

Perfluoroalkyl Grignard Reagents: NMR Study of 1-Heptafluoropropylmagnesium Chloride in Solution

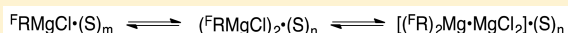
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S Supporting Information

ABSTRACT: We report on the generation of a perfluoroalkyl Grignard reagent (^FRMgX) by exchange reaction between a perfluoroalkyl iodide (^FR-I) and a Grignard reagent (RMgX). ¹⁹F NMR was applied to monitor the generation of *n*-C₃F₇MgCl. Additional NMR techniques, including ¹⁹F COSY, NOESY, and pulsed gradient spin-echo (PGSE) diffusion NMR, were invoked to assign peaks observed in ¹⁹F spectrum. Schlenk equilibrium was observed and was significantly influenced by solvent, diethyl ether, or THF.



INTRODUCTION

The first synthesis of a perfluoroalkyl Grignard reagent (^FRMgX) was developed by Haszeldine by reaction of a perfluoroalkyl iodide with magnesium metal.¹ ^FRMgX reacts with CO₂, ketones, and aldehydes similar to unfluorinated Grignard reagents. ^FRMgX has much poorer thermal stability than the corresponding RMgX. Hence, it is much more convenient to produce and use ^FRMgX at low temperature, preferably at -78 °C. However, the reaction between perfluoroalkyl iodide and magnesium requires warming to at least -10 to -20 °C to initiate, and this causes decomposition of the ^FRMgX reagent. Moreover, the yields are sensitive to the purity and size of magnesium metal.² To overcome these drawbacks, McBee and co-workers developed a fast and convenient method to generate ^FRMgX at low temperature.^{2,3} By mixing perfluoroalkyl iodide (^FRI) and RMgX in ethereal solvents, a halogen-magnesium exchange happens quickly, leading to ^FRMgX and alkyl iodide (RI).⁴ This exchange reaction is fast and quantitative even at -78 °C.⁵

In analogy with normal Grignard reagents,⁶ ^FRMgX reacts with electrophiles leading to organofluorine compounds.⁷ However, in practice, the applications have been quite limited due to poor stability and reactivity.⁸ Decomposition of ^FRMgX yields a protonated product (^FRH), perfluoroalkene, and traces of coupling product (^FR-^FR) as well as perfluoroalkene polymer.^{1b} Generation of perfluoroalkene involves either an α or a β magnesium-fluoride elimination. A single electron transfer (SET) pathway was suggested, which indicated the existence of a radical intermediate (^FR[•]) to explain the formation of the other decomposition by-products.⁹

Mechanistic studies of ^FRMgX are still insufficient.¹⁰ In the solid state, structural characterization of ^FRMgX is also lacking. ¹⁹F NMR has been applied several decades ago,¹¹ but unambiguous chemical shift values of ^FRMgX are difficult to find

in the literature due to instrumentation used in the earliest studies. However, mechanistic studies of these reagents are crucial for the improvement of stability and reactivity. For example, synthetic methodology development involving ^FRMgX reagents shows that some additives significantly stabilize ^FRMgX or improve the performance, but the reasons for these improvements are unclear.¹² Therefore, we report directly observation and characterization of various intermediates in the reactions involving ^FRMgX, and we supply NMR data in this study.

RESULTS AND DISCUSSION

To simplify the spectra, perfluoropropyl magnesium chloride (*n*-^FPrMgCl) was selected as the model of perfluoroalkyl Grignard reagents. Additionally, this compound is relatively stable. The preparation of *n*-^FPrMgCl is described in Figure 1, with chemical shift values (¹⁹F) of reactant¹³ and major

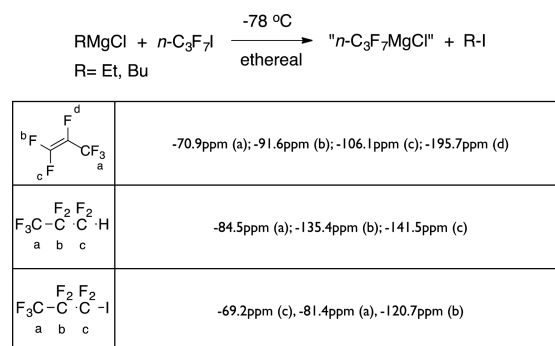


Figure 1. Preparation of *n*-^FPrMgCl, with ¹⁹F chemical shift values of reactant and major byproducts.

