Highly Reactive Magnesium and Its Application to Organic Syntheses

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A method for producing highly reactive magnesium slurries is presented, along with a brief comparison to other methods of activation. Reactions of the activated magnesium with a variety of functional groups are examined, including ethers, tosylates, and nitriles. Attempts were made to form Grignard reagents which contained ketone, ester, and nitrile functionality. The Grignard reagent from 8-bromooctane-1-nitrile was successfully prepared in moderate yield.

Introduction

The preparation of highly reactive magnesium by alkali metal reduction of magnesium salts has previously been reported.[2] Other methods of activation include evaporation of metal atoms[3] as well as the reversible formation of an anthracene complex with magnesium, thereby "dissolving" bulk magnesium and depositing activated magnesium.[4] We report here, the results of further activation studies using the reduction of magnesium salts approach and a survey of the chemistry resulting from this magnesium (Mg*).

Results and Discussion

Activation Studies. Table I contains data on the relative reactivities of Mg obtained by a variety of methods, as well as commercial powders. In those cases where the reaction rates were too great to be conveniently measured, the rates were slowed by decreasing the temperature or switching to less reactive substrates. Entries in Table I, not based on the lithium reduction of $MgCl_2$, are taken from the literature. The method of activation based on anthracene is not included, due to the lack of published data.

The current method recommended for producing Mg* is based on the use of lithium as the reducing agent. This method is preferred for its inherent safeness. Because of lithium's high melting point, it is not practical to use a solvent whose boiling point is high enough to fuse lithium. This problem is circumvented by performing the reductions at room temperature, using naphthalenes as an electron carrier to speed the reaction. Reduction is usually complete in 6–12 h. If naphthalene will interfere with additional reactions or product isolation, it may be removed by rinsing, prior to further reaction.

From Table I, it can be seen that the reduction method based on lithium equals or exceeds the other methods listed. The first three entries used 4-bromotoluene as the aryl halide. This was appropriate for measuring the reactivity of commercial magnesium (entries 1, 2, 4) but ineffective for the activated magnesium. 4-Chlorotoluene was more appropriate for Mg*. With the more reactive metals, the temperature was lowered to 0 °C, to slow the reactions down for better comparison (entries 6, 9–11). Entry 6 used chlorobenzene as the halide for direct comparison to the evaporated Mg slurry method of activation.[3]

Klabunde[3] has carried out control experiments, comparing the reactivity of magnesium atom slurries (entry 5) to magnesium chips, powder, and filings—freshly filed from a magnesium rod, under an argon atmosphere. None of the "normal" types of magnesium reacted with chlorobenzene in THF at room temperature. While magnesium atom slurries gave the Grignard reagent of chlorobenzene in respectable yield, they did not form the Grignard reagent from fluorobenzene, even after extended reflux.

Though the most reactive Mg* was produced by using the lithium reduction procedure in the presence of alumina, the presently preferred method is entry 11. Though not as reactive as 10, it is more reproducible. The procedures which do not employ alumina also extend equipment life and are thus safer.

Oxidative Addition to Carbon–Oxygen Bonds. Dibenzyl Ether + Mg*. Dibenzyl ether reacted with Mg* to yield a "Grignard reagent", which gave the expected carbonation product, phenylacetic acid, in moderate yield (42%). However, the reaction was slow, and only starting material was observed after refluxing 0.5 equiv of dibenzyl ether with Mg* for 12 h. After 5 days of reflux, toluene and benzyl alcohol were observed by gas chromatography, and the reaction was carbonated, producing phenylacetic acid.

Grignard reagent formation has generally been limited to alkyl and aryl bromides and iodides, due to reactivity constraints. However, with the advent of this method of magnesium activation, it soon became clear that some of the previous reactivity constraints had been rendered obsolete. For example, Bickelhaupt[5] formed 1-oxa-2-magnesiacyclohexane from Mg* in the presence of THF, after prolonged heating in a sealed tube. Yields were as high as 50%. This was the first example of direct oxidative addition of an alkyl ether to magnesium,[6] except for a special case cited by Maercker, involving allyl phenyl ethers.[7]

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(2) Rieke, R. D.; Hudnall, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 7178. Rieke, R. D.; Bales, S. E. *J. Chem. Soc., Chem. Commun.* **1973**, 879. Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775. Rieke, R. D. *Top. Curr. Chem.* **1975**, *59*, 1. Rieke, R. D. *Acc. Chem. Res.* **1977**, *10*, 301.

(3) Klabunde, K. J.; Efner, H. F.; Satek, L.; Donley, W. *J. Organomet. Chem.* **1974**, *71*, 309.

(4) Bogdanovic, B.; Liao, S.-T.; Schwickardi, M.; Sikorsky, P.; Spliethoff, B. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 818. Bönneman, H.; Bogdanovic, B.; Brinkmann, R.; He, D.-W.; Spliethoff, B. *Ibid.* **1983**, *22*, 728. Bogdanovic, B.; Liao, S.; Mynott, R.; Schlichte, K.; Westeppe, U. *Chem. Ber.* **1984**, *117*, 1378. Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 262. Bogdanovic, B.; Bönneman, H.; Goddard, R.; Startsev, A.; Wallis, J. M. *J. Organomet. Chem.* **1986**, *299*, 347.

(5) Freijee, F.; Schat, G.; Mierop, R.; Blomberg, C.; Bickelhaupt, F. *Heterocycles* **1977**, *7*, 237–240.

(6) In our work, connected with the preparation of Mg* originating from lithium reductions, thin films have been observed over THF, after it had stood in the presence of Mg* for a day at room temperature. Exposure times of longer than a week converted the THF to a thick jelly. Both of these instances referred to reactions that had been washed after reduction, eliminating the possibility of the THF degradation having arisen during the reduction procedure. Analysis of hydrolysis products by gas chromatography indicated the presence of butanol, suggesting a similar reaction to that of Bickelhaupt. It was not out intention to maximize the yield or pursue this particular facet of the active magnesium chemistry. It is significant to note that the reaction occurs fairly readily at room temperature. In addition, it should be recognized that slurries should be freshly rinsed prior to use, if competing reactions attributable to the THF degradation products are to be avoided.

(7) Maercker, A. *J. Organomet. Chem.* **1969**, *18*, 249–262.

