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# Direct Magnesiation of Polyfunctionalized Arenes and Heteroarenes Using $(tmp)_2Mg\cdot 2\,LiCl$**

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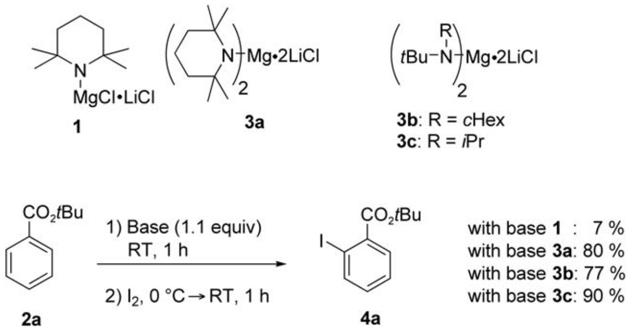
*Dedicated to Professor Herbert Mayr on the occasion of his 60th birthay*

Directed lithiations are important reactions for the functionalization of arenes and heterocycles.[1] In contrast, directed magnesiation with magnesium bases has been used much less often.[2] The pioneering work of Eaton et al.[3] demonstrated the potential of this approach using magnesium bis(2,2,6,6-tetramethylpiperamide), $(tmp)_2Mg$. However, the limited solubility of such bases in common organic solvents as well as the requirement for an excess of the magnesium bases (2–7 equiv) to achieve high conversions has precluded their general use. Recently, we have reported that mixed Li/Mg amides of the type $R_2NMgCl\cdot LiCl$ and in particular $(tmp)MgCl\cdot LiCl$ (**1**) are highly soluble magnesium bases readily able to deprotonate a broad range of unsaturated substrates.[4] However, some moderately activated arenes such as *tert*-butyl benzoate (**2a**) gave unsatisfactory results (Scheme 1). Therefore, we have developed a new class of mixed Li/Mg bases: magnesium bisamides complexed with lithium chloride, $(R_2N)_2Mg\cdot 2\,LiCl$ (**3**). The reagents **3a–c** were readily prepared by reacting $R_2NLi$ with $MgCl_2$ in THF at 0 °C for 0.5 h. Whereas with $(tmp)MgCl\cdot LiCl$ no significant deprotonation of **2a** was observed, the use of magnesium bisamides complexed with two equivalents of LiCl such as **3a–c** led to excellent results (Scheme 1).



***Scheme 1.*** Comparison between magnesium amide **1** and magnesium bisamides **3a–c**.

In general $(tmp)_2Mg\cdot 2\,LiCl$ (**3a**) proves to be the most powerful and selective base,[5] and the best results were obtained when it was freshly prepared. We have found that this base can also be conveniently made by reacting $(tmp)MgCl\cdot LiCl$ (**1**) with lithium 2,2,6,6-tetramethylpiperamide[6] for 30 min at 0 °C. Since **1** can be stored in THF at 25 °C for months, this alternative method appears to be the best for routine experiments. Moreover, this procedure can also be applied successfully for the preparation of **3a** in situ. On the other hand, $[tBu(iPr)N]_2Mg\cdot 2\,LiCl$ (**3c**) can be stored in THF at 4 °C for three weeks with no significant reduction of activity.

A number of aromatic and heterocyclic substrates were cleanly metalated with **3a** (Table 1). Thus, *tert*-butyl benzoate (**2a**) was converted to the *ortho*-magnesiated intermediate by reaction with **3a** within 1 h at 25 °C. After transmetalation with $CuCN\cdot 2\,LiCl$,[7] the reaction with benzoyl chloride provided the ketoester **4b** in 93 % yield (entry 1, Table 1). Remarkably, the magnesiated intermediates of the type $ArMg(tmp)\cdot 2\,LiCl$ obtained after the magnesiation with **3a** were smoothly transmetalated with $ZnCl_2$ (1.2 equiv) and underwent a Negishi cross-coupling[8] with ethyl 4-iodobenzoate (1.5 equiv) in the presence of $[Pd(dba)_2]$ (2 mol %), and $P(o\text{-furyl})_3$ (4 mol %) at 25 °C for 12 h, leading to the biphenyl derivative **4c** in 82 % yield (entry 2, Table 1).

