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Deprotonation of fluoro aromatics using lithium magnesates

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Abstract—3-Fluoropyridine was deprotonated on treatment with 1/3 equiv of Bu_3MgLi in THF at −10 °C. The lithium arylmagnesate formed was either trapped with electrophiles or involved in a palladium-catalyzed cross-coupling reaction with 2-bromopyridine. The use of a less nucleophilic lithium-magnesium-dialkylamide, $(TMP)_3MgLi$, allowed the reaction of 3-fluoroquinoline, giving the 2,2′-dimeric derivative. 2-Fluoropyridine and 2,6-difluoropyridine were deprotonated using 1/3 equiv of the highly coordinated magnesate Bu_4MgLi_2 in THF at −10 °C in the presence of a substoichiometric amount of 2,2,6,6-tetramethylpiperidine. 1,3-Difluorobenzene reacted similarly when treated with Bu_3MgLi; the reactivity of the base proved to be enhanced by the presence of TMEDA.

We describe the first deprotonation–electrophilic trapping sequences using magnesates.

The preparation of functional heterocycles is an important synthetic goal because of the multiple applications of these molecules.[1] Among the methods developed, lithiation is convenient to allow a number of polyfunctional azine (pyridines, quinolines,...) and diazine syntheses since lithiated derivatives display a high reactivity towards many electrophilic functions.[2] Nevertheless, this methodology often requires low temperatures, which can be difficult to realize on an industrial scale. In addition, unlike organoboron, organotin, organozinc and organomagnesium compounds, organolithiums can hardly be involved in cross-coupling reactions.[3]

Some substituted azines can be deprotonated at higher temperatures using the Hauser base TMPMgCl (TMP = 2,2,6,6-tetramethylpiperidino);[4] because of its weak reactivity when compared to alkylmagnesium halides, a large excess (6–8 equiv) has in general to be used to ensure good yields. Alkylmagnesium halides and dialkylmagnesiums rarely deprotonate such substrates because 1,4-addition reactions occur more easily.[5]

More recently, deprotonations of pyridine, quinoline and isoquinoline rings have been accomplished at room temperature through the formation of an arylzincate using lithium di-*tert*-butyl(2,2,6,6-tetramethylpiperidino)zincate or lithium di-*tert*-butyl(diisopropylamino)zincate as a base.[6]

The arylmagnesates reacting with a wider range of electrophiles than arylzincates, we have been interested in deprotonation reactions of aromatics using lithium magnesates.

Since a magnesium ate complex (R_3MgLi) was first published in 1951,[7] several investigations on its structure have been reported.[8] However, the synthetic applications of magnesate reagents remained unexplored until very recently.[9] While halogen–magnesium exchanges using organomagnesium ate complexes were described in the benzene, thiophene, pyridine and quinoline series,[9i,l,m,p–r] few studies have been devoted to aromatic deprotonation. Mulvey documented in 1999 the preparation of a mixed-metal sodium–magnesium macrocyclic amide, which behaves like a template for the site selective dideprotonation of benzene and toluene.[10] This

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process cannot be used as it is for synthetic purposes because it involves a large excess of arene (5 mmol out of the 5 mL used are consumed in the reaction). Very recently, Richey observed that treating benzene halides with magnesates partially results in benzyne formation.[9s] Even if the organometallic precursors have not been intercepted by electrophiles, the results show magnesates are capable of abstracting aromatic protons.

Herein, we describe the synthesis and reactivity of lithium arylmagnesates through the regioselective deprotonation of activated aromatic fluorides using lithium magnesates.

The first experiments were conducted on 3-fluoropyridine using 1/3 equiv of lithium tributylmagnesate (Bu_3MgLi) in THF at −10 °C. Trapping the intermediate lithium magnesate with iodine, 4-anisaldehyde, 3,4,5-trimethoxybenzaldehyde and allyl bromide afforded the iodide **1a**,[11] the alcohols **1b**,**c**[12] and the allylated compound **1d**[13] in moderate yields. The proton abstraction occurs at C4, as previously noticed using BuLi-TMEDA, LIC-KOR (mixture of BuLi and potassium *tert*-butoxide) or LDA in THF (thermodynamic control).[2a,b] The degradation of the arylmagnesate through 3,4-pyridyne formation is not observed at −10 °C (the yield is limited only by the deprotonation step), while 3-fluoro-4-lithiopyridine decomposes between −60 and −20 °C.[2a,b] In addition, the yields using BuLi-TMEDA (60%), Bu_3MgLi (55%) and Bu_3MgLi(TMEDA) (74%) were compared (3,4,5-trimethoxybenzaldehyde was used as the electrophile): the latter proved to be more efficient.