0022-3263/87/1952-3674$01.50/0

Table I. Comparison of Various Types of Magnesium

	source of Mg	temp, °C	substrate	% Grignard reagent after time, min 5	10	30	60
1	commercial[a]	25	$4\text{-BrC}_6\text{H}_4\text{CH}_3$	21	69	93	100
2	commercial[a,b]	25	$4\text{-BrC}_6\text{H}_4\text{CH}_3$	0	0	30	100
3	$MgCl_2$ + K	25	$4\text{-BrC}_6\text{H}_4\text{CH}_3$	100	100	100	100
4	commercial[a]	25	$4\text{-ClC}_6\text{H}_4\text{CH}_3$	0	0	0	0
5	evaporated[3]	25	ClC_6H_5	*d*	*d*	*d*	*d*
6	$MgCl_2$ + Li + np[c]	0	ClC_6H_5	21	52	81	100
7	$MgCl_2$ + K	25	$4\text{-ClC}_6\text{H}_4\text{CH}_3$	0	0	14	50
8	$MgCl_2$ + K[b]	25	$4\text{-ClC}_6\text{H}_4\text{CH}_3$	84	94	97	98
9	$MgCl_2$ + K[b]	0	$4\text{-ClC}_6\text{H}_4\text{CH}_3$	26	46	73	85
10	$MgCl_2$ + Li + np[c]	0	$4\text{-ClC}_6\text{H}_4\text{CH}_3$	30	60	85	96
11	$MgCl_2$ + Li + np	0	$4\text{-ClC}_6\text{H}_4\text{CH}_3$	19	38	74	88

[a] Poly Research 325 mesh. [b] Reduced in presence of KI (1 equiv based on Mg). [c] Reduced in presence of alumina. [d] 85% after 3 h.

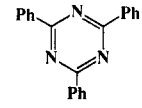
Formally, in the case of the ethers just cited, oxidative addition between magnesium and a C–O bond occurs. However, the reactions are slow, and the resulting yields are not high, suggesting, that even with highly reactive Mg, this reaction is not very general.

Reaction of Mg* with Benzyl Tosylate. Benzyl tosylate was reacted in a 2.5:1 ratio with Mg* in refluxing THF for 12 h. After carbonation and workup, the only acidic product isolated was 4-toluenesulfonic acid. The nonacidic phase gave the homocoupled product bibenzyl in an isolated yield of 84%. This points out a general problem of using tosylates for Grignard reagent formation, as Grignard reagents are known to cross-couple readily with them.[8] As we were not able to isolate a carbonation product, we cannot be absolutely certain that a Grignard reagent was present. It is possible that the homocoupled product may have arisen by the reductive cleavage of the benzyl tosylate to generate benzyl radicals, which simply dimerized. No attempts were made to detect free radical intermediates.

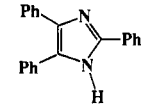
Phenyl Tosylate with Mg*. In an effort to test the limits of tosylates with Mg*, phenyl tosylate was explored. Phenyl tosylate was reacted in a 1:2 ratio with Mg* in refluxing THF. Gas chromatographic analysis after 1.5 h showed a trace of phenol, due to simple hydrolysis, but no benzene or biphenyl. Solvent removal from the aliquot gave a solid with a similar melting point to the starting material. Aliquots removed after 1, 3, and 29 days gave analogous results, yielding the conclusion that phenyl tosylate was inert to Mg*.

Hexane-1,6-diyl Ditosylate. Attention was then turned to alkyl tosylates. Realizing the likelihood of coupling, it was decided to encourage the possibility. Hexane-1,6-diyl ditosylate was selected to explore the possibility of ring formation vs. polymerization.

Hexane-1,6-diyl ditosylate was reacted by slowly adding a 0.1 M solution of the tosylate to an excess of Mg*. After 1 h at room temperature no cyclohexane was observed by gas chromatography. The reaction was brought to reflux for 1 h but still showed no sign of cyclization. No volatile products were detected by gas chromatography. Aliquots were removed at selected intervals over a period of 3 days. ^{1}H NMR analysis, after basic extraction to remove free 4-toluenesulfonic acid, showed an ever-increasing ratio of methylene protons (δ 1.0–1.8 (CH_2), and 3.9 (t, J = 6 Hz, CH_2OS)) to tosyl protons (δ 2.4 (s, $ArCH_3$), and 7.1–7.8 (m, ArH)]. This may be explained by assuming that coupling reactions were taking place, thereby decreasing the relative number of terminating tosyl functions. However, the degree of coupling was not great; by integration after 1 h of reflux, the average chain length was 6.9 carbons long. After 3 days the average chain length was 8.6 carbons. If one makes the assumption that only monomer and dimer were present, this latter number would correspond to a 43% conversion to dimer. The resulting solid had a pungent odor rather than the characteristic ester odor of the original tosylate.



2,4,6-triphenyl-1,3,5-triazine



2,4,5-triphenylimidazole

Figure 1.

A neat reaction was run by washing the magnesium slurry several times and then stripping off the solvent. After the addition of the tosylate and after the melt was maintained at 90–100 °C for 36 h, a brown, pungent-smelling oil resulted. ^{1}H NMR integration showed an average carbon chain length of 26.5 carbons. Infrared spectroscopy revealed no hydroxyl stretches, indicating that simple hydrolysis had not occurred. Furthermore, very little aromatic absorptions were observed, confirming the NMR results. A sample submitted for mass spectrometry showed masses to 1165 amu, but most of the sample could not be volatilized even at 300 °C, indicating that higher masses were probably present.

The lack of cyclization is perhaps not too surprising considering that the reaction was run neat rather than at high dilution. While the use of ditosylates to produce rings appears limited, the use of this reaction to homocouple monotosylates may be a viable approach.

Reaction of Magnesium with Nitriles. Benzonitrile + Mg*. When benzonitrile was reacted with Mg* in refluxing glyme, a deep red color developed after ~1 h. Gas chromatography revealed most of the starting material to be unconsumed. After refluxing overnight, the reaction mixture turned brown, and most of the starting material was consumed. An aliquot injected directly into the gas chromatograph did not reveal any benzil. Workup showed two main products, 2,4,6-triphenyl-1,3,5-triazine and 2,4,5-triphenylimidazole, in 26% and 27% yields, respectively (Figure 1).

The imidazole was quite unexpected but nevertheless present as the most abundant product. Its origin will be discussed below. A product with a TLC R_f equivalent to benzil was also present in less than 5 mol % yield, as were

(8) Wagner, R.; Zook, H. *Synthetic Organic Chemistry*; Wiley: London, 1953; p 11.

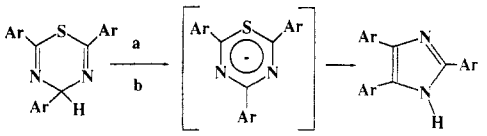


Figure 2. Extrusion reactions used to form imidazoles. Conditions: (a) aliphatic amines/benzene;[9] (b) *n*-butyllithium.[10]

Table II. Summary of the Various Methods Typically Employed in the Trimerization of Aromatic Nitriles

reagent	conditions	% yield
chlorosulfonic acid[52]	0 °C, 12 h	40
$AlCl_3$[53]	140–160 °C	1.5
PCl_5/HCl[54]	100–105 °C, 24 h	98
MeOH[14]	100–125 °C, 7500 atm	74–82
Na[55]	C_6H_6	none given[a]
RMgX[36]	boiling xylene	25
RLi[36]		16[b]

[a] It was later shown by Cook and Jones[52] that the only product from the action of Na on benzonitrile was 2,2,4,6-tetraphenyl-1,2-dihydro-1,3,5-triazine. [b] The product was not a simple trimer but rather 2,2,4,6-tetraphenyl-1,2-dihydro-1,3,5-triazine.[52]

numerous other unidentified products in low yields.