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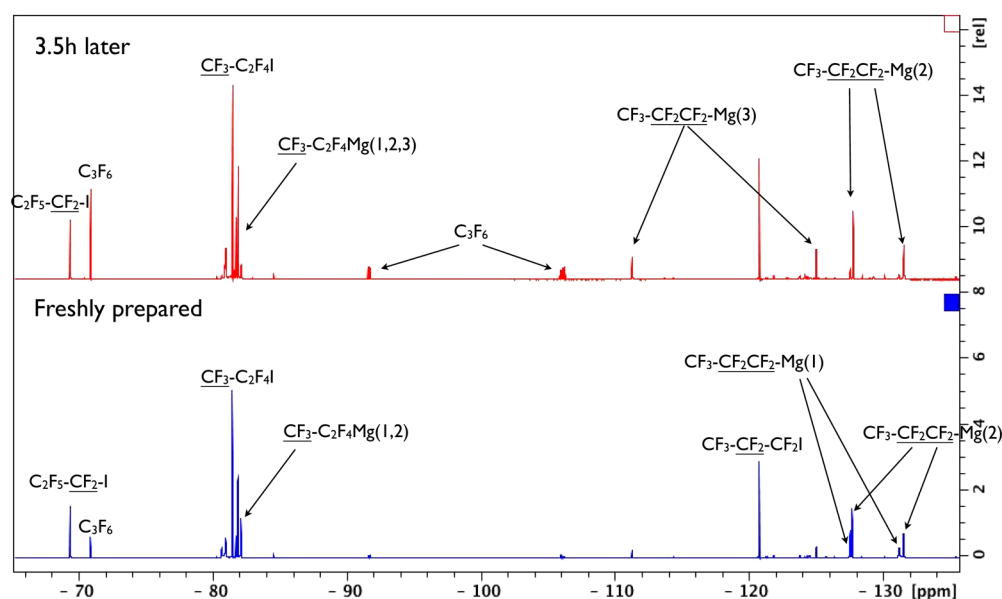


Figure 2. ^{19}F NMR, 0.4 M ether solution of $n\text{-}^{\text{F}}\text{PrMgCl}$ at $-78\text{ }^{\circ}\text{C}$.

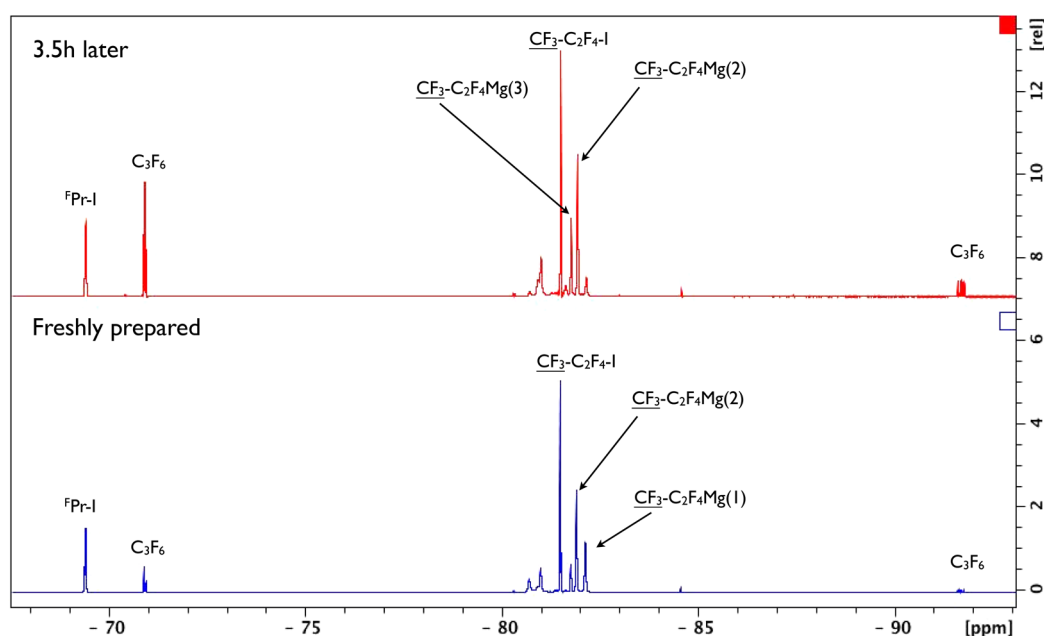


Figure 3. ^{19}F NMR, downfield region of Figure 2.

byproducts¹⁴ listed. Chemical shift values were measured in diethyl ether at $-78\text{ }^{\circ}\text{C}$ and calibrated to the chemical shift of C_6F_6 at -164.9 ppm .

