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Transition-Metal-Free Synthesis of Fluorinated Arenes from Perfluorinated Arenes Coupled with Grignard Reagents

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Supporting Information

ABSTRACT: A simple method to obtain organofluorine compounds from perfluorinated arenes coupled with Grignard reagents in the absence of a transition-metal catalyst was reported. In particular, the perfluorinated arenes could react not only with aryl Grignard reagents but also with alkyl Grignard reagents in moderate to good yields.

$$\mathrm{ArF_n} + \text{aryl-MgBr} \xrightarrow[\text{r.t., 24 h}]{\text{THF}} \mathrm{F_{n-1}Ar}\text{-aryl}$$

$$\mathrm{ArF_n} + \text{alkyl-MgBr} \xrightarrow[\text{r.t., 24 h}]{\text{THF}} \mathrm{F_{n-1}Ar}\text{-alkyl}$$

Organofluorine compounds are rare in nature but play significant roles in many fields such as material science,[1] pesticides,[2] fluoro-liquid crystals,[3] and pharmaceuticals.[4] The existence of one or more fluorine atoms in a drug molecule might have some decisive effects in changing its biological and chemical properties. Nucleophilic substitution (S_NAr)[5] and transition-metal-catalyzed coupling reactions[6] represent two main strategies for the synthesis of organofluorine compounds, and significant efforts have been made in these two fields. However, they suffer some drawbacks. For S_NAr reactions, a complicated reaction system is needed and the yield and selectivity are not satisfactory. For metal-catalyzed reactions, in some cases, harsh conditions are required. In addition, metal catalysts may contaminate products and bring adverse effects to health and the environment.

Actually, the direct reaction of fluorinated arenes with organometallic nucleophilic reagents in the absence of transition metal catalysts can be traced back to the 1960s.[7] In most cases organolithium reagents were used. However, due to their high reactivity, the selectivity of these reactions was poor. Di- and/or trisubstituted products were detected. Grignard reagents were also selected as nucleophilic reagents for the reaction with perfluorinated arenes,[8] but the yield was low. Since then, for a long time, researchers focused on finding new catalytic systems to synthesize fluorinated arenes and neglected this simple but powerful nucleophilic substitution reaction. This direct method may promote the development of more efficient pathways to obtain fluorinated arenes. Recently, Matsubara reported the cleavage of unactivated C−F bonds and nucleophilic substitution with magnesium reagents and without using a transition-metal catalyst.[9] However, the majority of those reactions occurred at higher temperatures and the yields were not satisfactory.

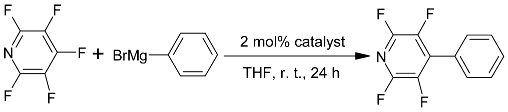
In this paper, we describe a simple method to synthesize organofluorine compounds by the reaction of perfluorinated arenes with Grignard reagents and without a transition-metal catalyst under mild conditions. It should be especially noted that the perfluorinated arenes could react with not only aryl but also alkyl Grignard reagents in good yields.

RESULTS AND DISCUSSION

The reaction was found while screening the reaction conditions of perfluorinated arenes with Grignard reagents in the presence of transition-metal catalysts. At the beginning, we also wanted to explore a new catalytic system for the nucleophilic substitution of perfluorinated arenes with Grignard reagents. However, we found that the yield of the product, 4-phenyltetrafluoropyridine, was only 10% when pentafluoropyridine reacted with phenylmagnesium bromide in the presence of $[Ni_2(iPr_2Im)_4(COD)]$ (**1**).[10] A large amount of homocoupling product (biphenyl) of phenylmagnesium bromide was confirmed according to GC-MS analysis. This might be understood from the work on the mechanism of nickel-catalyzed coupling of aryl halides by Kochi.[11] This result was in conformity with Radius's experiment.[10] However, when nickel complex **1** was taken out of the reaction mixture under the same conditions (as a control experiment), up to a 97% yield of 4-phenyltetrafluoropyridine could be achieved and the yield of biphenyl was very low (Table 1).

Encouraged by this result, we expanded the substrate scope of perfluorinated arenes and Grignard reagents. First, we carried out the substitution reactions of perfluorinated arenes with aryl Grignard reagents. Moderate to satisfactory isolated yields were obtained (Scheme 1). From these results it could be concluded

Table 1. Nucleophilic Substitution of Pentafluoropyridine and Phenylmagnesium Bromide with or without Metal Catalyst



entry	catalyst	yield (%)[a]
1	$[Ni_2(iPr_2Im)_4(COD)]$	10
2	none	97

[a]Yields of isolated products.