The imidazole was shown to arise, at least in part, from the triazine. 2,4,6-Triphenyl-1,3,5-triazine reacted with Mg* in refluxing THF to give 2,4,5-triphenylimidazole in 27% yield; 65% was unreacted starting material; 8% was unaccounted.

Giordano and Belli have formed imidazoles from 2,4,6-triaryl-4*H*-1,3,5-thiadiazines via a base-catalyzed extrusion of sulfur.[9] Schmidt et al.[10] also refer to an analogous extrusion of oxygen from the 4*H*-1,3-oxazine (Figure 2). Radzisewski[11] prepared imidazoles by the extrusion of nitrogen from triazines using Zn in refluxing acetic acid.

The trimerization of aromatic nitriles to give symmetrical triazines is not unknown, but generally, the reactions must be catalyzed by strong acids or a weak base and extremely high pressure. The action of *preformed* Grignard reagents also gives symmetrical triazines. Organoalkalis are also known to give trimers but not symmetrical triazines. A summary of the various methods which have been employed is given in Table II. It does not appear that anyone has previously demonstrated a direct reaction of magnesium to give the symmetrical triazines reported here.

1,4-Dicyanobenzene + Mg*. As expected, 1,4-dicyanobenzene reacted with Mg* to give a polymer. NMR and IR data were consistent with a polymerization to form triazines. Mass spectral studies provided little data on molecular weights.

The polymer did not form charge-transfer complexes with TCNQ or iodine. Preliminary electrochemistry in THF showed no oxidative peaks out to the solvent breakdown potential; the reductive peaks were not revesible. The polymer did not seem to offer any understanding possibilities as a conductor. However, it might be useful as a basic polymeric catalyst or as a size-exclusion medium for chromatography (the hexagonal cavities in a perfect polymer [formed by alternating triazine and benzene rings, three to a side] would be ~10 Å in diameter).

1,2-Dicyanobenzene + Mg*. 1,2-Dicyanobenzene reacted with Mg* in refluxing glyme to give first a purple and then a midnight blue solution after 2 min. A thin-layer chromatogram showed all of the starting material to be consumed after 5 min. Upon workup, phthalocyanine (38%) resulted. Linstead and Lowe[12] were only able to obtain a 9.6% yield from the direct reaction of magnesium with 1,2-dicyanobenzene. They had to heat the mixture to the boiling point of the nitrile (~295 °C) to initiate reaction. Magnesium-free phthalocyanine has been produced from diiminoisoindoline in 90% yields.[13]

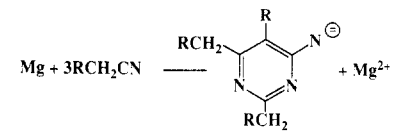


Figure 3. Assumed stoichiometry for the trimerization of alkyl nitriles. One nitrile is reduced to a primary amine, while Mg is oxidized.

Butyronitrile + Mg*. Butyronitrile did not react with activated magnesium after refluxing in glyme for 72 h. Neat butyronitrile, heated to its boiling point, 117 °C, gave a good yield of a trimerization product after 48 h. Isolation of the product showed it to be 4-amino-5-ethyl-2,6-dipropylpyrimidine. The yield cannot be positively stated, since the mechanism of the reaction is not clear. Since one nitrile of the trimer is reduced to a primary amine, it would appear that the stoichiometry is that shown in Figure 3, but the existence of other products was not investigated, and a different stoichiometry could be possible.

Assuming a 1:1 stoichiometry for Mg* to product, as shown in Figure 3, the yield was 98%. From the earlier work with aromatic nitrile, 2,4,6-tripropyl-1,3,5-triazine was expected to be the product. Cairns et al.[14] have shown that triazines rearrange to aminopyrimidines in ammoniacal methanol at 150 °C and 8500 atm. It is not known if the magnesium reaction follows a similar mechanism. However, the triazine structure was definitely eliminated as a possibility: solution IR clearly showed the existence of the amine, with two stretches at 3511 and 3408 cm^{-1}, as well as the confirming absorbances at 750 and 726 cm^{-1}. Further support was lent by the broad ^1H NMR absorbance at δ ~4.5. ^{13}C NMR showed the expected four aromatic carbons and eight aliphatic carbons.

Treatment of alkyl nitriles with metallic sodium[15] or Grignard reagents[16] is known to produce aminopyrimidines, but there have been no reports of such results by the direct action of metallic magnesium on alkyl nitriles.

Acetonitrile + Mg*. Acetonitrile did not react with activated magnesium at its boiling point. However, when heated in a sealed tube with Mg*, to approximately the same temperature required to induce the butyronitrile reaction, a good yield of the analogous aminopyrimidine was formed.

Multifunctional Grignard Reagents. The ability to form Grignard reagents at low temperature is an important feature of Mg*. There are numerous potential applications. The most obvious one is in the formation of Grignard reagents which decompose at ambient or elevated temperatures. The utility of Mg* has already been demosntrated in this respect with γ-halo ethers.[17]

Equally exciting and very useful from the synthetic point of view would be the ability to form Grignard reagents which incorporated more than the generally tolerated functional groups. This possibility is not as remote as was

(9) Giordano, C.; Belli, A. *Synthesis* **1975**, 167.
(10) Schmidt, R. R.; Mayer, W. J. W.; Wagner, H.-U. *Liebigs Ann. Chem.* **1973**, 2010.
(11) Radzisewski, B. *Chem. Ber.* **1892**, *15*, 1493.
(12) Linstead, R. P.; Lowe, A. R. *J. Chem. Soc.* **1934**, 1031–1033.
(13) Brach, P. J.; Grammatica, S. J.; Ossanna, O. A.; Weinberger, L. *J. Heterocycl. Chem.* **1970**, *7*, 1403–1405.
(14) Cairns, T. L.; Larchar, A. W.; McKusick, B. C. *J. Am. Chem. Soc.* **1952**, *74*, 5634.
(15) v. Meyer, E. *J. Prakt. Chem.* **1888**, *37* (2), 397.
(16) Baerts, F. *Chem. Zentralbl.* **1923**, *3*, 124.
(17) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1983**, *48*, 4141.

once assumed. Sato et al.[18] and Eberle et al.[19] have shown that at low temperatures (−70 °C) Grignard reagents react with acid chlorides to form ketones without competing formation of tertiary alcohols. These reactions were run without the benefit of inverse additions, proving that ketones were fairly resistant to attack by Grignard reagents at low temperature. Thus it should be possible to form polyfunctional Grignard reagents incorporating functionality of equal or lower reactivity than ketones. Ashby et al.[20] have studied the reaction kinetics for the reaction of benzophenone and benzonitrile with methylmagnesium bromide in diethyl ether at 25 °C. Generally, the rate constants for the ketone are about 4 orders of magnitude greater than those of the nitrile. Certainly nitriles should be good candidates in addition to chlorides and possibly even esters, for multifunctional Grignard reagents. The likelihood for success is increased if the functionality is remote from the site of Grignard formation. Thus 4-substituted bromobenzenes and ω-alkyl bromides of chain length greater than four or five carbons might be good models. Both bromobenzene and bromoalkanes readily react with Mg* at −78 °C.

