Metalation

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Mixed Mg/Li Amides of the Type $R_2NMgCl{\cdot}LiCl$ as Highly Efficient Bases for the Regioselective Generation of Functionalized Aryl and Heteroaryl Magnesium Compounds**

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The metalation of arenes is one of the most useful transformations in organic synthesis since it allows the regioselective functionalization of various aryl and heteroaryl derivatives.[1] Traditionally, strong bases such as alkyl lithium reagents (RLi) and lithium amides (R_2NLi) have been used for such deprotonations. However, these bases often lead to undesirable side reactions as a result of their high reactivity and their strong nucleophilicity (e.g. Chichibabin addition). Another serious limitation is the low stability of lithium amides in THF solutions at room temperature, which requires in situ generation of these reagents. Furthermore, the deprotonation of arenes by lithium bases requires very low temperatures (−78 to −90 °C), which complicates the scale-up of these reactions. Alternative methods have been developed using magnesium amides[2] such as **1**–**3**, amidozincates[3] of type **4**, and *n*BuLi/lithium aminoalkoxide aggregates which permit deprotonation of various heterocycles at the position α to the heteroatom (Scheme 1).[4] The problem of the low solubility of the magnesium amides R_2NMgCl (**1**) has been addressed by Eaton et al., who developed applications of magnesium amides of type R_2NMgR' (**2**) and $(R_2N)_2Mg$ (**3**). Nevertheless, for achieving high conversions it is usually necessary to use a large excess of the magnesium amides (2–12 equiv), which further complicates the reactions with electrophiles (up to 10 equiv of the electrophile may have to be used). Similarly, aminozincate requires the use of 3.5–4 equiv of an electrophile in subsequent quenching reactions.

Therefore, the development of an inexpensive, highly soluble magnesium base displaying high kinetic activity would be desirable. Recently, we found that the addition of lithium chloride to alkylmagnesium chlorides produces highly active reagents of the type $RMgCl_2^-Li^+$[5,6] and $R_2MgCl^-Li^+$,[7]

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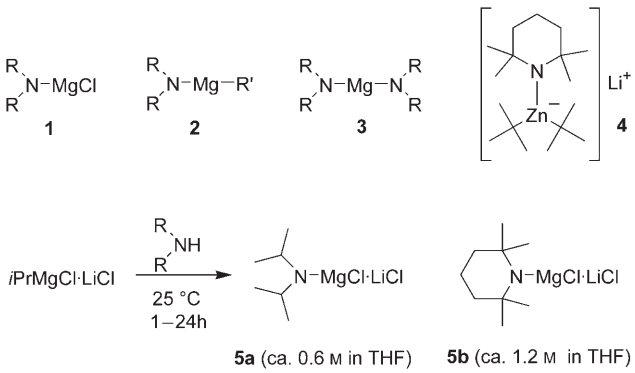
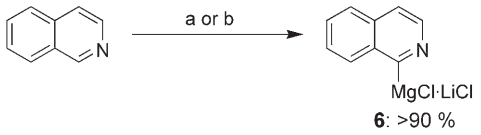


Scheme 1. Typical magnesium bases used for the magnesiation of arenes and heteroarenes and the preparation of the mixed Mg/Li amides.

which undergo Br/Mg exchange reactions with rates that are high compared to the those of the reactions with homoleptic reagents RMgX and R_2Mg without added LiCl.

We therefore prepared the corresponding mixed Mg/Li amides of type $R_2NMgCl{\cdot}LiCl$ **5** by reacting *i*PrMgCl·LiCl[5,6] with diisopropylamine or 2,2,6,6-tetramethylpiperidine (TMPH) in THF (25 °C, 1–24 h). The resulting Mg/Li reagents **5a** (R = *i*Pr) and **5b** (R_2N = 2,2,6,6-tetramethylpiperidyl) proved to have excellent solubility in THF (0.6 M and 1.2 M, respectively) as well as improved kinetic basicity and regioselectivity for the magnesiation of various aromatics and heteroaromatics.

