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(Perfluoroalkyl)polyfluoroarenes by copper-promoted cross-coupling of perfluoroalkyl halides and polyfluoroarenes

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Abstract

Group 11 and 12 metals act as halogen acceptors to promote a selective cross-coupling between perfluoroalkyl halides and polyfluoroarenes to give (perfluoroalkyl)polyfluoroarenes. This reaction is a non-catalytic, fluorine analog of Friedel–Crafts alkylation in hydrocarbon chemistry.

Introduction

Synthetic fluorocarbon chemistry does not yet have the generality of hydrocarbon chemistry. Many very useful hydrocarbon reactions have no analogy in the fluorocarbon field. One such lack is a general reaction to produce (perfluoroalkyl)polyfluoroarenes. Hydrocarbon chemists accomplish this goal by a Friedel–Crafts reaction of the requisite arene and an alkyl carbenium ion precursor.

This work began with a chance observation in our studies of halogen scrambling in polyhalobenzenes [1]. During that catalyst scouting effort, we observed that Pd–Al_2O_3 promoted the coupling of two C_6F_5Br compounds to give some perfluorobiphenyl. The major reaction remained halogen scrambling to $C_6F_4Br_2$ and C_6F_6. Continued scouting uncovered materials such as copper–chromite (Harshaw CU-0203, 80% CuO, 17% Cr_2O_3) which gave only perfluorobiphenyl.

Synthesis of perfluorobiphenyl from C_6F_5X is not a novel reaction. Liquid-phase couplings in the presence of copper are known [2], and other reactive metals promote this coupling under mild conditions [3, 4]. Cross-coupling of perfluoroalkyl halides and polyfluoroarenes has also been observed, but mostly in low yields. Examples included C_6F_5Br and $I(CF_2)_3I$ to give 7% $C_6F_5(CF_2)_3C_6F_5$ and $C_7F_{15}I$ and C_6F_5Br to give 12% $C_7F_{15}C_6F_5$ [4]. The major coupling product in both cases was perfluorobiphenyl. The general thrust of these papers was to aromatic hydrocarbon coupling partners, specifically C_6H_5I.

Results

Copper, tin, zinc and some other reactive metals promote a selective cross-coupling of perfluoroalkyl halides and polyfluoroarenes to give (per-

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fluoroalkyl)polyfluoroarenes. A specific example is the coupling of C_6F_6 and CF_3Br to give $C_6F_5CF_3$. A general equation is

$$R_fX + Ar_fYZ + M \longrightarrow R_f - Ar_fZ + MXY$$

The R_f group is preferably a straight-chain perfluoroalkyl C_nF_{2n+1}, where $1 < n < 12$. The lower values of n are preferably coupled in vapor-phase continuous reactors, and the higher n in liquid-phase slurry reactors. Only the heavier perfluoroalkylhalides, i.e., chlorides, bromides and iodides, work. Perfluoroalkanes are inert. The aromatic ring Ar_f can be a polyfluorobenzene, pyridine or naphthalene. For best results the aromatic ring should be nearly or completely fluorinated. Spectator substituents Z can include CN, hydrogen, other halogens, perfluoroalkyl or perfluoroaryl groups. Any aromatic ring halogen $Y = F$, Cl, Br or I can participate in the coupling reaction. The metals M are both halogen acceptors and perhaps also precursors to surface organometallic species. The metals exhibit different selectivities in the groups coupled and function optimally at different temperatures. Copper is the preferred metal.

Halogen acceptors

A series of reagents were tested for their ability to produce $C_6F_5CF_3$ from CF_3Br and C_6F_6. Liquid C_6F_6 and gaseous CF_3Br were fed at the indicated rates over about 5 ml solid reagent. The results are shown in Table 1. All metals do not produce $C_6F_5CF_3$ at levels above that of an empty tube. Aluminum, like Cr_2O_3 and Al_2O_3, gives mainly C_6F_5Br by halogen exchange, perhaps catalyzed by the aluminum oxide coating usually present on aluminum metal. Even reduction in hydrogen at 1 atm at high temperatures may not be sufficient to remove these coatings from electropositive metals such as aluminum.