Bromoaryl Nitriles + Mg*. 4-Bromobenzonitrile and (4-bromophenyl)acetonitrile gave mixtures of simple reductive cleavage products and other byproducts with little or no Grignard reagents. In the case of 4-cyanobenzyl bromide, reaction at −78 °C was rapid and complete. Deuterolysis of the resulting mixture gave 4,4′-dicyanobibenzyl (86%) and 4-deuteriobenzonitrile in a ratio of 6:1 (NMR yield). Unfortunately, although the benzylic system appeared to form the Grignard reagent easily, most of it coupled rapidly, even at low temperature, preventing its practical use as a Grignard reagent. Obviously, the aromatic nitriles tested were not acceptable candidates for the formation of polyfunctional Grignard reagents. However, this simple homocoupling reaction may prove to be of value in some cases.

Bromoacetonitrile. Activated magnesium consumed bromoacetonitrile within 5 min at −52 °C. No volatile products were detected. After the reaction mixture had been stirred overnight, brown solids were evident, but no identifiable products were obtained on workup. A similar reaction was carried out in the presence of a threefold excess of cyclohexene, to check for possible carbene formation. No 7-cyanobicyclo[4.1.0]heptane was detected by gas chromatography.

Ethyl 3-Bromopropionate. Activated magnesium did not appear to react with ethyl 3-bromopropionate at −78 °C. After the mixture was stirred for 2 h, benzoyl chloride was added dropwise. Following hydrolysis, NMR analysis as well as gas chromatographic results showed only ethyl 3-bromopropionate, benzoic acid, and benzil.

4-Bromobutyronitrile and 5-Bromovaleronitrile. Activated magnesium failed to react with 4-bromobutyronitrile or 5-bromovaleronitrile in THF at −78 °C or at −15 °C. After no reaction occurred, the reactions were allowed to warm slowly to room temperature, with aliquots being removed at regular intervals. Reactions did not occur until 20 °C in both cases, at which time polymer resulted.

8-Bromooctane-1-nitrile. Activated magnesium reacted rapidly with 8-Bromooctane-1-nitrile at −78 °C, until about two-thirds of the bromide was consumed. At this point, the Grignard reagent started diminishing. Carbonation and workup gave 8-cyanooctanoic acid (1,9-nonanedioic acid, mononitrile) in 26% yield.

It is common knowledge that carboxyl, hydroxyl, amino, and SO_3H functional groups are not tolerated in Grignard reagents due to their acidic protons. March[21] contends that carbonyls, esters, and nitriles are not tolerated due to the electrophilic nature of the carbons attached to the heteroatoms, thus making them susceptible to attack by Grignard reagents. This feature renders an insoluble polymeric coating on the surface of the magnesium, thereby inhibiting Grignard reagent formation entirely. But, in a later chapter, March references the work of Leroux,[22] who was able to form cyclobutanols and cyclopentanols from 4- and 5-bromo ketones, respectively. However, Leroux used a magnesium amalgam, which is quite different from free magnesium. Other authors have stated that ketones inhibited Grignard reagent formation completely.[23,24]

A polymeric network may be responsible for the inhibition of Grignard reagent formation on normal magnesium but must not be the limiting factor for reactions involving activated magnesium at low temperatures, since Sato[18] and Eberle[19] have shown that ketones (and by extension, nitriles) are not attacked at those temperatures.

A highly probable explanation for the lack of Grignard reagent formation at low temperatures of those halides which contain other functional groups (i.e., nitriles, esters, etc.) is the coordination of the heteroatoms to the magnesium surface. It is well documented that metal surfaces in general act as Lewis acids and coordinate with a variety of Lewis bases. Thus it would appear, for example, in the case of 4-bromobutyronitrile, that the nitrogen of the nitrile group coordinates to the surface of the magnesium, blocking all of the active sites. The end-on coordination would direct the bromine-containing end of the molecule away from the surface and also help prevent Grignard reagent formation. At higher temperatures, the coordinated nitriles would probably have enough kinetic energy to be in equilibrium with the solution nitriles. This would allow vacant sites to appear, hence allowing for occasional coordination of the bromine atom and Grignard reagent formation. In contrast, the longer carbon chain of 8-bromooctanenitrile must prevent some of the active sites from being occupied, allowing them to participate in Grignard reagent formation. Also, as the chain length is much longer, it may allow the bromine to extend back to the magnesium surface to react. Similar arguments explain the lack of Grignard reagent formation with ethyl 3-bromopropionate, only in this case it is the oxygen atoms of the ester functional group which are coordinated to the magnesium surface. In the case of bromoaryl nitriles, the primary pathway observed was reductive cleavage of the bromine. This is also readily explained with the coordination model. In this case, coordination of either the nitrile group or the benzene surface would allow for electron transfer from the magnesium surface to the carbon–halogen bond and cleavage of the halogen. If the resulting carbon radical was held away from the magnesium surface, only free radical chemistry and not Grignard reagent formation would be expected.

A few additional experiments were performed which lend support to the above hypothesis. Bromopentane was

(18) Sato, F.; Inoue, M.; Oguro, K.; Sato, M. *Tetrahedron Lett.* **1979**, *44*, 4304.
(19) Eberle, M. K.; Kahle, G. G. *Tetrahedron Lett.* **1980**, *21*, 2303.
(20) Ashby, E. C.; Neumann, H. M.; Walker, F. W.; Laemmle, J.; Chao, L.-C. *J. Am. Chem. Soc.* **1972**, *95*, 3330.
(21) March, J. *Advanced Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1977; pp 566–567.
(22) Leroux, Y. *Bull. Soc. Chim. Fr.* **1968**, *57*, 359.
(23) Bischoff, C. A. *Ber.* **1905**, *38*, 2078.
(24) Ahrens, F. B.; Stapler, A. *Ber.* **1905**, *38*, 3262.

added to activated magnesium at −78 °C. Reaction was almost instantaneous and complete by gas chromatography. Butyronitrile was added to the cold Grignard reagent. No attack of the Grignard reagent on the nitrile was observed even after 1 h.

In a reversal of the procedure, butyronitrile was added first to the chilled metal slurry, followed by bromopentane. In this case, no Grignard reagent formation was observed after more than 2 h. The presence of nitrile completely inhibited reaction of the bromide with the magnesium, presumably by coordination to active sites on the metal.

