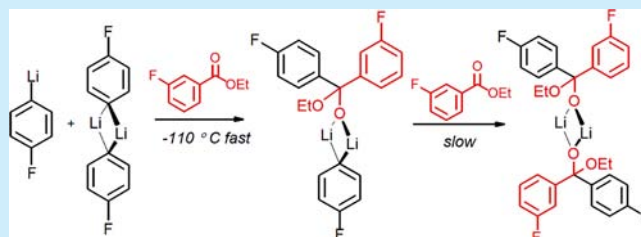# A Rapid Injection NMR Study of the Reaction of Organolithium Reagents with Esters, Amides, and Ketones

Kristin N. Plessel,[†] Amanda C. Jones,[†] Daniel J. Wherritt,[†] Rebecca M. Maksymowicz,[†] Eric T. Poweleit,[†] and Hans J. Reich*

Department of Chemistry, University of Wisconsin, 1101 University Avenue, Madison, Wisconsin 53706, United States

S *Supporting Information*

ABSTRACT: Unexpectedly high rates of reaction between alkyllithium reagents and amides, compared to esters and ketones, were observed by Rapid Inject NMR and competition experiments. Spectroscopic investigations with 4-fluorophenyllithium (ArLi, mixture of monomer and dimer in THF) and a benzoate ester identified two reactive intermediates, a homodimer of the tetrahedral intermediate, stable below −100 °C, and a mixed dimer with ArLi. Direct formation of dimers suggested that the ArLi dimer may be the reactive aggregate rather than the usually more reactive monomer. In contrast, RINMR experiments with ketones demonstrated that the ArLi monomer was the reactive species.

The reactions of organometallic reagents with aldehydes, ketones, esters, and other carbonyl compounds are widely employed C−C bond forming methods. A century of organic chemistry lore has defined aldehydes, acid chlorides, and anhydrides as most reactive, ketones intermediate, esters slower, and amides and carboxylate anions the least reactive. However, there is one important class of nucleophiles, the organolithium reagents, for which the evidence is more anecdotal than quantitative, since most reactions are too fast for normal kinetic measurements, even below −78 °C. The Rapid Injection NMR technique (RINMR)[1a,b] has provided an avenue for the study of such reactions.

n-Butyllithium in THF solution is a mixture of a dimer and tetramer.[2,3] The tetramer reacts only with the most active electrophiles such as benzaldehyde, DMF, and PhCOCl,[1a] but with esters, ketones, and amides, the tetramer dissociates to dimer faster than the reaction with the electrophile, and only the dimer is reactive. An interesting corollary here is that these Lewis basic electrophiles do not assist in tetramer dissociation.[4] A RINMR survey of the rate of reactions of *n*-BuLi dimer with common electrophiles is illustrated in Figure 1. As expected, acetone was more reactive than the ester methyl benzoate (although only by a factor of 8.6). To our surprise, however, the rate of reaction with the tertiary benzamide was comparable to the reaction with the ketones, and considerably faster than that with benzoate esters. Likewise, *N,N*-dimethylformamide (too fast to measure) reacted faster than ethyl formate (half-life of 1.1 s at −130 °C).

Similar results were found when competition experiments were performed by addition of *n*-BuLi into an excess of ester and amide in THF at −78 °C (Scheme 1). We used fluorine-substituted benzoate ester **1** and amide **2** to allow use of ^{19}F NMR spectroscopy for quantification. Since both **1** and **2** give a
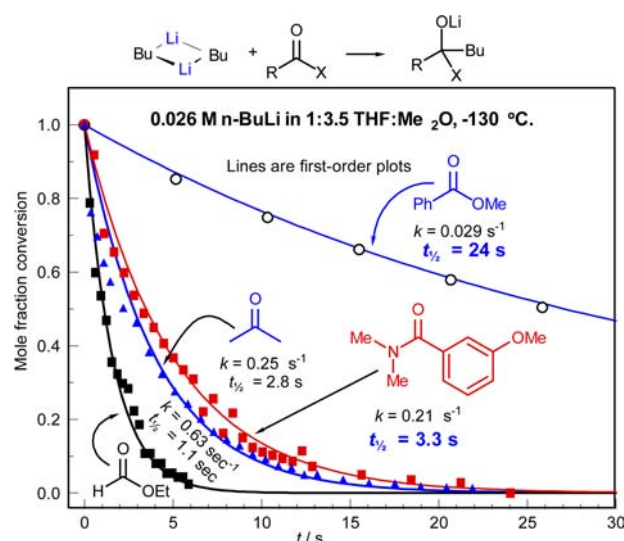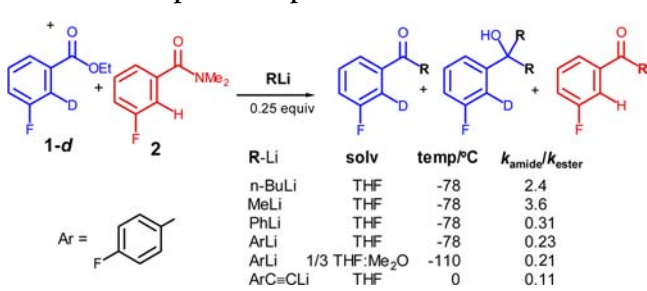