Several reactions are reported that use perfluoroalkyl Grignard reagents at low temperature followed by warming to $-20\text{ }^{\circ}\text{C}$ or room temperature.^{10e,f,15} Our VT NMR results show that $n\text{-}^{\text{F}}\text{PrMgCl}$ or $n\text{-}^{\text{F}}\text{BuMgCl}$ undergoes significant decomposition at $-20\text{ }^{\circ}\text{C}$ and also that they slowly decompose even at $-78\text{ }^{\circ}\text{C}$ in both THF and diethyl ether solutions, respectively. At higher concentrations, the decomposition occurs even more quickly. Hence, the successful applications reported at $0\text{ }^{\circ}\text{C}$ are probably due to a faster reaction of $^{\text{F}}\text{RMgX}$ with other reagents than self-decomposition. Therefore, all NMR experiments mentioned in this Article were performed

at $-78\text{ }^{\circ}\text{C}$ for both sample preparation and NMR analysis to minimize self-decomposition.

Perfluoropropyl Magnesium Chloride ($n\text{-}^{\text{F}}\text{PrMgCl}$) in Diethyl Ether Solution. A freshly made ether solution of $n\text{-}^{\text{F}}\text{PrMgCl}$ displays two sets of “ $^{\text{F}}\text{PrMg}$ ” peaks in ^{19}F NMR (Figure 2, bottom). These peaks are labeled as $^{\text{F}}\text{Pr-Mg}$ (1) and $^{\text{F}}\text{Pr-Mg}$ (2). After storage at $-78\text{ }^{\circ}\text{C}$ for 3.5 h, $^{\text{F}}\text{Pr-Mg}$ (1) can be barely detected, and $^{\text{F}}\text{Pr-Mg}$ (2) slightly increases. However, a new “ $^{\text{F}}\text{PrMg}$ ” species appears and is labeled as $^{\text{F}}\text{Pr-Mg}$ (3) (Figure 2, top). Full assignments for the peaks in Figures 2 are presented in Figures 3 and 4. The correlation of two adjacent CF_2 peaks from the same “ $^{\text{F}}\text{PrMg}$ ” species is supported by the cross peaks in ^{19}F COSY spectra (Figure 5) due to $^3J_{\text{FF}}$ couplings. There are several minor unassigned peaks in the ^{19}F spectra, which display numerous cross-peaks in