Conclusions

Highly reactive magnesium produced by the lithium reduction of $MgCl_2$ has been shown to undergo several new reactions not normally observed with standard types of magnesium. Among these reactions are the oxidative addition to carbon–oxygen bonds, as well as the trimerization of nitriles. The formation of the corresponding Grignard reagent from 8-bromooctanenitrile at low temperatures and its subsequent carbonation suggest the possibility of generating multifunctional groups containing Grignard reagents. Results of this study, however, show that this will not be a general approach with current methodology. It would appear that this approach will be possible for those molecules in which coordination of the functional group (i.e., nitrile, ester, etc.) also holds or allows the approach of the halogen-containing carbon to the magnesium surface. Additional studies in this direction are under way.

Experimental Section

Reagents. The preparation of activated magnesium, as well as the reactions of these slurries with substrates, was carried out under an atmosphere of prepurified argon, which was further purified by passage over BASF catalyst R3-11 at 160 °C. Subsequently the argon was passed over P_2O_5 and KOH to complete the purification sequence.

Tetrahydrofuran, 99.5+ %, and 1,2-dimethoxyethane, 99+ %, were purchased from Aldrich Chemical Company and purified by distilling from sodium/potassium alloy, under an atmosphere of argon, immediately before use. Lithium rod was purchased from Alfa or Roc-Ric. It was cut under heavy petroleum on the bench top, rinsed with hexanes, and then transferred to a tared weighing adapter under a flow of argon. The adapter was evacuated and back-filled several times, to eliminate hexanes and oxygen. After being weighed, the lithium was transferred to the reaction vessel under a flow of argon. Anhydrous magnesium salts were purchased from Cerac, Inc., and used as received. The salts were transferred to tared tubes and weighed by a single beam balance, under an atmosphere of argon, inside a Vacuum/Atmospheres recirculating glovebox. The tubes were sealed with latex septa, removed from the glovebox, and weighed on a Mettler H51 analytical balance. The contents of a tube were transferred to a reaction vessel under a flow of argon, by removing the septum and rapidly inverting the tube into the neck of the flask. The septum was quickly replaced, and the tube was weighed again, yielding an accurate mass. Electron carriers were weighed in normal atmosphere and then transferred to the reaction vessel under a flow of argon. The flask was then evacuated and back-filled several times. In latter experiments, the cutting of lithium, weighing of reagents, and transfers were completed in a drybox.

Gas chromatographic analyses were obtained on a Hewlett-Packard 57301 gas chromatograph, using an $^1/_8$ in. × 1.5 m stainless steel column packed with 10% SE-30 on 80/100 mesh Chromosorb P-DCMS, or a Varian Aerograph 920 gas chromatograph, using an $^1/_4$ in. × 10 ft stainless steel column packed with 20% Carbowax 20M on 100/120 mesh Chromosorb W-AW. IR data were recorded on a Perkin-Elmer 283 spectrophotometer using KBr pellets, melts, or solutions in the stated solvents and are reported as cm^{-1}. NMR data were collected on a Varian EM-390 90-MHz or XL-200 200-MHz spectrometer and are reported in the following form: δ chemical shift relative to tetramethylsilane (apparent peak multiplicity, coupling constant, peak area, peak character). Mass spectral data are reported in the form m/e (relative intensity to base peak which was assigned a value of 100%). Melting points were recorded on a Thomas-Hoover Unimelt and are corrected. Mg* was prepared as reported previously.[17,25] The moles of Mg* cited refer to the theoretical amount possible, based on the original amount of magnesium chloride. Reported yields have been corrected for the purity of starting materials and aliquots withdrawn.

All reagents, unless stated otherwise were purchased from Aldrich and used as received. Benzyl tosylate was prepared by using a slight variation of Tipson's method.[26] Phenyl tosylate was prepared by the literature method.[27] Hexane-1,6-diyl-ditosylate was prepared by using Tipson's unmodified procedure. The hexane-1,6-diyl ditosylate had mp 74–75 °C. 8-Bromooctane-1-nitrile was synthesized according to the literature procedure.[28]

For activation studies, aryl halides were drawn into a syringe, air was expelled, and the syringe was weighed. The contents of the syringe were then injected rapidly through the septum into the stirred slurry. The syringe was withdrawn and weighed a second time, to determine the amount of halide used.

Aliquots were withdrawn from the reaction flask at regular intervals. A syringe equipped with an 18 gauge stainless steel needle was flushed with argon several times. It was then inserted beneath the surface of the stirred slurry and the desired amount of the solution drawn into the syringe. The syringe was then withdrawn from the slurry and the needle inserted into a tube which had previously been charged with 1 mL of 3 N HCl and 1 mL of pentane. The needle tip was placed in the aqueous layer and the slurry expelled. The tube was capped with a septum and shaken.

Dibenzyl Ether with Mg*. Dibenzyl ether (8.00 mmol) was added to activated magnesium (16.69 mmol) in THF (20 mL), and reflux was initiated immediately. After 4 days, the slurry was cooled to room temperature, blanketed with freshly sublimed CO_2 for 3 h, and hydrolyzed with dilute HCl. After pouring into a separatory funnel containing diethyl ether, the ether was extracted thrice with 10% NaOH. The combined basic extracts were acidified and extracted multiply with diethyl ether. These ethereal extracts were dried over $MgSO_4$, filtered, and stripped by rotary evaporation to give phenylethanoic acid (326 mg, 42% corrected yield) as a clear colorless oil, which slowly crystallized: mp 75–77 °C (lit. mp 77 °C[29]); NMR (CS_2) δ 3.5 (s, 2 H), 7.1 (apparent s, 5 H) 11 (s, 1 H, br).[30]

Benzyl Tosylate with Mg*. Benzyl tosylate (6.29 mmol) was added to the stirred slurry of Mg* (17.80 mmol) in THF (20 mL) via a solid addition tube. The dissolution was somewhat endothermic. After the mixture was stirred for 0.5 h, reflux was initiated and continued for 12 h. The reaction was cooled to −78 °C and blanketed with freshly sublimed CO_2 for 3 h. The reaction was hydrolyzed with 10% HCl, poured into a separatory funnel, and extracted thrice with diethyl ether. The combined ethereal phases were extracted thrice with 10% NaOH. The organic phase was dried over $MgSO_4$ and stripped to give bibenzyl (481 mg, 84%): mp 51–52 °C (lit. mp 52.2 °C[31]); NMR (CCl_4)[32] δ 2.86 (s, 4 H), 7.1 (m, 10 H).

(25) Burns, T. P. Ph.D. Thesis, 1986, University of Nebraska, Lincoln, NE.

(26) Prepared according to the method of Tipson, with a slight variation: Tipson, R. S.; Clapp, M. A.; Cretcher, L. H. *J. Org. Chem.* **1947**, *12*, 135. It was flash recrystallized from MeOH, as opposed to slow recrystallization from $CHCl_3$/hexanes. Although there is a greater loss by this method of recrystallization, the resulting product is much more persistent. Tipson recorded that his product was stable at room temperature, in a vacuum desiccator, for 3 days before product decomposition. Prepared by our variation, the tosylate has shown no signs of decomposition after more than 4 years!

