</sub> followed by heating and treatment with HF, it has been possible to obtain a high dispersion of CuF<sub>2</sub> within the AlF<sub>3</sub> support, such that sintering can be minimized, if not prevented, even at high temperature. By selecting aluminum fluoride, an acidic (Lewis acid) support, to deposit copper fluoride, it has been possible to obtain highly dispersed copper fluoride species on aluminum fluoride.

The copper aluminum fluoride systems (both the commercial and coprecipitated) were tested in multiple cycles, in the oxyfluorination of benzene. After the initial activity experiment (single pass of benzene), the carrier gas was switched off, and the reactor was connected to the flow of anhydrous hydrogen fluoride (8 mL/min) and oxygen gases (10 mL/min) for 2.5 h. Then the reactor was flushed with argon for 0.5 h, and the reaction cycle (fluorination of benzene) was repeated. The coprecipitated copper aluminum fluoride remained very active and stable during multiple cycles, whereas when using the commercial metal fluoride mixture, the benzene conversion fell to zero within 3 cycles.

Thus the benzene–CuF<sub>2</sub> (copper aluminum fluoride) reaction has been demonstrated to be a two-phase, cyclic process in

which generation of the CuF<sub>2</sub> in situ from copper metal by successive reaction with oxygen and hydrogen fluoride at 500 °C was followed by reaction with benzene, the cycle being completed by reconversion of the copper metal residue back to CuF<sub>2</sub> followed by further reaction with benzene to obtain virtually identical yields of fluorobenzenes in each cycle. The binary fluoride system was found to be very stable through 20 recycled experiments, exhibiting constant activity of ~45% conversion with almost 80% selectivity towards monofluorobenzene (Figure 3).

X-ray diffraction patterns of the copper aluminum fluoride reagent are shown in Figure 4. In the fresh sample (calcined at 450 °C under Ar for 4 h), before reacting with benzene, crystalline phases due to AlF<sub>3</sub> are mainly seen along with very weak signals due to CuF<sub>2</sub>, which indicates that the CuF<sub>2</sub> is mostly dispersed within the AlF<sub>3</sub>. In the XRD pattern of the spent system (after reacting with benzene), strong crystalline signals due to Cu(0) appear as a result of the reaction of CuF<sub>2</sub> with benzene to form fluorobenzene. Crystalline signals of CuF<sub>2</sub> and loss of Cu(0) signals in the XRD pattern of the recycled material can be seen. This indicates that CuF<sub>2</sub> has been regenerated by treatment with oxygen and HF.

The copper aluminum fluoride has also been characterized by scanning electron microscopy (SEM) and energy dispersive spectrometry. A fresh sample (before reaction with benzene) exhibits uniform morphology and the presence of a high concentration of fluoride on the surface (Figure 5a). In the partially spent binary fluoride material (after limited reaction with benzene), a fine distribution of copper can be seen (Figure 5b). This indicates that the copper is not sintered or agglomerated even at the high reaction temperature. Thus, as mentioned above, it has apparently been possible to prevent copper sintering by use of the highly dispersed binary reagent when using limited amounts of benzene, under which conditions the Cu(II) is not exhaustively reduced. In the regenerated binary fluoride material, after 20 cycles, surface analysis shows a uniform morphology with a high concentration of fluoride (Figure 5c).

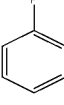
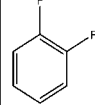
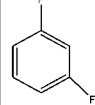
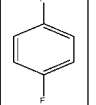
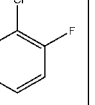
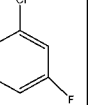
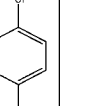
This new copper aluminum fluoride reagent has also been found to be active in fluorinating monofluorobenzene and pyridine (Table 2), with 1,3-difluorobenzene and 2-fluoropyridine being obtained as major products in those reactions, respectively.