Figure 1. RINMR rate study of the reaction of several carbonyl compounds with *n*-BuLi dimer. The tetramer of *n*-BuLi (ca. 60%) is unreactive on this time scale. The points are experimental data for disappearance of $(n\text{-BuLi})_2$ measured from the ^{7}Li NMR spectra; the lines are first-order plots with the rate constants shown.

common ketone product, one of them was labeled with deuterium (**1-d**) at the 2-position to distinguish the source. The ^{19}F NMR deuterium isotope shift of ca. 0.3 ppm allowed distinction between deuterated and undeuterated ketones. In these experiments the amide was 2.4 times as reactive as the ester toward *n*-BuLi, and 3.6 times more reactive with MeLi.

Scheme 1. Competition Experiments

R-Li	solv	temp/°C	k_{amide}/k_{ester}
n-BuLi	THF	−78	2.4
MeLi	THF	−78	3.6
PhLi	THF	−78	0.31
ArLi	THF	−78	0.23
ArLi	1/3 THF:Me$_2$O	−110	0.21
ArC≡CLi	THF	0	0.11

In contrast, the ester **1** was 3−4 times more reactive than **2** with the aryllithium reagents at −78 °C, and by a factor of 9 with lithium 4-fluorophenylacetylide at 0 °C,[5] still orders of magnitude less than predicted from other nucleophilic substitutions (e.g., the basic hydrolysis of ethyl benzoate is 645 times as fast as that of benzamide at 40 °C).[6]

Efforts to understand the origin of this effect in the *n*-BuLi RINMR kinetic studies provided only hints of answers. The initial rates of reaction of $(n\text{-BuLi})_2$ with ester **1** are first-order in ester, and those with amide **2**, at least first-order. Thus, in neither case is conversion of $(n\text{-BuLi})_2$ to a more reactive species (open dimer, monomer) rate limiting. A more detailed kinetic analysis of these reactions was thwarted by complex and not always reproducible kinetic behavior.

We thus directed our efforts to a study of the reactions of 4-fluorophenyllithium[7] (here referred to as ArLi). This lithium reagent does not show the "inverted reactivity" of the alkyllithiums, and there is the disadvantage of mostly working under Curtin−Hammett conditions. The two aggregates present, $(\text{ArLi})_1$ and $(\text{ArLi})_2$, interconvert rapidly on the time scale of addition to esters and amides, with a half-life of dimer dissociation, measured by ^{19}F DNMR coalescence, of less than 2 s at −140 °C. However, the RINMR experiments benefitted greatly from being able to simultaneously identify and quantify starting materials, intermediates, and products in real time by ^{19}F NMR spectroscopy.

An RINMR experiment in which excess **1** was injected into ArLi at −110 °C is shown in Figure 2. All of the ArLi was consumed within 10 s to form a single new species, the mixed dimer **3·ArLi**.[9] If only 0.5 equiv of ester was present, the reaction stopped here. With excess ester (as in the experiment shown) the reaction continues more slowly to cleanly form the homodimer of the tetrahedral intermediate $(3)_2$.[14] This part of the reaction shows an approximate first-order dependence on ester concentration, so **3·ArLi** is reacting directly, rather than via rate-limiting dissociation to monomeric ArLi. On warming above −100 °C the tetrahedral intermediates **3·ArLi** and $(3)_2$ decompose to ketone, which is converted to tertiary alkoxide if any ArLi remains in solution. The half-life of $(3)_2$ is ca. 4.7 h at −97 °C.