(27) Wentworth, S.; Sciaraffa, P. *Org. Prep. Proced.* **1969**, *1*, 225.

(28) Synthesized from the reaction of 1,7-dibromoheptane with NaCN in EtOH/water, followed by separation of products by annular distillation.

(29) Weast, R. C., Ed. *Handbook of Chemistry and Physics*, 55th ed.; CRC Press: Cleveland, OH, 1974; p C-91.

(30) Matches, Sadtler ^{1}H Index No. 117.

(31) Weast, R. C., Ed. *Handbook of Chemistry and Physics*, 55th ed.; CRC Press: Cleveland, OH, 1974; p C-287.

(32) Matches Sadtler ^{1}H Index No. 184.

Phenyl Tosylate with Mg*. Phenyl tosylate (8.66 mmol) was added via a solid addition tube to a stirred slurry of Mg* (16.69 mmol) in THF (20 mL). Gas chromatographic analyses of 1-mL aliquots removed after 1, 3, and 29 days showed no benzene or biphenyl. Crystals left after removal of solvent melted at 93 °C (phenyl tosylate, mp 94–95 °C).[33]

Hexane-1,6-diyl Ditosylate with Mg* in Refluxing THF. Mg* (19.67 mmol) was prepared and washed thrice. The solvent was removed and replaced with only 5 mL of THF. Hexane-1,6-diyl ditosylate (3.24 mmol) was weighed in a conical flask, which was evacuated and back-filled with argon a few times. The solid was dissolved in 30 mL of THF, to give a 0.108 M solution. This was added dropwise to the stirred slurry of magnesium, over a 20-min period. Reflux was initiated and continued 4 days. The solvent was removed by evacuation.

The remaining slurry was washed thrice with 20-mL portions of diethyl ether. A white solid (444.6 mg) was recovered from the ether. The solid had a pungent odor, very different from the starting material. The remaining slurry was refluxed with 30 mL of diethyl ether and then hydrolyzed with dilute HCl. After being poured into a separatory funnel, the solution was multiply extracted with diethyl ether, dried over $MgSO_4$, and stripped to give an additional white solid (39.9 mg): total product recovered, 484.5 mg (55% of the starting mass); NMR δ 1.0–1.8 (m, 6.6 H), 2.4 (s, 3 H, $ArCH_3$), 3.9 (t, J = 6 Hz, 2 H, CH_2O), 7.1–7.8 (m, 4 H, Ar H).

Hexane-1,6-diyl Ditosylate with Mg* (Neat). Mg* (19.67 mmol) was prepared and washed three times with fresh THF. After removal of the supernatant the fourth time, the remaining solvent was stripped off under vacuum. Hexane-1,6-diyl ditosylate (3.39 mmol) was added to the reaction flask under a flow of argon. The temperature was kept at 90–100 °C for 36 h. After cooling, the mixture was hydrolyzed by the addition of dilute HCl. Dichloromethane was added to the flask and the whole mixture poured into a separatory funnel. The aqueous phase was extracted thrice with dichloromethane. The combined organic phases were washed with water, dried over $MgSO_4$, and stripped to give a brown oil (130.2 mg): NMR δ 1.0–1.8 (m, 26.5 H), 2.4 (s, 3 H, $ArCH_3$), 3.9 (t, J = 6 Hz, 2 H, CH_2O), 7.1–7.8 (m, 4 H, ArH); IR 3070 vw, 2960–2860 st, 1640 w, 1365 m (SO_2 st asymmetric), 1175 cm^{-1} m (SO_2 st symmetric); low-resolution EI-MS (summary of several scans), base peak at either m/e 82 or 83, large peaks were also observed at 69, 81–84, 95–95, and 107–110.[34] Masses up to 1165 amu were observed.[35] The sample was heated in the probe to 350 °C, under high vacuum, but most of it could not be volatilized.

Benzonitrile + Mg*. Benzonitrile (53.86 mmol) was added rapidly via syringe to a refluxing slurry of activated Mg* (13.06 mmol), which had been prepared in glyme and washed thrice. Immediately, the slurry turned green and then changed to a brown-red over 0.5 h. After reluxing overnight the slurry was cooled and hydrolyzed with 3 N HCl and then multiply extracted with dichloromethane. After drying of the organic phases and after the solvent was stripped off, 3.6384 g of crude product resulted. A sample of the product (1.0434 g) was dissolved first in chloroform and then in isopropyl alcohol, but not all of it would dissolve.[36] The flask and the residual crystals were refrigerated. The resulting crystals were filtered and dried to give 2,4,6-triphenyl-1,3,5-triazine (136.6 mg), mp 231–233 °C (lit. mp 231–232 °C),[14] as a slightly yellow solid. The mother liquor was stripped down on silica gel, placed on a flash column, and eluted with 50% $CHCl_3$/petroleum ether to collect the first 10-mL fraction and then with 100% $CHCl_3$. After five additional 10-mL fractions were collected, the last fractions were eluted with 10% isopropyl alcohol/$CHCl_3$ followed by 100% isopropyl alcohol and were 20-mL cuts. The first fraction yielded additional 2,4,6-triphenyl-1,3,5-triazine (162.8 mg): mp 233–234 °C, sharp; total triazine, 299.3 mg (26%); IR[37] 3060 w, 1587 m, 1520 str, 1460, 1450 m, 1170 w, 1025 w, 840 w, 745 s, 685 cm^{-1} s; NMR[38] (CS_2) δ 7.4–7.9 (m, 3 H), 8.4–8.6 (m, 2 H).

Fraction 2 yielded some benzonitrile (not quantitated) and a waxy, white solid (38.2 mg, <5%). The solid was not further purified, but its R_f corresponded to a known sample of benzil under a variety of tlc conditions and had the characteristic IR absorbances of benzil:[39] 1675 br str, 1595, 1580 str, 1500 str, 1210, 1170 str, 880 str, 795 w, 720 str, 700, 680 m, 645 cm^{-1} str.

Fraction 6, 2,4,5-triphenylimidazole, was isolated as a slightly yellow solid (296.4 mg, 27%): mp 275–277 °C, (lit. mp 274–275 °C,[40] 275–276 °C[41]); IR[42] 3400 br w, 3100–2500 br m, 1590, 1560 w, 1490, 1470 m, 1445 m, 1110 m, 750 str, 685 cm^{-1} str; NMR (acetone-d_6) δ 2.8 (s, br, 4 H, NH-wet), 7.4–7.8 (m with big s, 13 H), 7.9–8.2 (m, 3 H); MS m/e 296 (100, $M^{\cdot+}$).

Other fractions, weighing 118.4 mg were not characterized but gave account for 74% mass balance.