Group 11 and 12 metals seem to be the best halogen acceptors. The copper–chromite Harshaw CU-0203 performs better after being heated to 600 °C in a hydrogen atmosphere than in a nitrogen atmosphere. This suggests

TABLE 1

Halogen acceptors

Reagent	Gas–liquid chromatography peak area (%), $C_6F_5CF_3$	Reagent	Gas–liquid chromatography peak area (%) $C_6F_5CF_3$
Cu shot	49	Ni	16
CU-0203	40	Ca	13
Zn[a]	17	Ag	13
Blank	5.7		
Co	3.1	Fe	1.3
AlF_3	3.9	Cr_2O_3	0.5

Feeds: C_6F_6, 1 ml h^{-1}; CF_3Br, 5 ml min^{-1}. 600 °C.

[a] 400 °C.

that copper metal is the active acceptor, and the chromium is merely serving as a binder. In a practical sense this is not an unimportant function. When copper shot was used as the halogen acceptor, the copper halide product fused in the reactor making cleaning very difficult. Spent copper–chromite was more easily removed.

Hexafluorobenzene and other perfluoroalkyl bromides

C_2F_5Br reacts with C_6F_6 in the presence of CU-0203 to give $C_6F_5C_2F_5$ [5, 6] but significant amounts of $C_6F_5CF_3$ also form. CF_2Br_2 decomposed to Br_2 and produced no coupling products. The vapor-phase coupling works best for a CF_3 group. At high temperatures, longer perfluoroalkyl chains decompose by successive extrusions of difluorocarbene in preference to cross-coupling.

Hexafluorobenzene and perfluoromethyl halides

C_6F_6 and CF_3Cl gave only traces of $C_6F_5CF_3$ at 600 °C with copper–chromite as halogen acceptor. C_6F_6 and CF_3I did not produce significant amounts of products with C–C bonds with copper as the halogen acceptor at 600 °C. Copious amounts of iodine formed and the aromatic remained largely unreacted. Coupling C_6F_6 and CF_3I is more successful in the presence of zinc at lower temperatures.

It seems necessary to match the reactivity of the organic halides and that of the inorganic halogen acceptor. Chlorides are so unreactive that extremely high temperatures must be used for the coupling. Iodides are so reactive that they tend to decompose without reacting with the aromatic. The intermediate reactivity of bromides seems to be the most useful. At 600 °C with flows of 1 ml h^{-1} for C_6F_6 and 5 ml min^{-1} for CF_3Br over 5 g of CU-0203, 40% of the initial reactor effluent was $C_6F_5CF_3$, confirmed by both gas chromatography (GC)–mass spectroscopy (MS) and ^{19}F nuclear magnetic resonance (NMR) spectroscopy.

Other substituted polyfluorobenzenes and CF_3Br

We studied the scope of the aromatic substrate by passing polyfluoroarenes and CF_3Br over CU-0203. Since CU-0203 is a reagent and not a catalyst, conversion depends on the total amount of halides already seen by the solid reagent. Isomer selectivity does not depend on conversion as long as sequential reactions can be ignored.

Pentafluorobenzene and CF_3Br react at 600 °C to give 30% conversion to a mixture of the three isomers of $HC_6F_4CF_3$ [7] in about equal amounts. A small amount of $C_6F_5CF_3$ also formed.

Perfluorotoluene and CF_3Br react at 600 °C to give 15% conversion to a mixture of the three isomers of perfluoroxylene [6, 8]. The isomer ratio obtained by integrating the CF_3 resonances of the NMR spectrum is 4% *ortho*, 71% *meta* and 25% *para*. We studied the relative cross-coupling rates of $C_6F_5CF_3$ and C_6F_6 by feeding CF_3Br and C_6F_6 to a larger amount of copper shot at several temperatures above 600 °C. A kinetic analysis [9] of the product distribution as a function of hexafluorobenzene conversion gave the relative cross-coupling rates:

$$C_6F_6 \xrightarrow{\approx 1} C_6F_5CF_3 \xrightarrow{0.3} C_6F_4(CF_3)_2$$

Bromopentafluorobenzene and CF_3Br react to form $C_6F_5CF_3$ as the major product. Two types of byproduct form by sequential coupling reactions. Perfluoroxylenes result from a sequential reaction of CF_3Br with the initially formed perfluorotoluene. $C_6F_5C_6F_4CF_3$ isomers form by initially coupling two aromatics to perfluorobiphenyl and sequential cross-coupling of perfluorobiphenyl with CF_3Br. The product contains only traces of $CF_3C_6F_4Br$ isomers [10, 11].

