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Addition reactions of organometallic reagents to nitrogen trifluoride and enhanced alkylalkyl coupling by NF3.

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Graphical Abstract Highlights R-NF<sub>2</sub> were prepared in moderate yields by treating solutions of NF<sub>3</sub> with R-Mg and R-Li reagents. R<sub>2</sub>CuX and R<sub>2</sub>Zn reagents undergo R-R coupling when reacted with solutions NF<sub>3</sub>. R-Ca and R<sub>3</sub>Al reagents are unreactive to soltions of NF<sub>3</sub>.

Abstract

A survey of the reaction of nitrogen trifluoride  $(NF_3)$  with various organometallic reagents finds that organomagnesium (Grignard) reagents are the most useful for producing N,N-difluoroaminoalkanes. Alkyl-alkyl coupling is a persistant side reaction. Organolithiums are marginally effective. Organocopper, organozinc reagents undergo primarily alkyl-alkyl coupling catalyzed by the presence of NF<sub>3</sub>. Organocalcium and organoaluminum reagents are unreactive.

Keywords: nitrogen trifluoride; organometallic; alkyl substitution; aromatic substitution; alkyl-alkyl coupling; difluoroalkylamines

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A survey of the reaction of nitrogen trifluoride (NF<sub>3</sub>) with various organometallic reagents finds that organomagnesium (Grignard) reagents are the most useful for producing N,Ndifluoroaminoalkanes. Alkyl-alkyl coupling is a persistant side reaction. Organolithiums are marginally effective. Organocopper, organozinc reagents undergo primarily alkyl-alkyl coupling catalyzed by the presence of NF<sub>3</sub>. Organocalcium and organoaluminum reagents are unreactive.

Highlights

 $R\text{-}NF_2$  were prepared in moderate yields by treating solutions of  $NF_3$  with R-Mg and R-Li reagents.

 $R_2CuX$  and  $R_2Zn$  reagents undergo R-R coupling when reacted with solutions  $NF_3.$ 

R-Ca and R<sub>3</sub>Al reagents are unreactive to soltions of NF<sub>3</sub>.

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#### 1. Introduction

#### 1.1 Known reactions of organometallics with nitrogen trifluoride

In an NMR study of N,N-difluoroaminoalkanes, we reported that select alkyl isomers had been prepared by the reaction of organomagnesium (Grignard) reagents with NF<sub>3</sub> [1]. At the time, the difluoroaminoalkane products were isolated without concern for yield. It was the intent of this current study to ascertain the efficiency and practicality of preparing N,N-difluoroaminoalkanes from Grignard reagents and subsequently from organometallics in general. We were to find that organomagnesium reagents are the only organometallic capable of producing useable quantities of difluoroaminoalkanes and that alkyl-alkyl coupling is enhanced by the presence of NF<sub>3</sub> and is a persistent problem with the methodology.

The reaction of NF<sub>3</sub> with organometallic reagents has been reported in the literature twice before. Methylmagnesium and ethylmagnesium bromides have been reacted with NF<sub>3</sub> to generate trimethyl- and triethylamine [2]. Japanese Patent 11343270 and its US equivalent (referenced) disclose the preparation of triphenylamines from reaction of complex aryllithium reagents with nitrogen trihalides. One example with NF<sub>3</sub> is given with a 23% yield [3]. In both cases, the NF<sub>3</sub> is fully substituted and no difluoroaminoalkanes are produced.

