CHEMISTRY

A "Greener" Synthetic Route for Fluoroaromatics via Copper (II) Fluoride

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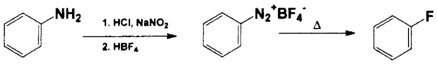
There is a strong economical and environmental driving force to develop a direct process for the conversion of hydrocarbons to fluorocarbons, selectively, without generating large quantities of waste. The direct synthesis of C−F bonds from C−H bonds with HF is thermodynamically unfavorable. However, the presence of oxygen and subsequent formation of water provide the thermodynamic driving force for the reaction to proceed via an intermediate metal fluoride. This concept provides the basis for an alternate synthesis route. A previous attempt at oxyfluorination of alkanes with CuF_2 was relatively unsuccessful because of the high C−H bond strength (*1*).



Scheme 1.

Fluorinated aromatics are widely used in the synthesis of pharmaceuticals and agrochemicals (*2*), with a volume exceeding 4000 metric tons per year (*3*). In particular, fluorobenzene is extensively used as a starting material for the industrial-scale manufacture of many fungicides and drugs (*3*). The classical synthetic route for fluorobenzene is the Balz-Schiemann reaction (*4*) involving diazotization of an aromatic amine in the presence of tetrafluoroboric acid (Scheme 1). The reaction in Scheme 1 produces large quantities of waste (such as $NaBF_4$ and NaCl) and is typical of the poor atom economy associated with fine chemical manufacturing.

Recent industrial advances (*5*) use HF in place of the fluoroboric acid; however, stoichiometric amounts of NaF and NH_4F salts are produced as waste with the fluorobenzene. Other approaches using HF exchange of chlorobenzene also generate HCl as waste (*6*). Aliphatic fluorocarbons are also produced by initial chlorination of a hydrocarbon followed by catalytic exchange with HF, yielding 2 mol of HCl waste for every carbon-fluorine bond produced (*7*).

We now report an environmentally acceptable process for the preparation of fluorobenzene from benzene, HF, and oxygen. This process produces H_2O as the only byproduct. Our general synthetic approach is shown below:

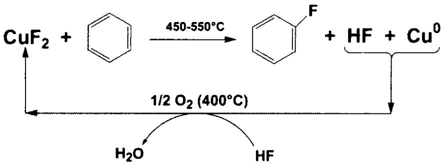
$$M-F_x + C-H \rightarrow M-F_{x-2} + C-F + HF \quad (1)$$

$$2HF + \tfrac{1}{2}O_2 + M-F_{x-2} \rightarrow M - F_x + H_2O \quad (2)$$

Key to the economical success of this process is finding a metal fluoride that is capable of oxidizing a C−H bond and being regenerated to the appropriate oxidized metal fluoride with oxygen and HF. A survey of metal oxidation-reduction potentials is shown in Table 1.

The metal fluorides with $E^0 > 1$ are strong oxidizing agents and can only be regenerated with elemental fluorine. This process is not economically viable because of the high cost of elemental fluorine. Those metal fluorides with $E^0 < 0$ are easy to prepare from HF and O_2 but are not strong enough to oxidize a C−H bond. The most attractive candidates are the ones with reduction potential in the range $1 > E^0 > 0$. Copper (II) fluoride provides an excellent platform for this chemistry, and the reaction cycle is shown in Scheme 2.

In a typical experiment, a reactor made from Inconel alloy (1.25-cm diameter) was charged with 5 g of copper oxide and heated to 400°C in a flow of HF to generate the CuF_2. Subsequently, a stream of vaporized benzene with N_2 as carrier gas was passed over CuF_2. An on-line gas chromatography–mass spectrometer was used to follow the course of the reaction. We found that the reaction was very specific (selectivity to fluorobenzene is >95%) and that the conversion of benzene was temperature dependent.



Scheme 2.

At 450°C, the conversion was 5%; it rose to ~30% at 550°C. When the conversion began to fall, the benzene feed was switched off, and an HF/O_2 stream was passed over the catalyst at 350° to 400°C to regenerate the copper fluoride. The reaction cycle could be repeated without loss of activity during the fluorination step. X-ray powder diffraction patterns of CuF_2 after exposure to benzene vapor at 500°C showed the formation of copper metal during the reaction, and the conversion is nearly stoichiometric. This process can also be used for other fluorinated aromatics such as fluorotoluenes and difluorobenzenes (*8*).

A simple, cost-effective method has been demonstrated for the production of fluorinated aromatics using principles of inorganic chemistry. It provides opportunities for industrial-scale production of fluoroaromatics without the waste disposal issues associated with current fluorination technologies.

Table 1. Oxidation-reduction potential for metals in various oxidation states. In the group with reduction potential $E^0 > 1$, the fluorides are strong oxidants and can be recycled with elemental fluorine. For the group with E^0 in the range $1 > E^0 > 0$, the fluorides are moderate oxidants and can be recycled with HF and O_2. For the group with $E^0 < 0$, the fluorides are inert toward C−H bonds. (E^0, reduction potential = 0.0 for $2H^+ + 2e^- \Leftrightarrow H_2$)

$E^0 > 1$	$1 > E^0 > 0$	$E^0 < 0$
$Co^{3+} + e^- \Leftrightarrow Co^{2+}$	$Cu^{2+} + 2e^- \Leftrightarrow Cu^0$	$Zn^{2+} + 2e^- \Leftrightarrow Zn^0$
$Ag^{2+} + e^- \Leftrightarrow Ag^{1+}$	$Ag^{1+} + e^- \Leftrightarrow Ag^0$	$Mg^{2+} + 2e^- \Leftrightarrow Mg^0$
$Pb^{4+} + 2e^- \Leftrightarrow Pb^{2+}$	$Te^{4+} + 4e^- \Leftrightarrow Te^0$	$Al^{3+} + 3e^- \Leftrightarrow Al^0$
$Ce^{4+} + e^- \Leftrightarrow Ce^{2+}$	$Hg^{2+} + 2e^- \Leftrightarrow Hg^0$	$Co^{2+} + 2e^- \Leftrightarrow Co^0$

References and Notes

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