1,4-Dicyanobenzene + Mg*. 1,4-Dicyanobenzene (14.7 mmol) was added via syringe to a refluxing slurry of activated magnesium (14.6 mmol) in glyme, as in the previous reaction, over 0.25 h. TLC samples were removed by inserting a 5-μL capillary through a large-bore needle which was used to penetrate the septum. Quenches showed most of the starting material to be consumed after 21 h. The stirring was discontinued and the mixture allowed to cool. The solution was transferred via cannula into a 250-mL separatory funnel containing chloroform and 3 N HCl. A thick syrup remained in the reaction flask. This was rinsed out with 10 mL of glyme, followed by chloroform. The phases stratified, but a brown solid remained between them. The aqueous layer and solid were retained in the separatory funnel and multiply extracted with chloroform. The combined chloroform layers were washed thrice with water and the aqueous layers reextracted with chloroform. The combined chloroform layers were dried over sodium sulfate and stripped to give an orange-brown solid (725 mg).

The nonsoluble liquid in the water layer was placed on a glass frit and rinsed with copious amounts of water, until the water came through colorless. The solid was dried by rinsing with methanol. A considerable amount of the solid dissolved and passed through the frit as a dark brown solution. This solution was stripped to give 1.0991 g of solid, which was brown.

The solid left on the frit was washed with hot methanol and an additional 75.5 mg of solid recovered. Infrared spectra were taken of each fraction. They were essentially identical except for intensities. Absorbances were observed at the following wavenumbers:[43] 2224 v str, 1738 m, 1679 strong, 1609 str, 1519 str, 848 str. The absorbance intensity at 2224 varied with solubility. The fractions softened over a wide temperature range beginning at 140 °C but not completely liquifying even at 340 °C.

1,2-Dicyanobenzene with Mg*. To 1,2-dicyanobenzene (14.7 mmol) dissolved in 100 mL of glyme was added activated magnesium (21.9 mmol) prepared as in the previous reaction. The transfer was complete in 2 min. The solution turned first purple and then black during the addition. Solution which splashed on the sides looked midnight blue. At 5 min after the addition, a TLC sample was removed by inserting a 5-μL capillary through a large-bore needle which was used to penetrate the septum. The aliquot showed all of the starting material to be consumed. The stirring was discontinued and the mixture allowed to cool. HCl (3 N; 50 mL) was added and the mixture turned purple again. The mixture was filtered through an ultrafine glass frit. The purple solution passed through, leaving a thick sludge. The sludge was washed with copious amounts of 3 N HCl, H_2O, EtOH, and Et_2O. Some of the blue-green color passed through the frit during the EtOH wash. The lustrous, blue-green needles were dried in

(33) Otto, R. *Chem. Ber.* **1886**, *19*, 1832.
(34) This pattern is an indication of S directly bonded to an aromatic ring—see: McLafferty, F. W. *Interpretation of Mass Spectra*; 3rd ed.; University Science Books: Mill Valley, CA, 1980; p 285.
(35) Fragmentation patterns mostly resembled a linear alkane (regular losses of 14 amu).
(36) Anker (Anker, R. M.; Cook, A. H. *J. Chem. Soc.* **1941**, 326) found a similar low solubility for imidazoles.
(37) Matches Sadtler IR Index No. 31570K.
(38) Matches Sadtler ^1H Index No. 19264.
(39) Matches Sadtler IR Index No. 186K.
(40) Philbrook, G. E.; Maxwell, M. A.; Taylor, R. E.; Totter, J. R. *Photochem. Photobiol.* **1965**, *4*, 1175.
(41) Tanino, H.; Kondo, T.; Okada, K.; Goto, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1479.
(42) Matches Sadtler IR Index No. 18343K.
(43) Matches data of: Shurvell, H. F. *Spectrochim. Acta* **1965**, *21*, 2141–2143.

a vacuum desiccator, over P_2O_5 (4.2053 g, 38%): IR[44] 1335 s, 1115 m, 1090, 1085, 1080 m, 1055 m, 885 m, shoulder, 750 m, 727, 710 cm^{-1} str.

Butyronitrile with Mg* (Neat). Freshly prepared magnesium (14.3 mmol) was washed four times with dry glyme, and the last wash was removed by cannula. The residual glyme was removed by subjecting the flask to vacuum at room temperature for ~2 h. Butyronitrile (172 mmol) was degassed by vigorous bubbling of argon for 1 h and then added neat to the magnesium and the flask heated to reflux for 48 h. The flask was allowed to cool. The reaction was worked up by quenching with an aqueous NH_4Cl solution. The aqueous solution was extracted six times with $CHCl_3$. The $CHCl_3$ was dried over Na_2SO_4 and stripped to give a white solid (3.241 g).

The solid (1.0424 g) was dissolved in $CHCl_3$ and stripped onto a small portion of silica gel. This was placed atop of a 5-in. flash column and eluted with 4% isopropyl alcohol/$CHCl_3$. Fractions 20–60 were concentrated to give a slightly yellow solid (1.2033 g, mass gain due to coordination of isopropyl alcohol):[45] mp 109–114 °C. A portion of the solid (0.5590 g) was recrystallized from hexanes to give 4-amino-5-ethyl-2,6-dipropylpyrimidine (0.4335 g, 98%): mp 115–116 °C, (lit.[15,46] mp 115 °C); ^1H NMR ($CDCl_3$) δ 0.8–1.3 (m, 9 H), 1.4–2.0 (m, 4 H), 2.3–2.8 (m, 6 H), 4.7 (s, br, 2 H); ^{13}C NMR[47] 12.3, 13.7, 13.9, 18.6, 21.8, 22.3, 35.5, and 40.2 (aliphatic), 112, 159.4, 163.8, and 165.3 ppm (Ar); IR ($CDCl_3$) 3511 str, 3408 str,[48] (evaporated film) 2935 str, 2851 str, 1745, 1710 br m, 1465 str, 1380 m, 750, 726 cm^{-1} w; MS, m/e 207 (19.4, M^+).

Acetonitrile + Mg*. Activated magnesium (13.24 mmol), which had been washed thrice with glyme and pumped to dryness, was transferred to a sealed tube reactor and acetonitrile (76.6 mmol) added. The tube was placed in a heating block which had been preheated to 120 °C. Heating was maintained at 120–130 °C for 14 h. Upon cooling, a yellowish solid resulted. The tube was subjected to vacuum to remove unreacted acetonitrile and then hydrolyzed with aqueous NH_4Cl. The solution was multiply extracted with $CHCl_3$, and the combined $CHCl_3$ layers were dried and stripped to give 2.425 g of crude product. A portion of the tan solid (1.0340 g) was purified by flash chromatography using isopropyl alcohol/$CHCl_3$ as elutant. 4-Amino-2,6-dimethylpyrimidine (636.3 mg, 93%) resulted as white crystals: mp 182–183 °C (lit.[49] mp 180–181 °C); NMR ($CDCl_3$) δ 2.5 (s, 1 H), 5.0 (s, br, 2 H), 6.1 (s, 1 H); IR 3540 m, 3420 str, 2930 w, 1620 str, 1570 str, 1470 str, 1420 str, 1190 str, 980 str, 830 cm^{-1} str; UV (EtOH) λ_{max} 234 nm.