#### 2. Results and Discussion

#### 2.1 Reaction of NF<sub>3</sub> with organomagnesium (Grignard) reagents

In reference 1 we had successfully prepared analytical quantities of 1-, 2-, and 3difluoroaminopentane and 1-, 2-, and 3-difluoroaminohexane by the reaction of the appropriate 1-, 2-, or 3-bromopentane or 1-, 2-, or 3-chlorohexane with magnesium metal followed by reaction with NF<sub>3</sub>. In light of refs. 2 and 3, it was assumed that multisubstitution reactions would be a likely problem, so reactions were performed at concentrations below 0.1M. Further, prepared solutions of the Grignard reagent were slowly added to saturated solutions of NF<sub>3</sub> at low temperature so as to maintain an excess of NF<sub>3</sub>. This methodology suffered principally from the loss of product during the distillative removal of the

gross excess of solvent. To make the process preparatively useful, we now would increase the concentration of organomagnesium reagent to ~1.0 M and attempt to use less of the saturated  $NF_3$  solution, hopefully maintaining  $NF_3$  concentration throughout the reaction by replacing reacted  $NF_3$  via a pressurized  $NF_3$  atmosphere. Such a procedure would be performed in a stainless steel pressure vessel (Parr Mini-Reactor).

In our initial experiment, an ice chilled 1.3M solution of *n*-pentylmagnesium bromide in ether was slowly transferred via nitrogen pressure into an equal volume of ice-chilled 150 psi NF<sub>3</sub> saturated ether in a SS steel pressure reactor. Product analysis by G.C. showed 22% difluoroaminopentane, 32% pentanenitrile, and 45% *n*-decane. The pentanenitrile is the HF elimination product from difluoroaminopentane, indicating an overall substitution level of 54%, very encouraging. However, the formation of *n*-decane, the dimer of *n*-pentane, is the result of alkyl-alkyl coupling. A direct acid/water quench of the initial Grignard reagent produced no *n*-decane. Clearly, the coupling was occurring post-Grignard formation. A similar experiment with 1.0 M benzylmagnesium chloride produced copious quantities of dibenzyl.

Our first suspicion was that iron or other metals from the stainless steel system were catalyzing the coupling, a well known catalytic reaction [4]. We immediately converted to an all glass and fluoropolymer system consisting of Fisher-Porter style glass pressure flasks with PTFE clad stir bars, FEP transfer tubes and PFA valves [5]. Additionally, we began using a higher purity 99.98% magnesium metal. The reaction was repeated, at lower concentration (0.1M) and lower temperature (-20°C), in the glass/fluoropolymer system. Substitution products, combined, amounted to 50%. Coupling still occurred at 28%, an improvement, but not any indication that changing from a metal reactor to a glass reactor was stopping the coupling. We learned also, that coupling was occurring to some extent during the initial formation of some Grignard reagents, particularly as we attempted higher concentrations. We found suitable results generating the Grignard at lower temperatures than normal and concentrations around 0.5M.

Table 1 shows the results of reacting various alkyl, aryl and benzyl Grignard reagents with  $NF_3$  in the glass/fluoropolymer system. All yields in the following tables are G.C. percentage unless otherwise stated.

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Reagent	Solvent	М	Temp (°C)	R-NF <sub>2</sub>	Dimer
1-pentyl-MgBr	ether	0.15	-20	50%	28%
2-pentyl-MgBr	ether	0.15	-30	38%	36%
		0.5	-78 to 0	29%	49%
3-pentyl-MgBr	ether	0.15	-30	42%	40%
2-hexyl-MgCl	ether	0.15	-22	24%	50%
3-hexyl-MgCl	ether	0.15	-30	48%	50%
	ether	0.5	-30	27%	
cyclohexyl-MgCl				(+ 32% c-	19%
				hexane and	
				22% c-hexene)	
benzylmagnesium chloride	ether	1.0	-20	0%	100%
	$\mathbf{O}$				
α-ethylbenzylmagnesium chloride	ether	0.5	-78 to 0	0%	76%
phenylmagnesium bromide	ether	0.15	-40	0%	19%

Table 1. Reaction of organomagnesium reagents with  $NF_3$ .

We performed several one-flask experiments where the pre-formed Grignard reagent was subjected to a pressurized atmosphere of  $NF_3$  to no benefit.