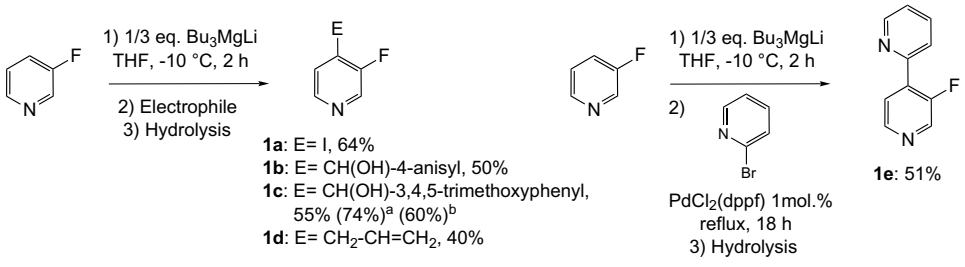
Since treatment of 3-fluoropyridine with BuLi-TMEDA or BuLi-DABCO complexes in diethyl ether leads to C2 metallation (kinetic control),[2] the reaction using Bu_3MgLi was also carried out in the less basic solvent diethyl ether at −10 °C. Under these conditions, a mixture was produced and the iodide **1a** was isolated in a low yield (<30%).

We previously reported the first cross-couplings with lithium arylmagnesates: the lithium tri(quinolyl)magnesates could react with aromatic halides under transition metal-catalysis to give the corresponding arylquinolines.[9q,r] Nevertheless, the yields of these reactions remained limited (0–60%) due to the way the lithium tri(aryl)magnesates were formed. Indeed, the bromine–magnesium exchange used generated bromobutane, which could consume the quinoline organometallics present in the reaction mixture by nucleophilic substitution. The access to arylpyridines was here investigated via hydrogen–magnesium exchange, avoiding such complications. To this purpose, the intermediate (3-fluoro-4-pyridyl)magnesate was subjected to reaction with 2-bromopyridine. As for the quinoline series couplings,[9q,r] the reaction was successful under palladium catalysis using 1,1′-bis(diphenylphosphino)ferrocene (dppf) as ligand, and afforded the bipyridine **1e**[14] in a yield comparable to those obtained when quenching with electrophiles (Scheme 1).

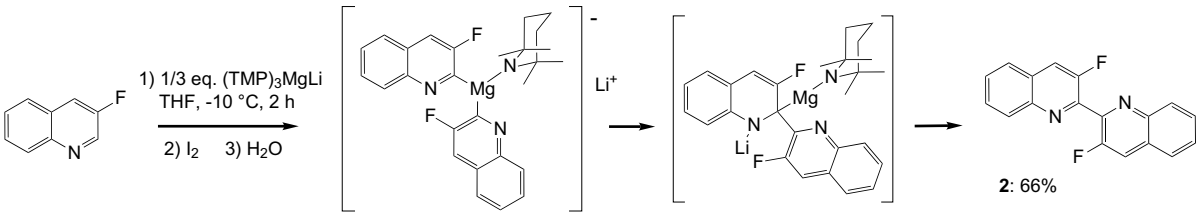
The procedure was applied to 3-fluoroquinoline[15] but only gave a complex mixture containing butylated products. Due to its lower LUMO level, quinoline is more prone to nucleophilic attack, and addition of either the base or the formed lithium arylmagnesate to the substrate is favoured over deprotonation. Predominant addition reactions have been previously observed during lithiation experiments using BuLi-TMEDA in diethyl ether while LDA in THF ensures a clean deprotonation.[2] We therefore turned to the less nucleophilic lithium-magnesium-dialkylamide $(TMP)_3MgLi$, which has never been employed for the purpose of deprotonating arenes. Such bases (diisopropylamino instead of TMP) have been regarded as sources of hyperbasic 'R_2N^-' anions, which separate from the cations '$LiMg[NR_2]_2^+$' in hydrocarbon solutions.[16] Insofar as THF is our solvent, one can wonder if 1 equiv or 1/3 equiv should be employed in the deprotonation process. Consequently, both experiments were performed in THF at −10 °C. After addition of iodine, iodinated 3-fluoropyridines were obtained in very low yields, the main product being the 2,2′-dimer **2**.[17] Since a better yield was obtained using 1/3 equiv of base, its formation could be explained by a deprotonation at C2, followed by the migration of the 3-fluoro-2-quinolyl group,[9k] as depicted in Scheme 2.