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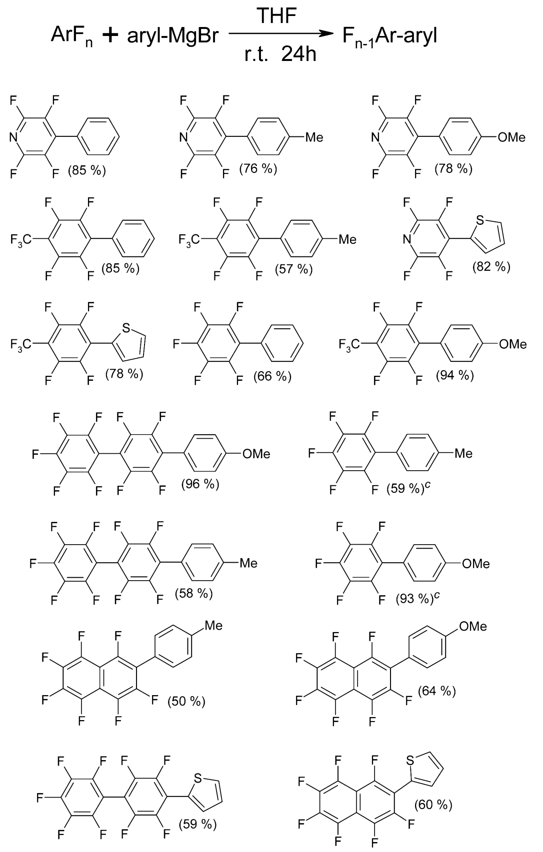
Scheme 1. Nucleophilic Substitution of Perfluorinated Arenes and Aryl Grignard Reagents without Metal Catalyst[a,b]

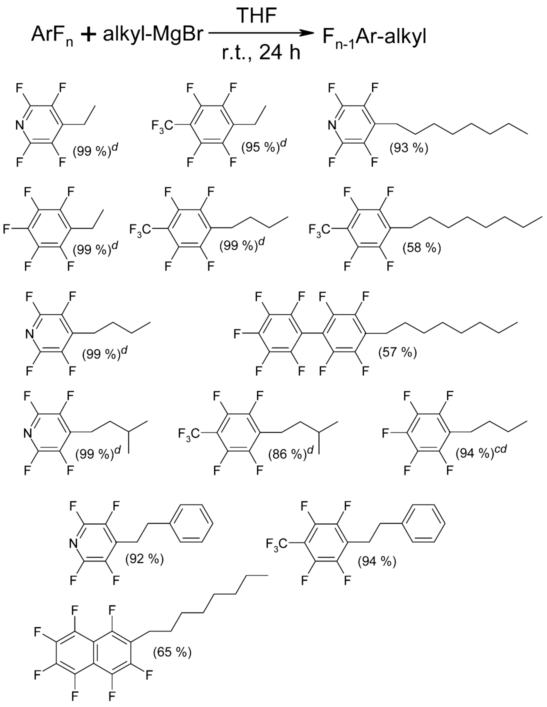


[a]Conditions: perfluorinated arene (1.0 mmol), Grignard reagent (1.5 mmol), THF (2 mL), room temperature, 24 h. [b]Yields of the isolated products are given in parentheses. [c]60 °C.

that *p*-methoxyphenylmagnesium bromide was superior to both phenylmagnesium bromide and *p*-methylphenylmagnesium bromide in most cases when the substituted phenyl Grignard reagents were employed in the substitution reactions. Furthermore, 2-thienylmagnesium bromide gave the corresponding substitution products in good yields. In all cases, the selectivities are very good. Only monosubstituted products were detected. The replacement of fluorine atoms occurred at the *para* position of the −N, $-CF_3$, or $-C_6F_5$ group and the *β*-position of octafluoronaphthalene.

Subsequently, we explored the nucleophilic substitution reactions of perfluorinated arenes with alkyl Grignard reagents. The related results are shown in Scheme 2. Ethyl, *n*-butyl, *iso*pentyl, *n*-octyl, and phenylethyl Grignard reagents were used in the substitution reactions with perfluorinated arenes. All of the corresponding organofluorine compounds were obtained in moderate to good yields. Only monosubstitution occurred with excellent selectivity at the position of alkylation. It should be especially noted that some products could not be successfully isolated because of the low boiling points and volatile properties. They were confirmed by *in situ* ^{19}F NMR spectroscopy and GC-MS. It should also be noted that this reaction did not occur with hexafluorobenzene as raw material at room temperature, but the substitution products from hexafluorobenzene could be obtained at 60 °C in high yields and with good selectivities (Schemes 1 and 2).