Attempts were made to <u>form</u> the Grignard reagents <u>under</u> an atmosphere of  $NF_3$ , so as to intercept the organomagnesium reagent or the organic radical before coupling occurred. In each case,

formation of the Grignard was completely inhibited. Logically, one might suppose that the NF<sub>3</sub> is reacting with the Mg metal to form an unreactive  $MgF_2$  coating on the Mg granules. However, at least for the case of phenyliodide, removing the NF<sub>3</sub> from such a system by repeated aspiration at 0°C resulted in the formation of the Grignard reagent, Ph-MgI. Hydrolysis yielded benzene and biphenyl.

### 2.2 Reaction of NF<sub>3</sub> with organolithium reagents

Assuming that our observed coupling is the combination of two alkyl radicals, we surmised that an organometallic reagent of more ionic character than a Grignard reagent might perform the substitution reaction in preference to the coupling. Organolithium became our next subject of study.

As organolithium reagents are apt to solvolyse ethers at temperatures above dry ice/acetone conditions, most reactions were performed in *n*-pentane. Due to their limited solubility in that solvent, they were formed with the assistance of TMEDA (and later without). *n*-Butyllithium and *n*-hexyllithium were purchased hexane solutions. Other alkyllithiums were prepared from the organohalide and lithium metal [6],[7] while the benzyllithium reagents were prepared from the benzylic alkane and *n*-BuLi [8]. The benzyllithium solution is essentially a slurry and really not suitable for this type of reaction. 2-lithioethylbenzene and diphenymethyllithium did not form under these conditions.

Reagent	Solvent	Temp (°C)	R-NF <sub>2</sub>	Dimer
•		,	_	
<i>n</i> -BuLi	pentane/TMEDA	0	а	Only octane obs'd
		_	_	,
			a	45% octane
<i>n</i> -BuLi	pentane	0	_	
		-	55% 4-octanone	
<i>n</i> -hexvl-Li	pentane	-78 to 0	29%	71%
	P			
			7%	
c-hexvl-Li	pentane/TMEDA	-30 to RT		24%
,	<b>1</b> • • • • •		(+ 69% c-hexane and c-hexene)	
			1	

Table 2. Reaction of organolithium reagents with NF<sub>3</sub>.

phenyl-Li	ether ether/THF	-78 to 0	0% (61% benzene)	31%
benzyl-Li	toluene	0 to 70	0%	Only dibenzyl obs'd

<sup>a</sup> obscured by solvent

The reactions of *n*-Bu-Li showed that dimer formation was still occurring for this R-Li. While both *n*-Bu-NF<sub>2</sub> and *n*-Bu-H were unobservable due to solvent interference in G.C., in the TMEDA free case, substitution was evidenced by the observation of 4-octanone. Its formation via *n*-Bu-NF<sub>2</sub> is described by Scheme 1. In the case of *n*-BuLi with TMEDA, it is likely that proton abstraction of the TMEDA to generate butane occurs faster than reaction with NF<sub>3</sub>. For the reaction of *n*-hexyl-Li, substitution is directly observed as *n*-hexyl-NF<sub>2</sub>. Phenyllithium reagent generated and added to ether/NF<sub>3</sub> or added to THF/NF<sub>3</sub> generated only benzene and biphenyl, hydrolysis predominating 2:1. In addition, these reactions produced much insoluble sludge, unseen in any other reactions in this study. In attempts to imitate Reference 3, that is the formation of trialkylamine by the slow addition of NF<sub>3</sub> to an ether solution of Ph-Li generated no detectable Ph<sub>3</sub>N (GC/MS). Biphenyl was formed in 13% while hydrolysis still predominated at 58%. Again the reaction produced much insoluble sludge.

The case of benzyllithium is of particular importance because it was prepared by the deprotonation of toluene. As such, at no time was a benzyl halide present in the reaction and, as such,  $S_N 2$  coupling of R-M + R-X is not possible (formal Wurtz coupling). Coupling of R-Li + R-Li is being initiated by the presence of NF<sub>3</sub> as it apparently is during the coupling of R-MgX with R-MgX. This despite the more ionic nature of R-Li.