Chloropentafluorobenzene and CF_3Br react to give comparable amounts of $C_6F_5CF_3$, $C_6F_5C_6F_5$ and C_6F_5Br. The products of coupling at aryl fluoride, $CF_3C_6F_4X$, $X \equiv Cl$, Br [12], were less than 1% each. Cross-coupling is not the dominant reaction in this case.

Pentafluorobenzonitrile and CF_3Br react at 600 °C to form $CF_3C_6F_4CN$ compounds [13]. Conversion was 35% to a nearly equimolar mixture of the three isomers.

Pentafluoropyridine and CF_3Br react at 650 °C to give 27% conversion to perfluoropicolines. The isomer ratio from ^{19}F NMR was 8% *ortho*, 80% *meta* and 12% *para* [14].

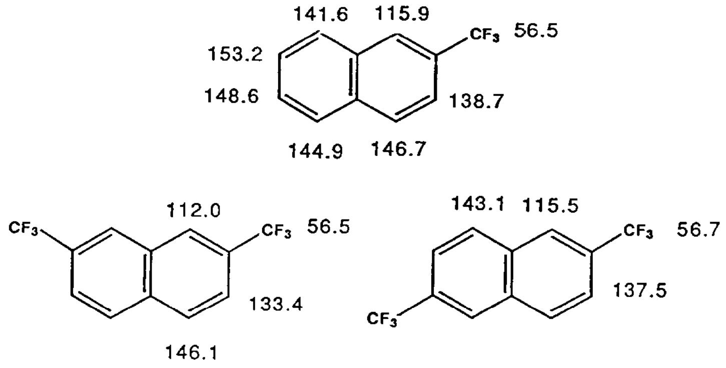
Perfluoronaphthalene and CF_3Br react at 600 °C to produce three products. GC–MS identified them as one isomer of trifluoromethylnaphthalene and two isomers of bis(trifluoromethyl)naphthalene in approximately equal amounts.

The CF_3 resonance of the trifluoromethylnaphthalene had two 20 Hz couplings. This pattern requires that the CF_3 be on the 2-position. Confirming this assignment is the observation of two ABs with large F–F coupling constants for the two pairs of non-equivalent α-fluorine atoms. The four-bond couplings are 76 Hz for the sterically constrained 1,5 pair next to the CF_3 and 58 Hz for the non-hindered 4,5 pair.

Both bis(trifluoromethyl)naphthalenes also had only 2-CF_3 groups, because their single CF_3 resonance also showed couplings to two adjacent fluorine atoms. The two isomers were identified as 2,6 and 2,7 by the symmetry of their spin systems. There are no visible cross-ring couplings in the 2,7 isomer because both the 1,8- and 4,5-fluorine atoms are chemically equivalent. The 2,6 isomer has one such pair with $J_{AB} = 73$ Hz. We did not see any 2,3-bis(trifluoromethyl)naphthalene nor any trifluoromethylnaphthalenes with a CF_3 in the 1 position. The chemical shifts of the fluoronaphthalenes are shown in the structures in Scheme 1.

Perfluorobiphenyl and CF_3Br react at 650 °C to give all three isomers of $C_6F_5C_6F_4CF_3$ [15], identified by ^{19}F NMR. The isomer ratio was 5% *ortho*, 68% *meta* and 27% *para*. Several isomers of $(CF_3)_2$– and $(CF_3)_3$–biphenyls were identified by GC–MS, but we did not pursue the specific isomer assignments.

There are three types of isomer pattern from cross-coupling. There are equal amounts of the three isomers from $Z \equiv H$ or CN. There is very little



Scheme 1.

ortho and approximately a statistical ratio of *meta* and *para* with CF_3, C_6F_5 and pyridyl. Ipso attack dominates for Cl and Br.

Iodides and CU-0203

Iodopentafluorobenzene and CF_3I react with CU-0203 at 450 °C to give a good yield of $C_6F_5CF_3$ together with some perfluoroxylene and all three isomers of $CF_3C_6F_4I$ [16]. The yield of the $CF_3C_6F_4X$, X≡I, is higher than for the other pentafluorophenyl halides, X≡Br, Cl.