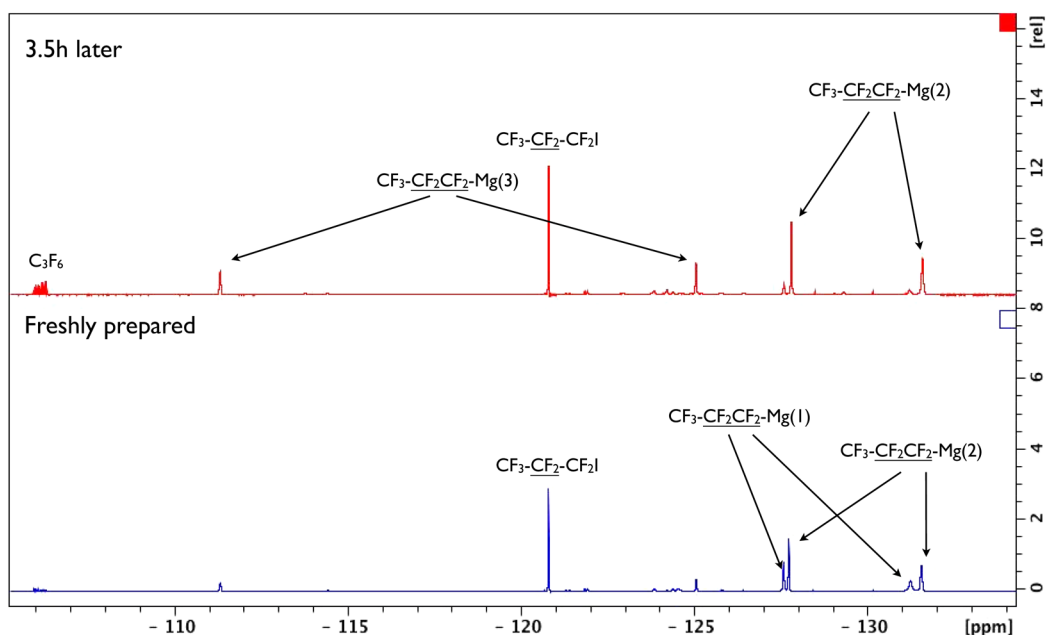


Figure 4. ^{19}F NMR, upfield region of Figure 2.

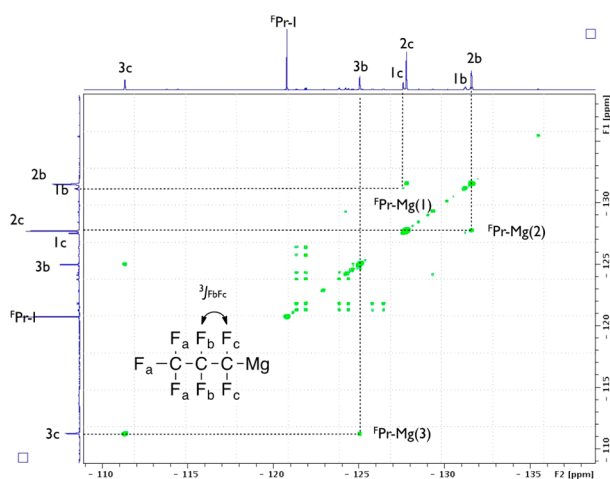


Figure 5. $\{^{19}\text{F}, ^{19}\text{F}\}$ COSY NMR, 0.4 M ether solution of $n\text{-}^{\text{F}}\text{PrMgCl}$ at $-78\text{ }^{\circ}\text{C}$.

the ^{19}F COSY spectra. These impurities are assigned to traces of perfluoro-*n*-hexane and polymer byproducts whose formations involve a heptafluoropropyl radical intermediate. These long-chain perfluoro byproducts present multiple $^4J_{\text{FF}}$ coupling cross-peaks, which usually have much stronger intensities than $^3J_{\text{FF}}$ coupling cross-peaks in ^{19}F COSY spectra. A significant amount of perfluoropropene (C_3F_6) was observed after 3.5 h as the decomposition product of all “ $^{\text{F}}\text{PrMg}$ ” complexes in solution.

If the sample concentration is lowered to 0.2 M, $^{\text{F}}\text{Pr-Mg}$ (1) is the dominant magnesium species in the solution at first, suggesting that $^{\text{F}}\text{Pr-Mg}$ (1) is relatively more stable in dilute solution (Figure 6). However, 3.5 h later, $^{\text{F}}\text{Pr-Mg}$ (2) is still the dominant intermediate, and $^{\text{F}}\text{Pr-Mg}$ (3) begins to appear.

Perfluoropropyl Magnesium Chloride ($n\text{-}^{\text{F}}\text{PrMgCl}$) in THF Solution. A much cleaner ^{19}F NMR spectrum was observed when THF was the solvent. As shown in Figure 7, $^{\text{F}}\text{Pr-Mg}$ (3) is the only detectable magnesium species. The ^{19}F

COSY spectrum (Figure 8) clearly distinguishes two CF_2 peaks of $^{\text{F}}\text{Pr-Mg}$ (3), because the CF_3 peak only exhibits a cross peak with CF_2 (c) but not with CF_2 (b). This indicates there is a four-bond coupling between F(a) and F(c), as $^4J_{\text{FF}}$ is usually stronger than $^3J_{\text{FF}}$ for unbranched perfluoroalkyl groups.¹⁶ It is noteworthy that identical ^{19}F spectra are obtained when ether is the solvent and when commercial *n*-BuMgCl that we utilized to prepare the $n\text{-}^{\text{F}}\text{PrMgCl}$ reagent was dissolved in THF. The common feature between these two reactions is the presence of THF when the $n\text{-}^{\text{F}}\text{PrMgCl}$ is formed. It is noteworthy that the species in solution are not observed in the same proportions when THF is subsequently added to a solution of the $n\text{-}^{\text{F}}\text{PrMgCl}$ reagent initially formed in the absence of THF (Figure S4).