The regioselectivity of the deprotonation is surprising, since lithiation using lithium dialkylamides occurs at C4;[2a,b] it could be attributed to the important size of $(TMP)_3MgLi$, when compared with the lithium bases. Indeed, the hydrogen at C5 could hinder access of the base to H4, preventing proton abstraction at this site.

To evaluate the scope of this reaction, it was next extended to 2-fluoropyridine.



Scheme 1. Reagents and conditions: [a]Using 1/3 equiv Bu_3MgLi(TMEDA), THF, −10 °C, 2 h; [b]Using 1 equiv BuLi, 1 equiv TMEDA, THF, −75 °C, 2 h.



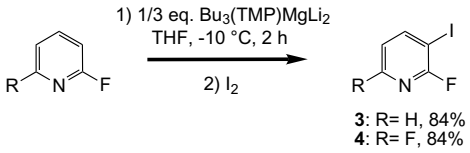
Scheme 2.

Lithiation of the substrate at C3 has been reported using LDA, alkyllithiums being less efficient due to competitive addition reactions.[2] Various attempts to use lithium trialkylmagnesates in THF at −10 °C, with or without TMEDA, were unsuccessful and the substrate was recovered. Considering the migratory aptitude of TMP over alkyl groups,[6] lithium dialkyl(2,2,6,6-tetramethylpiperidino)magnesates were also tested, without success. This could be justified by comparing the hydrogens total atomic charges of the substrates (Table 1): the hydrogen at C3 of 2-fluoropyridine is less acidic than the one at C4 of 3-fluoropyridine.

Since dilithium tetramethylzincate has been shown to exhibit a higher reactivity compared to lithium trimethylzincate in various reactions including halogen–metal exchange,[18] we decided to turn to highly coordinated magnesates and chose easily accessible dilithium tetrabutylmagnesate (Bu_4MgLi_2).

No reaction was noted when 2-fluoropyridine was exposed to 1/3 equiv of Bu_4MgLi_2 in THF at −10 °C. Interestingly, the course of the reaction was completely modified using a combination of Bu_4MgLi_2 and HTMP (1/3 equiv) followed by iodine to afford the compound **3** in a good yield.[19] The same result was obtained with 2,6-difluoropyridine, giving the iodide **4**[20] (Scheme 3).

This result demonstrates the catalytic role of the amine for the deprotonation.[21]

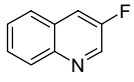
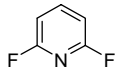
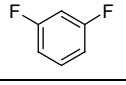


Scheme 3.

The hydrogen–magnesium exchange reaction was likewise effected with 1,3-difluorobenzene, and the magnesate formed intercepted to produce the expected iodide **5a**[22] (entry 1). In this case, the yield was similar using Bu_3MgLi (entry 2), and could be improved by adding TMEDA (entry 3). The results are comparable to those obtained[22] through lithiation using alkyllithiums. For example, the reaction conducted using BuLi and 3,4,5-trimethoxybenzaldehyde furnished the alcohol **5b**[23] in a 81% yield (Table 2, entry 4).

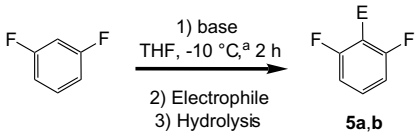
In conclusion, 3-fluoropyridine was deprotonated using Bu_3MgLi in THF at −10 °C; the (3-fluoro-4-pyridyl)magnesate generated was either intercepted with electrophiles or cross-coupled in a 'one-pot' procedure. 3-Fluoroquinoline was surprisingly deprotonated at C2 using $(TMP)_3MgLi$; the arylmagnesate could not be intercepted with electrophiles but underwent a 1,2-migration to afford the 2,2′-dimer after hydrolysis and autooxidation. Bu_4MgLi_2, when associated with HTMP (33 mol%), proved to be more reactive for less activated

Table 1. Substrate hydrogen's total atomic charges[a]

Substrate	2	3	4	5	6	7	8
	0.225		**0.237**	0.222	0.208		
	0.226		**0.236**	0.211	0.209	0.210	0.228
		**0.232**	0.225	0.217	0.215		
		**0.238**	0.236	0.238			
	**0.244**		0.228	0.222	0.228		

[a] The total atomic charges were determined by ab initio calculations using Gaussian 94 at the HF/6-31G(d) level after energy minimization using cvff-300-1.01 (Cerius2 4.9).