Scheme 2. Nucleophilic Substitution Reaction of Perfluorinated Arenes and Alkyl Grignard Reagents without Metal Catalyst[a,b]



[a]Conditions: perfluorinated arene (1.0 mmol), Grignard reagent (1.5 mmol), THF (2 mL), room temperature, 24 h. [b]Yields of the isolated products are given in parentheses. [c]60 °C. [d]Yields based on the *in situ* ^{19}F NMR.

The substitution reaction of perfluorinated arenes with Grignard reagents in the absence of a transition-metal catalyst might proceed via a four-membered-ring transition state similar to the case in Matsubara's report.[9] The C−F bond cleavage and C−C bond formation occur simultaneously.

In comparison with the results by Harper,[8] we found the reaction selectivities and yields were improved under our experimental conditions. Some of Harper's experiments were carried out at higher temperatures, while most of the reactions in this work proceeded at room temperature except for hexafluorobenzene as starting material (at 60 °C). It was also found that an increase in temperature is not an appropriate way to improve the yield. In contrast, higher temperatures reduce the yields of the expected products, because higher temperatures favor the formation of the homocoupling byproducts of Grignard reagents. In other words, higher temperatures will reduce the selectivity of the reaction. In addition, it was also found that pentafluorobenzene could not participate in this nucleophilic substitution because of its low reactivity.

■ CONCLUSION

In summary, a simple method to obtain organofluorine compounds from perfluorinated arenes coupled with Grignard reagents in the absence of a transition-metal catalyst at room temperature was reported except for the case of hexafluorobenzene (at 60 °C). In particular, the perfluorinated arenes could react with not only aryl but also alkyl Grignard reagents in moderate to good yields.

EXPERIMENTAL SECTION

All reactions were carried out under nitrogen with dry solvents under anhydrous conditions. $[\mathrm{Ni}_2(i\mathrm{Pr}_2\mathrm{Im})_4(\mathrm{COD})]$ was prepared according to the reported procedure.[10] C_5F_5N, C_7F_8, C_6F_6, $C_{12}F_{10}$, and $C_{10}F_8$ were obtained from ABCR. The Grignard reagents were prepared from the corresponding bromide and magnesium turnings in anhydrous tetrahydrofuran (THF) according to known procedures[12] and were titrated prior to use. All other chemicals were used as purchased. NMR spectra were obtained on a Bruker Avance 300 spectrometer (300 MHz for ^{1}H NMR; 75 MHz for ^{13}C NMR; 282 MHz for ^{19}F NMR).

Typical Procedure for Nucleophilic Substitution Reactions between Pentafluoropyridine and Phenylmagnesium Bromide Catalyzed by $[\mathrm{Ni}_2(i\mathrm{Pr}_2\mathrm{Im})_4(\mathrm{COD})]$ (1). Under an N_2 atmosphere nickel complex **1** (10.5 mg, 0.02 mmol) was dissolved in 1 mL of THF. Pentafluoropyridine (166 mg, 1 mmol) and phenylmagnesium bromide (1.5 mmol, 1.2 mL/1.3 M in THF) were added. The reaction mixture was stirred for 24 h at room temperature and was quenched by 100 mL of H_2O. The product was extracted three times with 150 mL of Et_2O. The organic layers were combined and dried over Na_2SO_4. All volatiles were removed under reduced pressure. The crude product was purified by column chromatography over silica gel with petroleum ether as eluent to provide the corresponding product.

Typical Procedure for Nucleophilic Substitution Reactions between Perfluorinated Arenes and Grignard Reagents without Nickel Catalyst. Under an N_2 atmosphere the perfluorinated arene (1 mmol) was dissolved in 1 mL of THF. Grignard reagent (1.5 mmol) was added to this solution. The mixture was stirred until the completion of the reaction. The reaction was quenched with 100 mL of H_2O, and the product was extracted three times with 150 mL of Et_2O. The organic layers were combined and dried over Na_2SO_4. All volatiles were removed under reduced pressure. The crude product was purified by column chromatography over silica gel with petroleum ether as eluent to provide the corresponding product.

ASSOCIATED CONTENT

Supporting Information

Text and figures giving experimental details and NMR spectra of fluorinated arenes. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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