It is also worth noting that two CF_2 groups of $^{\text{F}}\text{Pr-Mg}$ (3) show significantly different chemical shifts as compared to the corresponding CF_2 groups in $^{\text{F}}\text{Pr-Mg}$ species (1) and (2). Moreover, THF accelerates the formation of $^{\text{F}}\text{Pr-Mg}$ (3). We assume that $^{\text{F}}\text{Pr-Mg}$ (3) is a dialkyl magnesium “($n\text{-}^{\text{F}}\text{Pr}$) $_2\text{Mg}$ ” species, and both (1) and (2) are alkyl magnesium halide “ $n\text{-}^{\text{F}}\text{PrMgCl}$ ” type species, due to relatively slow $^{\text{F}}\text{R}$ group exchange (Scheme 1).¹⁷

Schlenk Equilibrium. A ^{19}F pulsed-gradient spin-echo (PGSE) experiment was applied to measure self-diffusion coefficients of these various magnesium species in ether solution to ascertain information about the aggregation state. As shown in Figures 9, S1, and S2, $^{\text{F}}\text{Pr-Mg}$ (2) has size similar to that of $^{\text{F}}\text{Pr-Mg}$ (3) and is larger than $^{\text{F}}\text{Pr-Mg}$ (1). Moreover, exchange cross-peaks are observed between $^{\text{F}}\text{Pr-Mg}$ (1) and (2), and also between $^{\text{F}}\text{Pr-Mg}$ (2) and (3) as seen in the $\{^{19}\text{F}, ^{19}\text{F}\}$ NOESY experiment (Figure 10).

In consideration of all of the observations above and as shown in Scheme 1, we assign structures to and interpret the Schlenk equilibrium¹⁸ of “ $n\text{-}^{\text{F}}\text{PrMgCl}$ ” in ethereal solution as follows. $^{\text{F}}\text{Pr-Mg}$ (1) is $n\text{-}^{\text{F}}\text{PrMgCl}$ monomer, generated immediately upon mixing of the two reactants. This monomer is not a stable aggregate and will self-aggregate to a halide-bridged dimer, which we assign to the species (2), that is, $(^{\text{F}}\text{Pr-Mg-X})_2$. THF enhances Schlenk equilibrium, that is, disproportionation

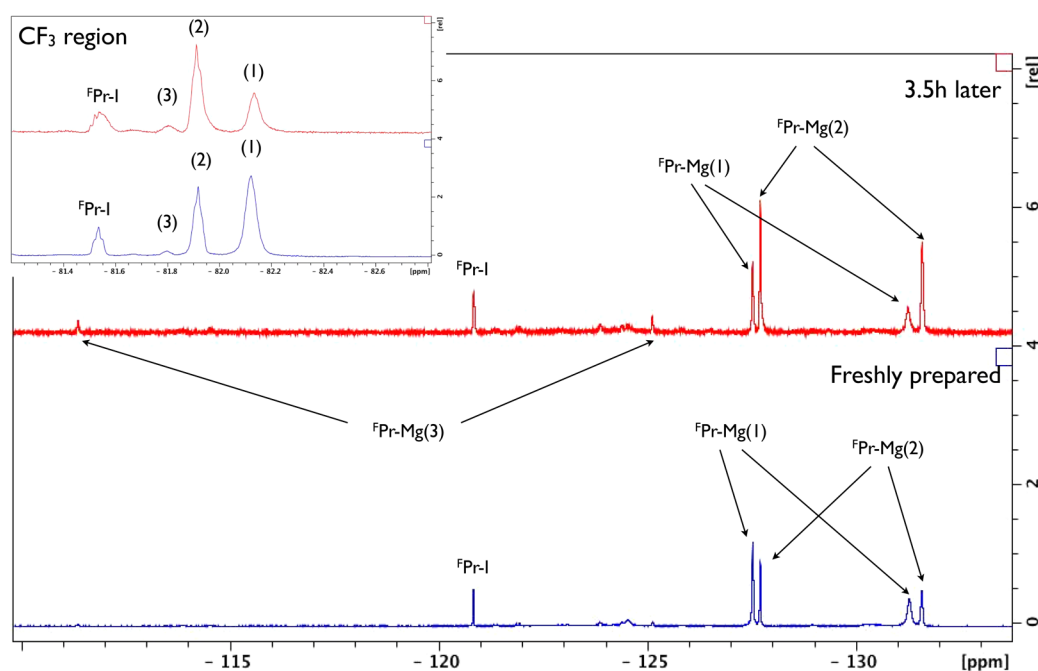


Figure 6. 0.2 M ether solution of $n\text{-}^{\text{F}}\text{PrMgCl}$ at $-78\text{ }^{\circ}\text{C}$.