In preliminary experiments, we examined the magnesiation of isoquinoline. Reaction with 2 equiv of **5a** provided only the magnesiated isoquinoline **6** after 12 h at 25 °C (Scheme 2). After iodolysis the iodoisoquinoline **7a** was



Scheme 2. Magnesiation of isoquinoline. a) **5a** (2 equiv), THF, 25 °C, 12 h; b) **5b** (1.1 equiv), THF, 25 °C, 2 h.

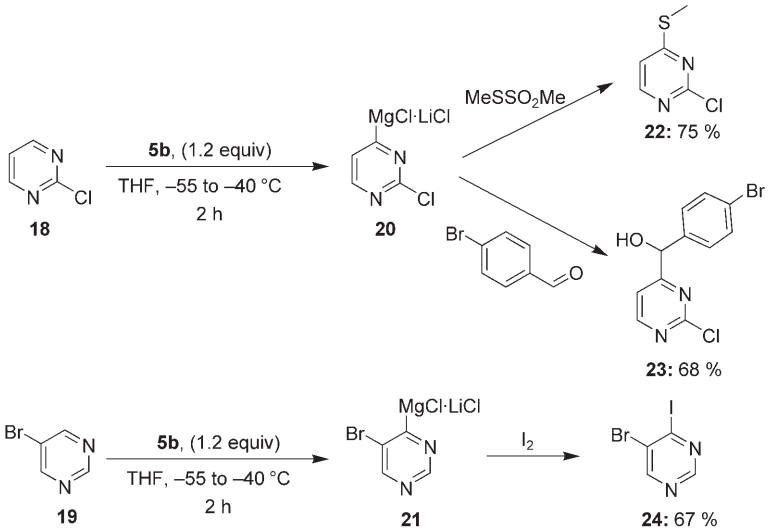
isolated in 81 % yield. In strong contrast, the sterically more hindered and less aggregated reagent **5b** led to complete magnesiation within 2 h at 25 °C. Remarkably, only 1.1 equiv of this base was required to achieve complete metalation. The resulting Grignard reagent **6** provided, after iodolysis, the isoquinoline **7a** in 92 % yield (entry 1, Table 1).

In the presence of substoichiometric amounts of CuCN·2 LiCl (20 mol %), the addition of benzoyl chloride (1.2 equiv) provided the ketone **7b** in 86 % yield (entry 2, Table 1). The presence of an excess of the magnesium amide often hampers palladium-catalyzed cross-couplings. We found that the Grignard reagents generated by deprotonation with **5b** (1.1 equiv) such as **6** were readily transmetalated to give the corresponding zinc derivative ($ZnCl_2$ (1.1 equiv), 0 °C, 5 min) and underwent a Negishi cross-coupling reaction using [$Pd(dba)_2$] (5 mol %), $P(2\text{-fur})_3$ (7 mol %) with ethyl 4-iodobenzoate (1.2 equiv; 50 °C, 12 h) leading to the arylated isoquinoline **7c** in 82 % yield.

This method of metalation is general, and 3-bromoquinoline was also metalated by **5b** (1.1 equiv, −25 °C, 0.5 h) leading to the 2-magnesiated quinoline **8** (entries 4 and 5). Thus, the quenching of **8** with I_2 and DMF provided the functionalized quinolines **9a** and **9b** in 87 and 91 % yield, respectively. Whereas the deprotonation of 2,6-dichloropyridine with $iPr_2NMgCl{\cdot}LiCl$ (**5a**) and lithium diisopropylamide (LDA)[9j] provided a 1:1 mixture of 3- and 4-magnesiated 2,6-dichloropyridine, the use of TMPMgCl·LiCl (**5b**) furnished only the 4-magnesiated pyridine **10**. Its reaction with typical electrophiles (I_2, DMF, and PhCHO) provided the expected products **11a–c** in 84–93 % yield (entries 6–8).