Scheme 1. Formation of 4-octanone



#### 2.3 Reaction of NF<sub>3</sub> with organocopper and organocuprate reagents

Preformed copperphenylacetylide [9] was reacted as a slurry with NF<sub>3</sub> in THF overnight at  $100^{\circ}$ C. The only observed product is bis-diphenylacetylene. In addition, a small amount of copper plating was observed on the wall of the flask.

 $(n-\text{Hexyl})_2\text{Cu}(\text{CN})$ Li reacted instantaneously with NF<sub>3</sub> in ether at -50°C (as observed by formation of white CuFX salts) to generate dodecane in 83% <u>isolated</u> yield. (Benzyl)<sub>2</sub>Cu(CN)Li likewise generated dibenzyl instantly and exclusively. Dialkylcuprates tend to be radical addition reagents (think 1,4-carbonyl addition) and paired with NF<sub>3</sub> makes an excellent coupling system.

Scheme 2. Reactions of copper reagents with NF<sub>3</sub>.



### 2.4 Reaction of NF3 with organocalcium reagents

Organocalcium reagents are very reactive but more difficult to prepare than other organometallics [10]. Initially, we prepared organocalcium reagents from activated calcium powder by the method of Westerhauser [11]. For the reaction of Ph-Cal with NF<sub>3</sub>, there was no reaction (only benzene observed after work-up). For the reaction of c-hexyl-CaBr, a mixture of 39% cyclohexane, 18% cyclohexene, and 23% bicyclohexyl was isolated, indicating poor reactivity for the alkylcalcium. Both reactions were repeated with active calcium generated from lithium biphenylide with Cal<sub>2</sub> [12]. For the cases of PhCal and c-hexyl-CaI, no addition to NF<sub>3</sub> was observed. We have no observations of coupling for the Ph-CaI reaction as the biphenyl co-reagent masked the observation of the biphenyl coupling product. Catalytic biphenyl (10%) was ineffective. For the reaction of c-hexyl-CaI, the products of cyclohexane, cyclohexene, and bicyclohexyl were all again observed with no discernable c-hexyl-NF<sub>2</sub>.

Ca/Hg amalgam was only partially reactive with Ph-Br to produce  $\sim$ 1/4 strength Ph-CaBr. The grey suspension turned to chocolate brown upon exposure to NF<sub>3</sub>, however no reaction products (neither substitution nor dimerization) were observed.

#### 2.5 Reaction of NF<sub>3</sub> with organozinc reagents

(*n*-hexyl)<sub>2</sub>-Zn in NF<sub>3</sub>/ether produced a white precipitate as it warmed from 0 to 20°C. Small amounts of 1- and 2-NF<sub>2</sub>-hexane were observed, but the principle product was 46% dodecane (coupling product). Repeating the experiment in THF/toluene [13] increased the production of difluoaminohexanes to 22% and reduced the dodecane to 16%. However, the apparent gain was offset by the generation of 24% heptylbenzene and 25% dibenzyl by cross-coupling and coupling of the toluene respectively.

We attempted to formalize the above observed coupling of  $Bn_2Zn$  by preparing  $Bn_2Zn$  from BnLi slurry and injected it into a saturated NF<sub>3</sub>/ether solution at -78°C and allowing to warm to room temperature. The reaction generated a white precipitate but upon quenching produced only toluene. Solvolysis was the only reaction. As with BnLi, solubility was an issue with  $Bn_2Zn$ .

(c-Hexyl)<sub>2</sub>Zn in THF/toluene is mostly unreactive up to room temperature.

#### 2.6 Reaction of NF<sub>3</sub> with organoaluminum reagents

Organoaluminum reagents are generally found in two reagent forms, the trialkylaluminum and the sesquihalide. The sesquihalide is formally  $R_{3/2}AIX_{3/2}$  and is a mixture of  $RAIX_2$  and  $R_2AIX$ . We tested both forms for reactivity with NF<sub>3</sub>. For our tests, the sesquihalides and the trialkylaluminums were prepared from the addition of R-Li to  $AICI_3$  in ether [14].