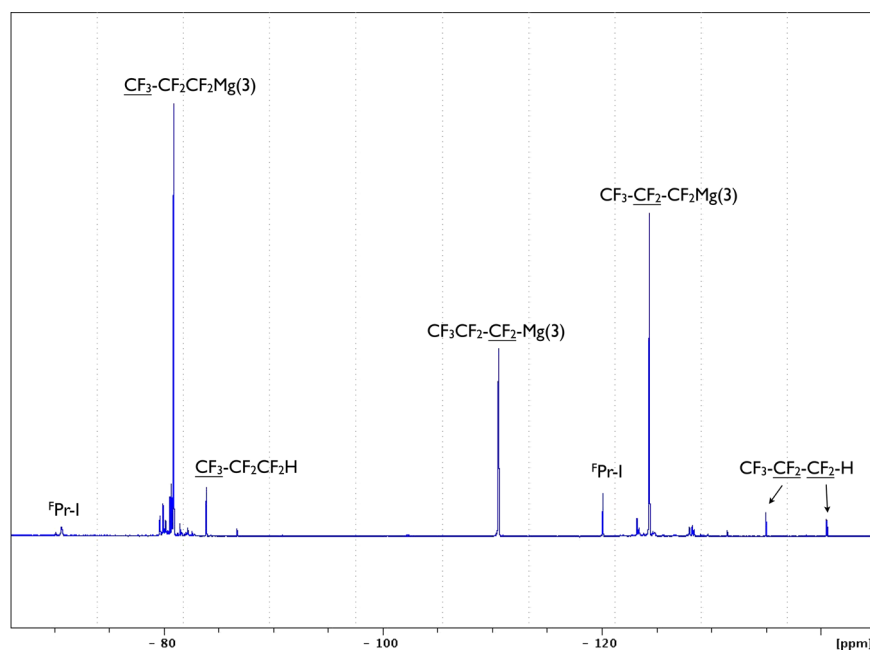


Figure 7. 0.4 M THF solution of $n\text{-}^{\text{F}}\text{PrMgCl}$ at $-78\text{ }^{\circ}\text{C}$.

of dimer (2) to a mixed dimer depicted as (3) consisting of $^{\text{F}}\text{Pr}_2\text{Mg}\cdot\text{MgX}_2$ with bridging halides. Our observations above also clearly suggest that the mixed dimer (3) is more stable when solvated by THF than by ether. All of these solution-state structures are analogous to known crystal structures of non-fluorinated Grignard reagents.¹⁹

CONCLUSION

Although we have observed Schlenk equilibrium in ether solution of $n\text{-C}_3\text{F}_7\text{MgCl}$, this equilibrium favors the “ $^{\text{F}}\text{RMgX}$ ” species in this solvent. $n\text{-C}_3\text{F}_7\text{MgCl}$ slowly decomposes even at $-78\text{ }^{\circ}\text{C}$ and generates perfluoropropene (C_3F_6) as the major

decomposition product. Increasing temperature or increasing concentration accelerates the decomposition. In THF, Schlenk equilibrium strongly favors the formation of the mixed dimer consisting of a dialkyl magnesium species, $^{\text{F}}\text{RMg}^{\text{F}}\text{R}$, and MgX_2 with bridging halides.