Zinc as halogen acceptor

Zinc can function as a halogen acceptor in the vapor-phase cross-coupling reaction. It functions optimally at lower temperatures than CU-0203 or copper metal. Although bromides do give some cross-coupled products, the zinc-promoted reaction works better with iodides.

Bromopentafluorobenzene and CF_3I react with zinc at 400 °C to form $C_6F_5CF_3$. Bromopentafluorobenzene and $CF_3CF_2CF_2Br$ react with zinc at 500 °C to give mostly the two homocoupling products perfluoro-n-hexane and perfluorobiphenyl. There is only 10% of the cross-coupling product n-$C_3F_7C_6F_5$ [17].

Iodopentafluorobenzene and n-C_4F_9I react with zinc at 400 °C to give both homocoupling and cross-coupling products. The cross-coupled product $C_4F_9C_6F_5$ [18] was 45% of the effluent together with 8% of the *cis* and *trans* olefins $CF_3CF_2CF{=}CFC_6F_5$.

Liquid-phase reactions

Simple (perfluoroalkyl)polyfluoroarenes can be made in good conversions and yield by the vapor-phase process. Longer-chain perfluoroalkyl halides could not be used because they extrude difluorocarbene. Using a liquid-phase slurry process solves this problem. Such a reaction had been demonstrated using copper, but with dipolar-aprotic solvents such as dimethylsulfoxide [2]. Yields reported were low and homocoupling of the aromatic halide to perfluorobiphenyl was the major product. In our hands, reduction of the aromatic halide by the hydrogen donor solvent was also a significant side reaction.

The cross-coupling reaction can be run without added solvent. Simply mixing the polyfluoroaromatic and perfluoroalkyl halide with copper and heating produced good yields of the cross-coupled products. The copper, however, must be dried thoroughly. As received, copper powder is rust colored; when dry it is gold. Adsorbed water reduces the F-aromatic halides, leading to significant yield losses.

We tested some other metals for their ability to promote the liquid-phase cross-coupling of iodopentafluorobenzene and $C_7F_{15}I$. Tin proved useful as a liquid-phase halogen acceptor. The products from the copper and tin reactions were completely different. While tin gave a 1:1 adduct $C_7F_{15}C_6F_4I$, copper gave at least two isomers of the 2:1 adduct $C_6F_5C_6F_4C_7F_{15}$. Note that in the tin-promoted reaction the metal accepts an aromatic fluoride in preference to iodide.

Perfluorobiphenyl is the initial product in the copper reaction. The same $C_6F_5C_6F_4C_7F_{15}$ isomers form from heating perfluorobiphenyl and $C_7F_{15}I$ with copper. Chloropentafluorobenzene and $C_7F_{15}I$ do not react with copper when heated at 250 °C for 20 h.

Copper promotes the liquid-phase cross-coupling of a mixture of iodopentafluorobenzene with primary diiodides $I(CF_2)_nI$. GC–MS identified at least six isomers with $m/e = 930$ corresponding to $C_6F_5C_6F_4(CF_2)_6C_6F_4C_6F_5$, from $n = 6$.

Homocouplings

Why does the cross-coupling dominate over the two possible homocouplings? One surprising result emerged when we passed the individual components down a hot tube filled with copper shot. Table 2 shows the temperature at which the on-line GC analysis showed that half the starting halide had disappeared. Stability decreased with increasing atomic weight of the halogen. Pentafluorophenyl halides were more stable than their trifluoromethyl analogs. A control experiment showed that the decomposition of CF_3Br was the same in the presence of SiC or copper.