In addition, the reagent of nominal composition CuAl<sub>2</sub>F<sub>8</sub> has been found to be effective in converting chloroaromatics to fluoroaromatics. Results for the reactions of chlorobenzene, dichlorobenzenes, chlorotoluenes and chlorofluorobenzenes are summarized in Tables 3 and 4, with the fluorination of 1-chloronaphthalene being shown in Scheme 4.

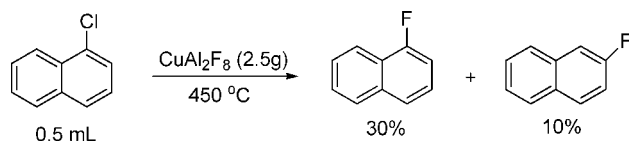
Other than results presented in our recent related patent, which claimed low conversions of chloroaromatics to fluoroaromatics using either CuF<sub>2</sub> (500 °C) or AgF (350 °C), there appear to be no reports of fluorodechlorination of chloroaromatics, other than classic S<sub>N</sub>Ar reactions, such as the reaction of *p*-chloronitrobenzene with fluoride ion.<sup>31</sup> On the other hand, cuprous salts (sometimes with Cu(II) catalysis) have long been known to promote replacement of unactivated aryl halogens

(31) Finger, G. C.; Kruse, C. W. *J. Am. Chem. Soc.* **1956**, *78*, 6034–6037.

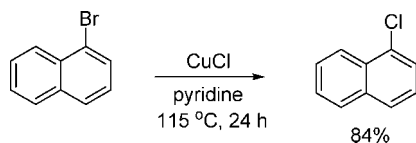
**Table 4.** Yields of fluorobenzenes from chlorobenzenes

Reactants 2.5g, 500°C 0.5ml chloroaromatic compound	% Yield of Products						
							
Chlorobenzene	57	1	4	0	3.5	2.5	0
1,2-Dichlorobenzene	10	4	3	1	20	0	0
1,3-Dichlorobenzene	6	1	12	0	0	12	0
1-Chloro-2-Fluorobenzene	39	16	21	7	17	0	0
1-Chloro-3-Fluorobenzene	12	0	62	3	0	23	0
1-Chloro-4-Fluorobenzene	4	0	11	42	0	0	43

**Scheme 4.** Fluorination of 1-chloronaphthalene



**Scheme 5.** CuCl reaction with aryl bromides



with nucleophiles,<sup>32</sup> the best known example being the conversion of aryl bromides to aryl nitriles through reaction with CuCN.<sup>33,34</sup> Less known is the little studied conversion of aryl bromides to chlorides through treatment with CuCl,<sup>35,36</sup> which is shown in Scheme 5.

To our knowledge, however, there have been no previous reports of the use of a transition metal fluoride to convert a nonactivated aryl chloride to an aryl fluoride. As one can see from the tables, the reaction is not regioselective and thus cannot involve a simple Cl-F replacement process. The study of this

reaction is still in its preliminary stages, and thus we will refrain from speculating about a possible mechanism.

## Conclusions

The newly synthesized copper aluminum fluoride of nominal composition CuAl<sub>2</sub>F<sub>8</sub> exhibits improved activity towards fluorination of aromatic compounds in comparison to the physical mixture of commercial CuF<sub>2</sub> and AlF<sub>3</sub>. It has also been shown to maintain reactivity through 20 reaction cycles of regeneration. The high fluorination ability and recyclability of the binary fluoride might be due to the high dispersion of CuF<sub>2</sub> on AlF<sub>3</sub>, which combined with the use of limited amounts of benzene in each run seems to inhibit sintering of copper.

The main advantages of this new process are (1) safety; the process design avoids the possibility of runaway reactions that can be encountered when using the diazonium ion based synthesis, and (2) minimal waste; with virtually no waste, the new process is extremely environmentally friendly. When this is combined with the ability to recycle the Cu reagent, the cost of the process should also be very attractive.

## Acknowledgment

Support of this research in part by DuPont is acknowledged with thanks. We also wish to thank Dr. Ed Mahler for his very helpful insights regarding the recycling process.

Received for review November 20, 2007.

OP700266Y

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