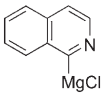
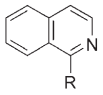
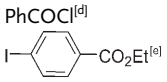
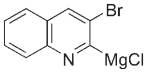
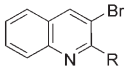
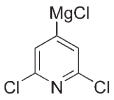
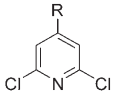
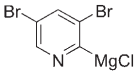
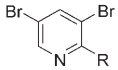
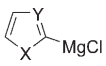
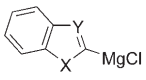
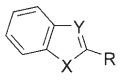
Interestingly, metalation of 3,5-dibromopyridine with LDA proceeded selectively at the 4-position,[7b] while in the case of TMPMgCl·LiCl (**5b**) (1.1 equiv, −25 °C, 0.5 h) regioselective metalation in the 2-position was observed, leading after the reaction with I_2 and DMF to the corresponding pyridines **13a** and **13b** in yields of 89 and 85 %, respectively (entries 9 and 10). The magnesiation of heterocycles bearing more acidic protons[8] such as thiazole, thiophene, furan, benzothiophene, and benzothiazole proceeded smoothly between 0 °C and 25 °C leading to the organomagnesium derivatives **14a–c** and **16a–b**. After trapping with standard electrophiles, the expected products **15a–c** and **17a–b** were obtained in 81–98 % yield (entries 11–15).

The metalation of pyrimidine derivatives is a challenging problem because of the propensity of these heterocycles to undergo addition reactions with organometallic reagents.[7b,9] We found that the inverse addition of the pyrimidine derivatives **18** and **19** to a THF solution of **5b** (1.2 equiv) at −55 °C provided completely regioselectively the corresponding magnesiated derivatives **20** and **21**, which react with a wide range of electrophiles leading to the functionalized pyrimidines **22–24** in good yields (Scheme 3).



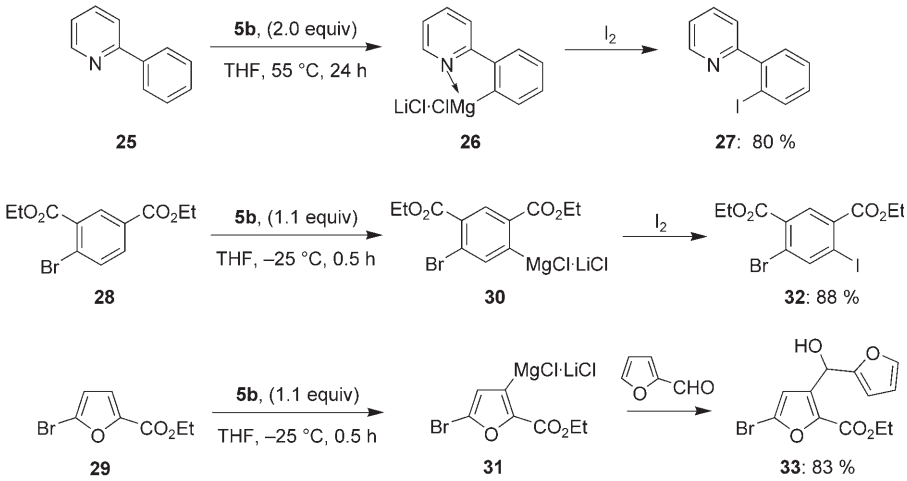
Scheme 3. Regioselective magnesiation of pyrimidines.

Table 1: Products obtained by the magnesiation of heterocycles with **5b** and reaction with electrophiles.

Entry	Magnesium reagent[a]	*T* [°C], *t* [h][b]	Electophile	Product	Yield [%][c]
					
1	**6**	25, 2	I_2	**7a**: R = I	92
2	**6**	25, 2	PhCOCl[d]	**7b**: R = COPh	86
3	**6**	25, 2		**7c**: R = 4-$EtO_2CC_6H_4$	82
					
4	**8**	−25, 0.3	I_2	**9a**: R = I	87
5	**8**	−25, 0.3	DMF	**9b**: R = CHO	91
					
6	**10**	25, 0.1	I_2	**11a**: R = I	93
7	**10**	25, 0.1	DMF	**11b**: R = CHO	90
8	**10**	25, 0.1	PhCHO	**11c**: R = CH(OH)Ph	84
					