Table 2. Deprotonation of 1,3-difluorobenzene using lithium magnesates



Entry	Base	Electrophile	E	Product	Yield (%)
1	1/3 equiv $Bu_3(TMP)MgLi_2$	I_2	I	**5a**	73
2	1/3 equiv Bu_3MgLi	3,4,5-Trimethoxybenzaldehyde	CH(OH)-3,4,5-Trimethoxyphenyl	**5b**	74
3	1/3 equiv Bu_3MgLi(TMEDA)	3,4,5-Trimethoxybenzaldehyde	CH(OH)-3,4,5-Trimethoxyphenyl	**5b**	86
4	1 equiv BuLi	3,4,5-Trimethoxybenzaldehyde	CH(OH)-3,4,5-Trimethoxyphenyl	**5b**	81

[a] −75 °C using BuLi.

substrates such as 2-fluoropyridine. 1,3-Difluorobenzene reacted similarly when treated with Bu_3MgLi; the reactivity of the base proved to be enhanced by the presence of TMEDA. The results suggest that the mechanism does not proceed via aryllithiums species, since these are not stable at −10 °C, but via arylmagnesates. In addition, Bu_3MgLi is assumed to be the reactive species since Bu_2Mg does not allow deprotonation and BuLi adds easily to azine rings.

The main advantage of this methodology is the relative stability of the organometallic species formed: hydrogen–lithium exchange has to be performed at low temperature (−75 °C) in order to prevent side reactions such as nucleophilic additions or elimination of lithium fluoride while hydrogen–magnesium exchange proceeds at −10 °C.

Deprotonation using Bu_3MgLi, typical procedure: BuLi (6.0 mmol) was added to a solution of $MgBr_2$ (2.0 mmol) in THF (3 mL) at −10 °C. After stirring for 1 h at −10 °C, 3-fluoropyridine (0.52 mL, 6.0 mmol) was introduced at −30 °C. After 2 h at −10 °C, a solution of I_2 (1.5 g, 6.0 mmol) in THF (3 mL) was added and the mixture was stirred for 18 h at rt. Addition of water (0.5 mL) and $Na_2S_2O_3$ (until bleaching), dilution with CH_2Cl_2 (50 mL), drying over $MgSO_4$ and column chromatography using CH_2Cl_2 as an eluent afforded compound **1a** (64% yield).