Neither  $Ph_{3/2}AlCl_{3/2}$  nor  $Ph_3Al$  showed any reactivity in -78°C reactions that were allowed to stir to room temperature overnight. Similarly, *n*-hexyl<sub>3/2</sub>AlCl<sub>3/2</sub> and *n*-hexyl<sub>3</sub>Al were also unreactive under the same conditions. Non-reactivity included no discernable formation of dimers.

### 2.7 Mechanistic considerations

For the literature reaction of *n*-heptyl-MgBr + benzyl chloride (at reflux temperatures), the principle products are heptane, heptene and bibenzyl [15]. The critical mechanistic steps are the separation of heptyl radical from MgBr radical and the subsequent extraction of CI radical by MgBr radical to form MgBrCI and benzyl radical (which dimerizes). We envision a similar mechanism by which NF<sub>3</sub> forces the separation of alkyl radical from MgX even at low temperature as shown in Scheme 3, Reaction 1. Dimerization of R<sup>-</sup> competes with R-NF<sub>2</sub> formation, Reaction 2 vs. Reaction 3. However, Reaction 4, the dimerization of 'NF2, also competes with Reaction 3, allowing alkyl dimerization to outpace R-NF<sub>2</sub> formation. We attempted but were unable to verify the existence of F<sub>2</sub>N-NF<sub>2</sub> in our reaction gas space by GC or GC/MS.

Scheme 3. Mechanistic steps.

1)	$R-MgX + NF_3 \longrightarrow R + FMgX + NF_2$
2)	R' + R' → R-R
3)	$\dot{R} + \dot{N}F_2 \longrightarrow R - NF_2$
4)	$F_2N + NF_2 \longrightarrow F_2N - NF_2$

### 3. Conclusion

This survey of reacting organometallic reagents with nitrogen trifluoride shows that organomagnesium (Grignard) reagents are the reagent of choice for the generation of R-NF<sub>2</sub>. All other organometallics were either unreactive or caused dimerization of the alkyl substituent. Even the Grignards suffered large loss of yield due to dimer formation. In many cases, dimerization occurs to varying degrees during generation of the organometallic and we have not differentiated that quantity from the final observed dimer quantity. Quantities of R-NF<sub>2</sub> and dimer listed in Table 1 and Table 2 are then those observed for the formal conversion of R-X to R-NF<sub>2</sub>.

### 4. Experimental

### 4.1 General

Alkyl halides, Li foil, Cal<sub>2</sub>, CuCN, and ZnBr<sub>2</sub> were from Aldrich. Magnesium was Aldrich 99.98 granular. *n*-Butyllithium and *n*-hexyllithium were hexane solutions purchased from Fisher/Acros. Nitrogen Trifluoride was from Fluoromar. THF and ether were distilled from sodium/benzophenone.

250ml and 500ml Fisher-Porter reaction flasks with a working pressure limit of 150 psi were manufactured by Quark Glass Inc. PFA needle valves were manufactured by Whitey Inc.

Products were identified by GC analysis vs. authentic samples and GC/MS. Both instruments used 60 M DB-1701 capillary columns.

### 4.2 Cautionary Notes

Nitrogen trifluoride is toxic by inhalation and should only be used in a well ventilated environment. It is apparent to us that the N,N-difluoroamino products are toxic as well. In addition, trace by-products may be toxic and concentrated during distillation. Compounds containing multiple NF<sub>2</sub> groups have been used as high energy propellant oxidizers [16] and their inadvertent concentration may pose additional risk.

Reactions performed in pressurized glass apparatus should be performed behind an adequate blast shield and hood sash. In addition, personal protective equipment included a heavy leather jacket, ballistic vest, additional neck protection, leather gloves and a safety helmet with double thickness full face shield. Hearing protection is worn at all times as the bursting of even small diameter plastic tubing can cause serious hearing damage.

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