Similarly, the magnesiation of $PhCO_2iPr$ (**2b**) with **3a** (25 °C, 1 h) gave after copper(I)-mediated acylation with propionyl chloride the ketone **4d** in 78 % yield (entry 3, Table 1). Additionally, the reactions of **3a** and **3c** (1.2 equiv) with ethyl naphthoate (**2c**) led to the corresponding *ortho*-magnesiated intermediates within 3 h at O °C. Iodolysis, bromolysis with $(BrCl_2C)_2$, or Negishi cross-coupling with 4-iodo benzonitrile afforded the corresponding functionalized derivatives **4e–g** in 81–83 % yield (entries 4–6, Table 1). The presence of an electron-withdrawing group such as a bromine substituent in the case of *tert*-butyl 4-bromobenzoate (**2d**) accelerated the metalation, furnishing the magnesiated product within 1 h at −20 °C. Quenching with iodine afforded *tert*-butyl 4-bromo-2-iodobenzoate (**4h**) in 71 % yield (entry 7, Table 1). A copper(I)-mediated benzoylation with benzoyl chloride gave the corresponding *tert*-butyl 2-benzoyl-4-bromobenzoate (**4i**) in 77 % yield (entry 8, Table 1). Although benzonitriles are metalated sluggishly with **1**, the use of **3a** (1.2 equiv) led to a complete magnesiation of benzonitrile **2f**

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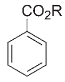
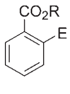
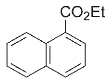
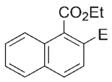
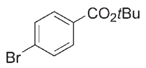
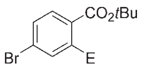
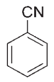
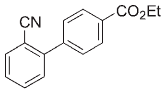
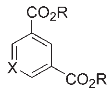
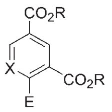
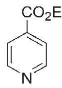
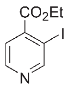
*Table 1:* Products of type **4** obtained by the magnesiation of arenes with $(tmp)_2Mg\cdot 2\,LiCl$ (**3a**) and reactions with electrophiles.

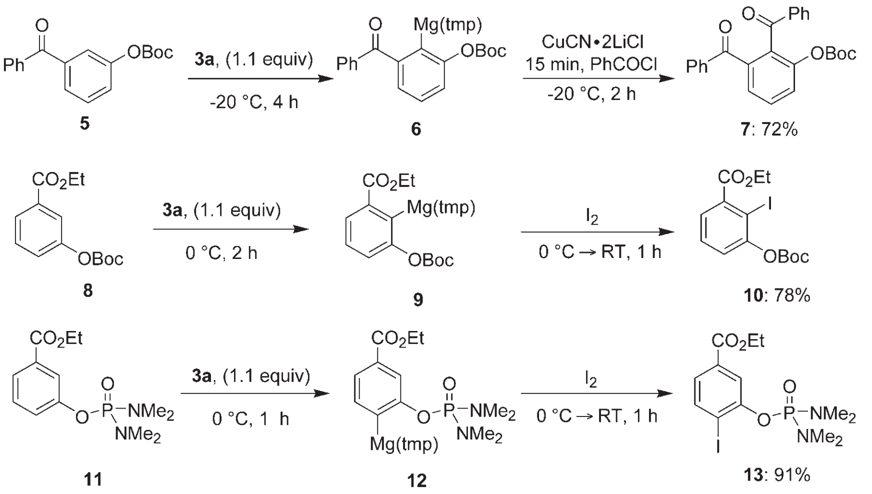
| Entry | Substrate | | $T$ [°C], $t$ [h] | $E^+$ | | Product | Yield [%][a] |
|---|---|---|---|---|---|---|---|
| 1 |  | **2a**: R = *t*Bu | 25, 1 | PhCOCl |  | **4b**: E = COPh, R = *t*Bu | 93[b] |
| 2 | | **2a**: R = *t*Bu | 25, 1 | $p$-$IC_6H_4CO_2Et$ | | **4c**: E = $p$-$C_6H_4CO_2Et$, R = *t*Bu | 82[c] |
| 3 | | **2b**: R = *i*Pr | 25, 1 | EtCOCl | | **4d**: E = COEt, R = *i*Pr | 78[b] |
| 4 |  | **2c** | 0, 3 | $I_2$ |  | **4e**: E = I | 83 |
| 5 | | **2c** | 0, 3 | $(BrCl_2C)_2$ | | **4f**: E = Br | 83 |
| 6 | | **2c** | 0, 3 | $p$-$IC_6H_4CN$ | | **4g**: E = $p$-$C_6H_4CN$ | 81[c] |
| 7 |  | **2d** | −20, 1 | $I_2$ |  | **4h**: E = I | 71 |
| 8 | | **2d** | −20, 1 | PhCOCl | | **4i**: E = COPh | 77[b] |
| 9 |  | **2e** | −30, 3 | $p$-$IC_6H_4CO_2Et$ |  | **4j** | 70[c] |
| 10 |  | **2f**: R = *t*Bu, X = CH | 0, 1 | $I_2$ |  | **4k**: E = I, X = CH, R = *t*Bu | 94 |
| 11 | | **2f**: R = *t*Bu, X = CH | 0, 1 | $p$-$C_6H_4CO_2Et$ | | **4l**: E = $p$-$IC_6H_4CO_2Et$, X = CH, R = *t*Bu | 88[c] |
| 12 | | **2g**: R = Et, X = N | −40, 3 | $I_2$ | | **4m**: E = I, X = N, R = Et | 77 |
| 13 | | **2g**: R = Et, X = N | −40, 3 | $(BrCl_2C)_2$ | | **4n**: E = Br, X = N, R = Et | 70 |
| 14 | | **2g**: R = Et, X = N | −40, 3 | $p$-$IC_6H_4CN$ | | **4o**: E = $p$-$C_6H_4CN$, X = N, R = Et | 73[c] |
| 15 |  | **2h** | −40, 12 | $I_2$ |  | **4p** | 66 |