Careful quench of reactions of **1** and ArLi below −100 °C gave a nearly quantitative yield of ketone, with a ketone to tertiary alcohol ratio greater than 200/1. This clean ketone synthesis directly from aryllithium and ester reagents inspired investigation of possible synthetic applications. Unfortunately, this method requires that the addition of RLi to ester be fast below −100 °C, which is true only in a few specific cases. With *n*-BuLi the dimer reaction is fast enough, but the tetramers of both *n*-BuLi and MeLi react too slowly for a synthetically viable reaction. Disappointingly, synthetic application appears to be limited to benzophenone formation from methyl or ethyl benzoate esters.
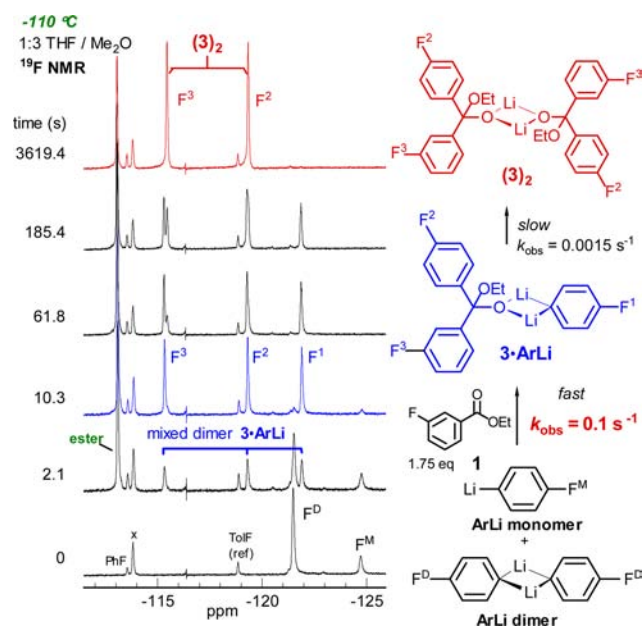

Figure 2. ^{19}F RINMR experiment: injection of 1.75 equiv of ester **1** into a solution of 75 mM 4-fluorophenyllithium.

Intermediates **3·ArLi** and $(3)_2$ appear to be the first spectroscopically characterized anionic tetrahedral intermediates of esters which do not bear special stabilizing features such as cyclic structures (lactone adducts),[16] strongly chelating groups,[10] or very electronegative[17] substituents. Amide tetrahedral intermediates are much more stable, and several have been characterized.[15,18]

A similar experiment with amide **2** was 1/160 as fast under comparable conditions and gave a mixture of at least four tetrahedral intermediates. Three ^{19}F NMR peaks which might correspond to ca. 20% of the mixed dimer between ArLi and the tetrahedral intermediate were present during the reaction.

These experiments raise several interesting questions. First, the competition experiment in Scheme 1 run under comparable conditions (k_{ester}/k_{amide} = 4.8) seems inconsistent with the RINMR rate data (k_{ester}/k_{amide} = 160). This relative reactivity issue was clarified by a more careful RINMR examination of the amide and ester reactions. Solutions of mixed dimer **3·ArLi**, stable at −110 °C, could be prepared by addition of 0.5 equiv of ester to ArLi. This should also be the principal species present initially in the ester−amide competition experiments. We were then able to compare the reactivity of ester **1** and amide **2** with **3·ArLi** using separate injections of electrophile, and found ester to be only twice as fast. The ester showed pseudo-first-order kinetics with an excess of **3·ArLi** (i.e., dissociation of the mixed dimer is not the rate-limiting step), and the amide, more complex behavior which we could not clarify. Thus, in the competition experiment, during the first half of the reaction almost all of the ArLi reacts with ester to form **3·ArLi** (approximately 99% ester, 1% amide reacts). Once the free ArLi is depleted, the mixed dimer **3·ArLi** is the sole source of the nucleophile, and it reacts only twice as fast with ester (66%) as with the amide (33%), leading to a calculated k_{ester}/k_{amide} of 4.9, close to the competition experiment values of 4.8 at −110 °C and 4.3 at −78 °C.[19]

A second question concerns the exclusive formation of the mixed dimer **3·ArLi** from the ester, which raises the interesting possibility that ester reacts preferentially with the dimer of ArLi. Lower aggregates are almost invariably more reactive than higher

ones.[1a,d,21a] Although numerous mixed aggregates have been observed when different aggregated lithium species are combined,[2,22] these are virtually always equilibrium situations. The very reasonable assumption that the reaction of RLi aggregated substrates to form mixed aggregates as kinetic products (i.e., dimer to dimer or tetramer to tetramer) has only recently been experimentally confirmed.[19]