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11. Compound **1a**: mp 90 °C. The physical and spectral data are identical to those described: Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron* **1993**, *49*, 49–64, ^{13}C NMR ($CDCl_3$): 159.1 (d, J = 256), 145.6 (d, J = 5.1), 137.1 (d, J = 26), 133.7 (s), 92.4 (d, J = 23).
12. Compound **1b**: mp 145 °C; ^{1}H NMR ($CDCl_3$): 8.44 (d, 1H, J = 4.9), 8.35 (s, 1H), 7.63 (t, J = 5.7, 1H), 7.30 (d, J = 8.3, 2H), 6.88 (d, J = 8.7, 2H), 6.07 (s, 1H), 3.79 (s, 3H), 2.37 (s, 1H); ^{13}C NMR (DMSO-d_6): 159.0 (s), 156.5 (d, J = 253), 146.4 (s), 141.4 (s), 137.6 (d, J = 20), 135.3 (s), 128.1 (s), 122.3 (d, J = 32), 114.1 (s), 67.6 (s), 55.3 (s); IR (KBr): 3138, 3006, 2838, 1611, 1510, 1260, 1067, 1032, 803 cm^{-1}. Compound **1c**: mp 124–125 °C; ^{1}H NMR ($CDCl_3$): 8.37 (d, 1H, J = 4.9), 8.32 (d, 1H, J = 1.5), 7.58 (t, 1H, J = 5.6), 6.60 (s, 2H), 6.03 (s, 1H), 3.81 (s, 6H), 3.80 (s, 3H), 2.16 (s, 1H); ^{13}C NMR ($CDCl_3$): 156.4 (d, J = 256), 153.2 (s, 2C), 145.7 (d, J = 5.1), 140.0 (d, J = 11), 137.4 (d, J = 25), 137.3 (s), 137.2 (s), 121.4 (d, J = 1.5), 103.1 (s, 2C), 68.7 (d, J = 1.4), 60.7 (s), 55.9 (s, 2C); IR (KBr): 3181, 2838, 1590, 1509, 1494, 1464, 1419, 1322, 1233, 1230, 1068, 1010, 810, 664 cm^{-1}.
13. Compound **1d**: colourless oil; ^{1}H NMR ($CDCl_3$): 8.39 (s, 1H), 8.33 (d, 1H, J = 4.5), 7.17 (t, 1H, J = 5.7), 5.93 (m, 1H), 5.16 (m, 2H), 3.44 (d, 2H, J = 6.8); ^{13}C NMR ($CDCl_3$): 158.0 (d, J = 254), 145.4 (d, J = 5.1), 137.5 (d, J = 25), 135.5 (d, J = 14), 133.3 (s), 124.8 (d, J = 1.5), 117.6 (s), 32.0 (d, J = 2.9); IR (KBr): 2956, 2359, 1586, 1551, 1438, 1297, 1155, 1126, 980, 785 cm^{-1}.
14. Compound **1e**: mp < 50 °C; ^{1}H NMR ($CDCl_3$): 8.77 (d, 1H, J = 4.1), 8.57 (d, 1H, J = 2.6), 8.53 (d, 1H, J = 4.9), 7.99 (t, 1H, J = 5.8), 7.90 (d, 1H, J = 7.9), 7.82 (t, 1H, J = 7.2), 7.36 (t, 1H, J = 6.0); ^{13}C NMR ($CDCl_3$): 156.4 (d, J = 257), 149.7 (d, J = 2.9), 149.4 (s), 145.4 (d, J = 5.1), 138.5 (d, J = 27), 136.1 (s), 133.1 (d, J = 8.7), 124.3 (d, J = 10), 123.4 (s), 123.3 (s); IR (KBr): 3408, 3054, 1587, 1574, 1488, 1463, 1435, 1415, 1263, 1204, 1053, 798 cm^{-1}.
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17. Compound **2**: mp 149 °C; ^{1}H NMR ($CDCl_3$): 8.30 (d, 1H, J = 8.3), 7.98 (dd, 1H, J = 5.3, 3.8), 7.89 (d, 1H, J = 7.9), 7.75 (td, 1H, J = 7.1, 1.1), 7.65 (t, 1H, J = 7.5); ^{13}C NMR ($CDCl_3$): 154.5 (dd, J = 262, 1.8), 144.8 (m, 2C), 129.5 (s), 128.6 (s), 128.6 (s), 127.8 (s), 126.6 (s), 119.2 (m); IR (KBr): 3061, 2969, 1613, 1496, 1453, 1414, 1355, 1340, 1326, 1316, 1216, 1157, 1141, 895, 780, 751 cm^{-1}.
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19. Compound **3**: mp < 50 °C. The physical and spectral data are identical to those described: Estel, L.; Marsais, F.; Quéguiner, G. *J. Org. Chem.* **1988**, *53*, 2740–2744. ^{13}C NMR ($CDCl_3$): 161.2 (d, J = 233), 149.6 (d, J = 2.9), 146.6 (d, J = 13), 122.4 (d, J = 4.3), 75.8 (d, J = 43).
20. Compound **4**: colourless oil; ^{1}H NMR ($CDCl_3$): 8.20 (q, 1H, J = 7.9), 6.70 (dd, 1H, J = 8.3, 2.6); ^{13}C NMR ($CDCl_3$): 160.6 (m, 2C), 153.4 (dd, J = 7.4, 2.9), 108.2 (dd, J = 35, 5.9), 69.1 (dd, J = 41, 5.9); IR (KBr): 3093, 2928, 1595, 1568, 1449, 1425, 1407, 1398, 1377, 1302, 1268, 998, 816 cm^{-1}.
21. Diisopropylamine acts as a catalyst for the deprotonation of arenes with alkyl and aryllithiums: Mallet, M. *J. Organomet. Chem.* **1991**, *406*, 49–56.
22. (a) Compound **5a**: colourless oil. The physical and spectral data are identical to those described: Roe, A. M.; Burton, M. A.; Willey, G. L.; Baines, M. W.; Rasmussen, A. C. *J. Med. Chem.* **1968**, *11*, 814–819; (b) Rausis, T.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, 3351–3358, IR (KBr): 2956, 2927, 2857, 1626, 1591, 1463, 1431, 1284, 1235, 990, 777, 691, 561 cm^{-1}.
23. Compound **5b**: mp 94–95 °C; ^{1}H NMR ($CDCl_3$): 7.26 (quint., 1H, J = 7.0), 6.91 (t, 2H, J = 8.1), 6.63 (s, 2H), 6.16 (d, 1H, J = 8.3), 3.82 (s, 9H), 2.86 (d, 1H, J = 8.3); ^{13}C NMR ($CDCl_3$): 160.3 (dd, J = 249, 8.7, 2C), 152.7 (s, 2C), 137.8 (s), 136.6 (s), 129.1 (t, J = 11), 119.1 (t, J = 16), 111.5 (m, 2C), 102.3 (s, 2C), 66.8 (s), 60.3 (s), 55.6 (s, 2C); IR (KBr): 3420, 2975, 2940, 2845, 1623, 1595, 1504, 1471, 1414, 1332, 1233, 1126, 1075, 992, 818, 793, 780 cm^{-1}.