EXPERIMENTAL SECTION

Procedures for NMR Experiments. NMR samples were transferred into NMR tubes via cannula. NMR tubes were evacuated in vacuo, flame-dried, and filled with argon before use. ^{19}F chemical shifts were referenced to C_6F_6 at -164.9 ppm . All NMR experiments were acquired on a 600 MHz spectrometer equipped with a z -axis

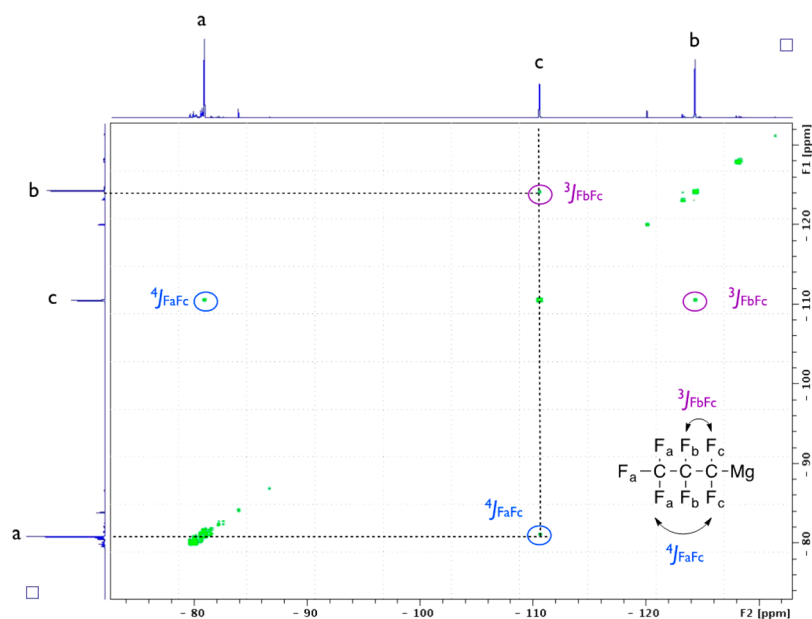
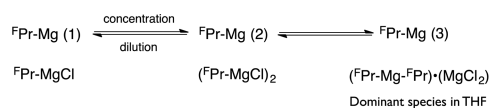


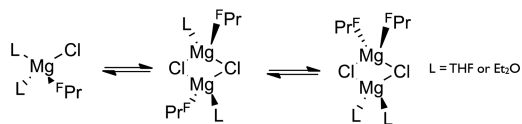
Figure 8. $\{^{19}\text{F}, ^{19}\text{F}\}$ COSY NMR, 0.4 M THF solution of $n\text{-}^{\text{F}}\text{PrMgCl}$ at $-78\text{ }^{\circ}\text{C}$.

Scheme 1. Schlenk Equilibrium Observed in Ethereal Solutions

" $n\text{-}^{\text{F}}\text{PrMgCl}$ " in ethereal solutions:



Possible major species in solution:

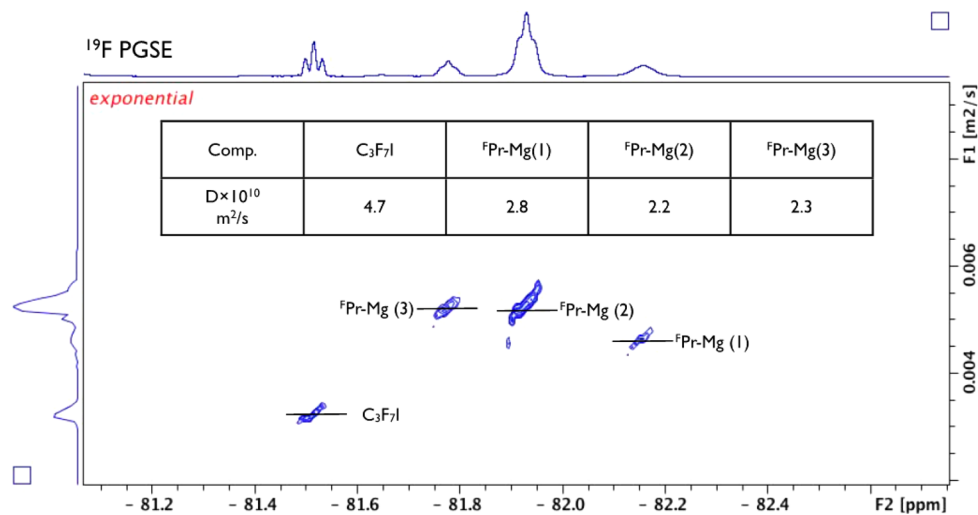


gradient multinuclear broadband fluorine observe (BBFO) smartprobe. The maximum spectral width (sw) is no more than 60 ppm for