4-Cyanobenzyl Bromide + Mg*. Activated magnesium (14.3 mmol) was cooled to −78 °C in THF (20 mL). The bromonitrile (5.0 mmol) was dissolved in THF (5 mL) and added via syringe to the chilled slurry, dropwise, over an 8-min period. The drops were run down the side of the chilled reaction flask, so that they were precooled as they entered the solution. After 15 min, the mixture was quenched by injecting a solution of D_2O (5 mL) in THF (5 mL) and then allowing the slurry to warm to room temperature. The solution was removed via cannula, with most of the unreacted magnesium adhering to the flask. After being partitioned, the organic phase was dried over Na_2SO_4, filtered, and stripped to give a white solid (729 mg). ^1H NMR analysis of this crude product showed it to contain 4,4′-dicyanobibenzyl and 4-deuteriobenzonitrile in a 6:1 ratio (as well as small amounts of THF and naphthalene). The white solid was recrystallized from dichloromethane to give 4,4′-dicyanobibenzyl as white crystals (0.499 g, 86%): mp 199–201 °C (lit.[50] mp 198 °C); NMR (CD_2Cl_2) δ 3.0 (s, 4 H), 7.2 (d, J = 9 Hz, 4 H), 7.5 (d, J = 9 Hz, 4 H); MS, m/e 232 (22.2, $M^{\cdot+}$).

4-Bromobutyronitrile and 5-Bromovaleronitrile with Mg* (−78 °C). 4-Bromobutyronitrile and 5-bromovaleronitrile were reacted in a similar fashion. In a typical reaction, activated magnesium (21.9 mmol) in THF (20 mL) was cooled to −78 °C. 4-Bromobutyronitrile (19.2 mmol) was dissolved in THF (5 mL) and added via syringe over a 15-min period. Aliquots were removed immediately after the addition and after 0.5 and 1 h analyzed by gas chromatography. The reaction temperature was ramped at 10 °C/h, with aliquots being removed every 15 °C. Every aliquot was identical with the original one, except when the temperature reached 20 °C, which showed a disappearance of starting material. Carbonation of the reaction mixture and workup by the usual method gave only a polymeric oil with no definitive NMR spectrum. The reaction was not characterized further.

A second reaction involving similar amounts of reagents was carried out. The reaction temperature started out at −15 °C. Aliquots were removed at −15, −10, 0, 10, 15, and 20 °C. Reaction, as signified by consumption of starting material, was only observed at 20 °C. The reaction was not characterized further.

8-Bromooctanenitrile with Mg* (−78 °C). Activated magnesium (11.6 mmol) in THF (30 mL) was cooled to −78 °C. 8-Bromooctanenitrile (2.8 mmol) was added dropwise over a 3.5-min period. Aliquots were removed at selected intervals. Their times, in minutes, and % conversion to octanenitrile are listed: 2 (16%), 12 (78%), 24 (78%), 33 (79%), 43 (74%), 51 (74%). After 51 min, it was clear that the conversion had maximized and was beginning to deteriorate. The cold mixture was blanketed with CO_2 for 1 h and then allowed to warm to room temperature. The solution was worked up by basic extraction and reacidification, followed by partitioning into $CHCl_3$. The solution was dried over Na_2SO_4 and stripped to give 8-cyanooctanoic acid as a clear, slightly yellow oil (123.4 mg, 26%): NMR[51] ($CDCl_3$) δ 1.1–2 (m, 10 H), 2.2–2.5 (m, 4 H) [COO*H*, not clearly observed by NMR]; IR (neat, capillary) 3600–3040 br str, 2960, 2870 str, 2600–2400 br m, 2260 m sharp, 1715 str, 1470, 1430 m, 930 br w, 790 m, 760 cm^{-1} str.

Bromopentane with Mg* (−78 °C), Followed by Addition of Butyronitrile. Activated magnesium (19.9 mmol) in THF (20 mL) was cooled to −78 °C. Decane (1.9 mmol) was added and a base line aliquot removed for analysis by gas chromatography. Bromopentane (7.0 mmol) was added in one portion. An aliquot removed after 1 min showed all of the bromopentane to be consumed, and a large pentane peak had appeared. Butyronitrile was added over a 2-min period, beginning 9 min after the bromopentane addition was complete. An aliquot withdrawn after 1 min showed a large butyronitrile peak and a comparable pentane peak to that before the nitrile addition. Aliquots at 15 min and 1 h were unchanged.

Butyronitrile with Mg* (−78 °C), Followed by Addition of Bromopentane. Activated magnesium (20.1 mmol) in THF (20 mL) was cooled to −78 °C. Decane (2.2 mmol) was added and a base line aliquot removed for analysis by gas chromatography. Butyronitrile (6.5 mmol) was added and another reference aliquot removed. Bromopentane was then added in one portion. After the solution was stirred for 1 min, an aliquot was removed and analyzed by gas chromatography. There was no evidence of pentane or any decrease in butyronitrile. The reaction was followed by gas chromatography for 2 h, without any decrease in starting material concentration or appearance of new peaks in the chromatogram.

Acknowledgment. This investigation was supported in part by Grant GM 35153 of the National Institutes of Health.

(44) Lack of strong absorbances at 715 and 999 cm^{-1} proves that phthalocyanine is not metal free. No distinct absorbances were observed at frequencies higher than 1650 cm^{-1}—see: Kobayashi, T.; Kurokawa, F.; Uyeda, N.; Suito, E. *Spectrochim. Acta, Part A* **1970**, *26A*, 1305–1311.

(45) These types of compounds are known to complex alcohols fairly strongly. Ankar, R. M.; Cook, A. H. *J. Chem. Soc.* **1941**, 327.

(46) Baerts, F. *Chem. Zentralbl.* **1923**, *3*, 124.

(47) Spectrum taken on Varian XL-200 instrument with a spectral frequency of 50.309 MHz, with Me_4Si as internal standard.

(48) These bands due to the NH_2 did not show up in the solid-phase IR but in solution are very indicative of a primary amine.

(49) Osborne, D. R.; Wieder, W. T.; Levine, R. *J. Heterocycl. Chem.* **1964**, *1*, 145.

(50) *Dictionary of Organic Compounds*, 5th ed.; Chapman and Hall: New York, 1982; Vol. 1, p B-00990.

(51) Matches closely in peak shape and chemical shifts the spectrum for 9-cyanononanoic acid Sadtler ^1H NMR 2178.

(52) Cook, A. H.; Jones, D. G. *J. Chem. Soc.* **1941**, 278–282.

(53) Scholl, R.; Nörr, W. *Chem. Ber.* **1900**, *33*, 1054.

(54) Yanagida, S.; Yokoe, M.; Katagiri, I.; Ohoka, M.; Komori, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 306.

(55) Hofmann, E. *Chem. Ber.* **1868**, *1*, 198.