Some surprisingly small rate differences between monomer and dimer enolates in a crossed Claisen condensation prompted Streitwieser, Leung, and Kim[21b] to suggest that esters may be unusually reactive toward dimers as a consequence of lithium coordination to both oxygens, as in **4**. Such double activation is not available for amides or ketones. Formation of the precomplex **4** requires the less stable E conformation of the ester. A reasonable estimate of the barrier for ester rotation (9−10 kcal/mol[23]) is close to or below the barrier for the reaction of Figure 1 (10.1 kcal/mol).[24]
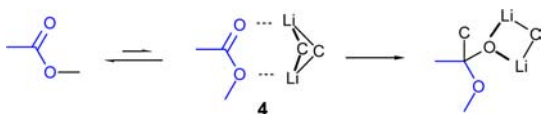
Several tests of the hypotheses that the ArLi dimer is involved in the formation of **3·ArLi** did not give clear answers. Addition of PMDTA (N,N,N',N'',N''-pentamethyl-diethylenetriamine) to ArLi converts it to a PMDTA-complexed monomer. This monomer is about 1/45 as reactive toward ester **1** as the THF-solvated monomer/dimer mixture, as expected if the dimer is the reactant. Other explanations are plausible, such as a suppression of Lewis acid assistance by lithium by complexation to PMDTA.[1b,20c]

When the ester addition was performed in a less polar solvent (1:7 Me_2O/Et_2O mixture), where monomer ArLi could no longer be detected, only a factor of 2 reduction in the addition rate was observed, even though the monomer concentration was reduced by at least a factor of 25. A subtle effect, but it is consistent with reaction of the dimer.

It is not possible to perform experiments with ester **1** under non-Curtin−Hammett conditions to specifically identify the reactive ArLi aggregate, since the ArLi dimer-to-monomer interconversion is several orders of magnitude faster than the reaction with **1**.[7] More reactive esters were also too slow: isopropyl 3-fluorobenzothioate ($t_{1/2}$ is 15 s at −130 °C), methyl trifluoroacetate ($t_{1/2}$ ca. 25 s at −137 °C), ethyl formate ($t_{1/2}$ ca. 2.5 s at −137 °C).

The higher reactivity of ketones gave some hope that an RINMR experiment could be run under non-Curtin−Hammett conditions. The reaction of ArLi with excess 3,4′-difluorobenzophenone at −124 °C was much slower than ArLi aggregate interconversion ($t_{1/2}$ 30 s). The kinetic product appears to be the lithium alkoxide monomer, strongly suggesting that the ArLi monomer is the reactive species. The monomer then forms a dimer, as well as a mixed dimer (analogous to **3·ArLi**) if excess ArLi is present, which reacts much more slowly with the ketone, the reaction being essentially complete at 4000 s.

3-Fluoroacetophenone (**5**) was more reactive. At 135 °C all of **5** has reacted after 1.6 s, and again the first formed product is a monomeric alkoxide **(6)₁**. If excess ArLi is present, **(6)₁** heterodimerizes with a half-life of ca. 8 s to form the mixed dimer **6·ArLi**[25] or homodimerizes to **(6)₂** if ketone is in excess. If the addition of excess ArLi to **5** was performed at the higher temperature of the ester experiments (−110 °C), the first observed product was the mixed dimer **6·ArLi**. With excess

ketone, on the other hand, only trace amounts (<15%) of **6·ArLi** was formed. This is because addition of ArLi to ketone is faster than either the cross dimerization to form **6·ArLi** or the homodimerization to form **(6)₂**. Thus, the formation of **3·ArLi** as the sole kinetic product in the ester reaction is plausible even if the ArLi monomer is the active reagent.

Figure 3 shows an experiment where excess **5** was injected into a solution of ArLi at our lowest accessible temperature, −140 °C.
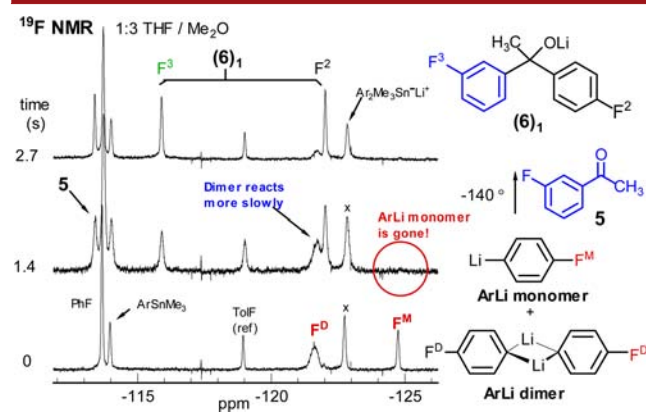

Figure 3. 19F RINMR experiment: injection of 2.5 equiv of ketone **5** into a solution of 75 mM 4-fluorophenyllithium at −140 °C in 1:3 THF/Me_2O.