9	**12**	−25, 0.5	I_2	**13a**: R = I	89
10	**12**	−25, 0.5	DMF	**13b**: R = CHO	85
					
11	**14a**: X = O, Y = CH	25, 24	DMF	**15a**: R = CHO	81
12	**14b**: X = S, Y = CH	25, 24	DMF	**15b**: R = CHO	90
13	**14c**: X = S, Y = N	0, 0.1	PhCHO	**15c**: R = CH(OH)Ph	94
					
14	**16a**: X = S, Y = CH	25, 24	DMF	**17a**: R = CHO	93
15	**16b**: X = S, Y = N	0, 0.1	I_2	**17b**: R = I	98

[a] Lithium chloride and TMPH are complexed to the Grignard reagent. [b] Reaction conditions for the deprotonation with **5b** (1.1 equiv). [c] Yield of isolated, analytically pure product. [d] A transmetalation with CuCN·2 LiCl (0.2 equiv) was performed. [e] Obtained by palladium-catalyzed cross-coupling after transmetalation with $ZnCl_2$.

The mixed Mg/Li amide **5b** is also well suited for the regioselective metalation of polyfunctional aromatic systems. Thus, the reaction of 2-phenylpyridine (**25**) in THF at 55 °C with **5b** (2.0 equiv) for 24 h provides the Grignard reagent **26**; this is a rare case where a phenyl ring is preferentially metalated over a pyridine ring.[10] After iodolysis, the *ortho*-iodinated product **27** was obtained in 80% yield. Interestingly, the metalation of polyfunctional arenes such as the bromodiester **28** and bromoester **29** also succeeded using only a stoichiomet-



Scheme 4. Regioselective magnesiation of polyfunctional aromatic systems.

ric amount of base **5b** (1.1 equiv) in THF (−25 °C, 0.5 h) leading regioselectively to the arylmagnesium species **30** and **31**, which after reaction with electrophiles furnished the polyfunctional aromatic derivatives **32** and **33** in 83–88% yields. (Scheme 4)

In summary, we have prepared new mixed Mg/Li-bases of the general type $R_2NMgCl{\cdot}LiCl$ which have a high kinetic activity because of the presence of LiCl which, we tentatively propose, breaks up oligomeric aggregates of magnesium amides. The use of TMPMgCl·LiCl, which has an excellent solubility and is stable for more than 6 months as THF solution at 25 °C, allows the regioselective functionalization of various aromatic and heteroaromatic compounds. It provides access to new magnesium species not readily available by Br/Mg-exchange reactions or previously reported metalation procedures. Extensions of this method are currently underway in our laboratories.

Experimental Section

1) Synthesis of **5b:** A dry and argon-flushed 250-mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with freshly titrated *i*PrMgCl·LiCl (100 mL, 1.2 M in THF, 120 mmol). TMPH (19.8 g, 126 mmol, 1.05 equiv) was added dropwise at room temperature. The reaction mixture was stirred at room temperature until gas evolution ceased (ca. 24 h).

2) Typical procedure: Synthesis of **7a**: A dry and argon-flushed 10-mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with **5b** (5 mL, 1.2 M in THF, 6.0 mmol). Isoquinoline (703 mg, 5.45 mmol) in THF (5 mL) was added dropwise at room temperature. During the addition the reaction mixture became red, and the metalation was complete after 2 h. (The reaction progress was checked by removal of reaction aliquots, which were quenched with a solution of I_2 in THF and analyzed by GC; the conversion was more than 98%.) A solution of I_2 in THF (6 mL, 1.0 M in THF, 6.0 mmol) was slowly added at −20 °C. The reaction mixture was quenched with sat. aqueous solution of NH_4Cl (10 mL). The aqueous layer was extracted with diethyl ether (4 × 10 mL), and the combined extracts were dried with Na_2SO_4 and concentrated in vacuo. The crude residue was purified by filter column chromatography (silica; CH_2Cl_2/pentane) affording **7a** (1.33 g, 92%) as slightly yellow crystals (m.p. 74–76 °C).

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