all 2D ^{19}F NMR experiments due to the requirement of uniform excitation over the entire bandwidth of observed resonances. $\{^{19}\text{F}, ^{19}\text{F}\}$ COSY and NOESY spectra were acquired by standard programs for ^1H acquisition that had been modified for acquisition of ^{19}F spectra. Mixing time of ^{19}F NOESY experiments was 0.3–0.8 s. For ^{19}F PGSE experiments, a 10A z-axis gradient amplifier was employed, with maximum gradient strength of 0.5 T/m. A standard pulse program dstebppg3s was selected, employing a double stimulated echo sequence, bipolar gradient pulses for diffusion, and three spoil gradients. Diffusion time was 100 ms, and the rectangular gradient pulse duration was 1000 μs . Individual rows of the quasi-2-D diffusion databases were phased and baseline corrected. Actual diffusion coefficients used for D-FW analysis were obtained using the T1/T2 analysis module in commercially available software.

General Procedures for Preparing $^{\text{F}}\text{RMgX}$ NMR Sample.

To a 0.4 M RMgX (1.0 mmol) solution in 2.5 mL of ethereal solvent at $-78\text{ }^{\circ}\text{C}$ under Ar atmosphere was slowly added slightly excess $^{\text{F}}\text{R-I}$ (1.1 mmol). The reaction mixture was allowed to stir at $-78\text{ }^{\circ}\text{C}$.



Complex Size: $\text{C}_3\text{F}_7\text{I} \ll ^{\text{F}}\text{Pr-Mg (1)} < ^{\text{F}}\text{Pr-Mg (2)} \approx ^{\text{F}}\text{Pr-Mg (3)}$

Figure 9. ^{19}F PGSE data and results of 0.4 M ether solution of $n\text{-}^{\text{F}}\text{PrMgCl}$ at $-78\text{ }^{\circ}\text{C}$.

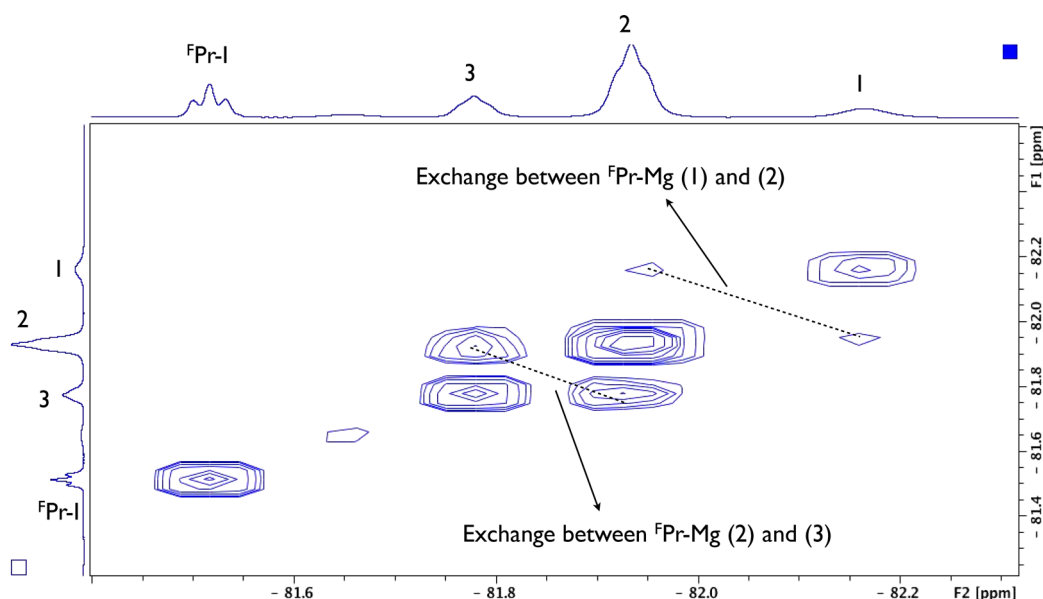


Figure 10. $\{^{19}\text{F}, ^{19}\text{F}\}$ NOESY of 0.4 M ether solution of $n\text{-}^{\text{F}}\text{PrMgCl}$ at $-78\text{ }^{\circ}\text{C}$.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00807.

NMR spectra including PGSE, COSY, and ^1H (PDF)

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Notes

The authors declare no competing financial interest.

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