The ArLi monomer has reacted completely within 1.4 s after the injection. However, there was still a significant concentration of ArLi dimer present, so the ketone unambiguously reacts more rapidly with the monomer.[26] We are just slightly under the "Curtin−Hammett limit."

Our experiments have not answered the initial question on the unusual reactivity effects toward amides and esters shown by alkyllithium reagents, which must have their origin in the higher basicity of amides vs esters toward lithium cations.[27,28] Using the RINMR technique we were able to study the reaction of 4-fluorophenyllithium with esters, amides, and ketones, observe in unprecedented detail the progression of tetrahedral intermediates and alkoxides formed, and obtain specific information about the aggregation and mixed aggregation processes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, NMR spectra, and kinetic traces of all experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: reich@chem.wisc.edu.

Present Address

†Kristin N. Plessel, University of Wisconsin-Rock County, 2909 Kellogg Ave, Janesville, WI 53546. Amanda C. Jones, Department of Chemistry, Salem Hall, Wake Forest University, Winston-Salem, NC 27109. Daniel J. Wherritt, The Samuel Roberts Noble Foundation, 2510 Sam Noble Pkwy, Ardmore, OK 73401. Rebecca M. Maksymowicz, 2 Pear Tree Cottage, Aldsworth, Cheltenham, Gloucestershire, GL54 3QZ, U.K. Eric T. Poweleit, 229 Chemistry Building, University Park, PA 16802.

Notes

The authors declare no competing financial interest.

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(5) The complexity of RLi behavior is illustrated by the selectivity of the Weinreb oxalamide Me(MeO)NC(=O)C(=O)OEt, where an aryllithium reacts with the amide carbonyl, and *n*-BuLi reacts with the ester, the opposite selectivity as observed in Scheme 1. Chiu, C. C.; Jordan, F. *J. Org. Chem.* **1994**, *59*, 5763.

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(10) A tetrahedral intermediate (presumably stabilized by chelation) was detected after addition of 1-methyl-2-lithiobenzimidazole to methyl benzoate (^{13}C signal of the acetal carbon at δ 101.9): Asakawa, K.; Dannenberg, J. J.; Fitch, K. J.; Hall, S. S.; Kadowaki, C.; Karady, S.; Kii, S.; Maeda, K.; Marcune, B. F.; Mase, T.; Miller, R. A.; Reamer, R. A.; Tschaen, D. M. *Tetrahedron Lett.* **2005**, *46*, 5081.

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(14) The structure assignment of $(\mathbf{3})_2$ was based on its mode of formation, its decomposition to ketone at −95 °C, and the observation of the ketal carbon at δ 102.8 in the ^{13}C enriched substrate.[10] The dimer aggregation state was inferred from a DOSY[11−13] molecular weight estimation in Me$_2$O solution at −115 °C: 559 g/mol (calcd 632.5 g/mol for bis Me$_2$O solvate). A closely related tetrahedral intermediate $(\text{Ph}_2(\text{Me}_2\text{N})\text{COLi})$ crystallizes from THF as a bis-solvated dimer.[15a]

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(25) The NMR properties of **6·ArLi** were very similar to those of **3·ArLi**. The same heterodimer was formed if the tertiary alcohol was treated with excess ArLi at −110 °C. Monomeric **6** was not formed even when deprotonated by a monomeric base at temperatures where the dimerization of **6** is slow. We hypothesize that any $(\mathbf{6})_1$ generated could rapidly form the strongly hydrogen bonded dimer (RO−H−OR$^-$ Li$^+$), which is then deprotonated to form $(\mathbf{6})_2$. Alternatively, the hydrogen bonded alcohol could be deprotonated directly to form RO−H−OR$^-$ Li$^+$.

(26) Analysis of the concentration vs time curve shows that monomeric ArLi is at least 3.5 times as reactive as the dimer towards **5**.

(27) Addition of LiI in THF affects the ^{19}F NMR shifts of **2** but not those of **1** (see Supporting Information).

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