Significantly, the preferred temperature for the cross-coupling is below the $T_{1/2}$ of either of the components. A possible sequence is to form a surface

TABLE 2

Decomposition of alkyl and aryl halides

Compound	$T_{1/2}$ (°C)	Compound	$T_{1/2}$ (°C)
CF_3I	450	C_6F_5I	575
CF_3Br	625	C_6F_5Br	710
CF_3Cl	660	C_6F_5Cl	725
C_3F_7Br	560	C_6F_6	>725

TABLE 3

^{19}F nuclear magnetic resonance chemical shifts of (perfluoroalkyl)perfluorobenzenes

Compound	Chemical shifts			
	Ortho	*Meta*	*Para*	Side chain
Toluene	140.0	159.9	147.2	56.4
Ethylbenzene	138.0	159.5	146.0	86.2, 111.1
Propylbenzene	138.0	159.4	145.7	80.7, 127.6, 107.9
Butylbenzene	137.8	159.4	145.6	81.6, 124.0, 123.2, 107.1
o-Xylene	145.5	(≈ 138)		54.8
m-Xylene	114.9	159.9	125.2	56.5
p-Xylene	138.0			57.4
1,3,5-Trimethylbenzene		100.7		56.6

TABLE 4

^{19}F nuclear magnetic resonance chemical shifts of substituted trifluoromethylpolyfluorobenzenes

Compound	Chemical shifts
2-Cyanoperfluorotoluene	129.8 136.7 141.5 144.7
3-Cyanoperfluorotoluene	107.1 117.8 120.5
4-Cyanoperfluorotoluene	126.6 133.7
2-Hydroperfluorotoluene	137, 152, 147, 139
3-Hydroperfluorotoluene	116, 131, 160, 124
4-Hydroperfluorotoluene	137, 139

organometallic intermediate of the aliphatic compound which then reacts with the aromatic [19].

Product identification by fluorine nuclear magnetic resonance

Tables 3 and 4 list the fluorine chemical shifts of some of the (perfluoroalkyl)polyfluoroarenes produced in this work. We developed our fluorine NMR database concurrently with these synthetic studies [20].

Experimental details

General remarks

^{19}F NMR spectra in $CDCl_3$ were recorded on a Nicolet NT-220 spectrometer at 23 °C and 188.2 MHz. Positive chemical shifts are to a high field of trichlorofluoromethane. GC was done on a Varian-6000 gas chromatograph equipped with a flame ionization detector. The column, 30 m capillary coated with FS-1265, a CF_3CH_2O–silicone derivative, separated most of the mixtures by empirical formula. The column only rarely separated individual isomers. This chemistry is also discussed in a patent [21].

A typical liquid-phase reaction

A mixture of 0.5 g of C_6F_5Br, 1.0 g of $C_7F_{15}I$ and 0.5 g of dried copper powder (molar ratio, 1:1:1) was heated at 250 °C for 20 h. GC–MS of the reaction mixtures showed 30% $C_7F_{15}I$, 16% C_6F_5Br, 12% $C_6F_5C_6F_5$ and 7.8 and 4.3% of two isomers of $C_7F_{15}C_6F_5C_6F_5$.

A typical vapor-phase reaction

Liquids were fed using a Sage syringe pump. Typically 5 g of coupling reagent was placed in a $\frac{3}{4}$ in.×5 in. Vycor® reactor heated by a split-tube furnace. Typical liquid flow rates were 0.5–2 ml h^{-1}. Typical gas flow rates were 4–20 ml min^{-1}. Optionally 5–20 ml min^{-1} of N_2 was fed as a carrier gas. Aromatic solids were fed by passing perfluoroalkyl halide vapor through a melt held at a temperature just below the atmospheric pressure boiling points. The reaction effluent was passed through heated lines to a Valco® ten-port sample valve in our gas chromatograph. Selected samples were condensed at − 78 °C and products submitted for GC–MS or ^{19}F NMR analysis.

A specific vapor-phase reaction

The reactor was charged with 5 g of CU-0203 and heated to 600 °C. The feed rate of liquid C_6F_6 was 1 ml h^{-1} and that of gaseous CF_3I was 5 ml min^{-1}. A sample was collected after 0.5 h on stream. ^{19}F NMR analysis showed the aromatic product to consist of 72% C_6F_6 and 16% $C_6F_5CF_3$.

Conclusion

Copper, as a halogen acceptor, promotes cross-coupling of perfluoroalkyl halides and polyfluoroarenes to give (perfluoroalkyl)polyfluoroarenes. All four halogens (fluorine, chlorine, bromine and iodine) on arene can be the site of C–C bond formation. The chemistry works for benzenes, pyridines and naphthalenes as the aromatic ring. Tolerated ring substituents which are not displaced in the coupling reaction include R_f, CN and H.

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