[a] Yield of analytically pure product. [b] Transmetalation with $CuCN\cdot 2\,LiCl$ (0.2 mol%) was performed. [c] Obtained by palladium-catalyzed cross-coupling after transmetalation with $ZnCl_2$ (1.2 to 1.3 equiv).

at −30 °C within 3 h. After Negishi cross-coupling with ethyl 4-iodobenzoate, the corresponding functionalized biphenyl derivative **4j** was obtained in 70 % yield (entry 9, Table 1). A 1,3-diester such as **2f** was magnesiated regioselectively with **3a** in position 4 and not in position 2 as a result of steric hindrance, providing after iodolysis or Negishi cross-coupling reaction with ethyl 4-iodobenzoate the corresponding derivatives **4k** and **4l** in 94 % and 88 % yield, respectively (entries 10 and 11, Table 1). The directed metalation of pyridines is of great importance.[9] Ester-substituted pyridines are also excellent substrates for base **3a**, and the diester **2g** was converted to the corresponding 2-magnesiated pyridine (−40 °C), which provided after iodolysis, bromolysis with $(BrCl_2C)_2$, or Negishi cross-coupling with 4-iodobenzonitrile the expected polyfunctional pyridines **4m–o** in 70–77 % yield (entries 12–14, Table 1). Similarly 4-carbethoxypyridine (**2h**) reacted smoothly with **3a** (−40 °C, 12 h) leading after iodolysis to the 3-iodopyridine **4p** in 66 % yield (entry 15, Table 1).

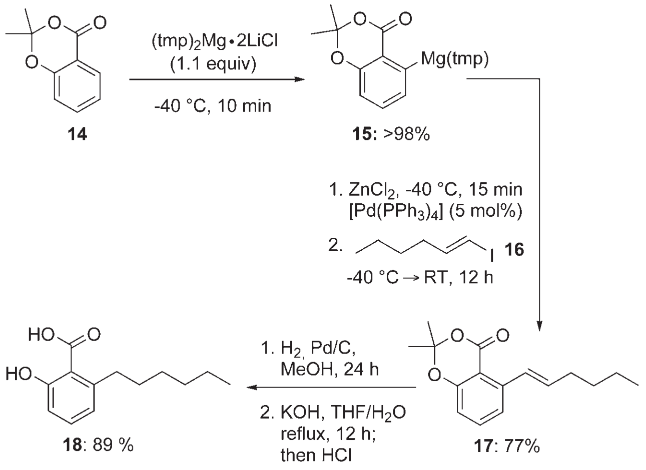
The new class of mixed Mg/Li bases of type **3** also tolerates sensitive functional groups such as a ketone, a carbonate (OBoc; Boc = *tert*-butoxycarbonyl), or a bis(dimethylamino) phosphonate group ($OP(O)(NMe_2)_2$). Thus, the unsymmetrical benzophenone **5** bearing a Boc group as a directing group was converted to the magnesiated intermediate **6** (−20 °C, 4 h) leading, after a copper(I)-mediated benzoylation with benzoyl chloride to the 1,2-diketone **7** in 72 % yield. Similarly, the Boc-protected ethyl benzoate **8** was selectively converted to the magnesium intermediate **9** within 2 h at 0 °C, providing after iodolysis the corresponding 2-iodobenzoate **10** in 78 % yield. The role of the Boc group is to direct the magnesiation and to enhance the rate of metalation. Interestingly, the powerful and more bulky bis(dimethylamino)phosphonate directing group allows a magnesiation of **11** within 1 h at 0 °C. Remarkably, the $OP(O)(NMe)_2$ group selectively directs the metalation to position 4 leading to the magnesiated reagent **12** (Scheme 2). Quenching of **12** with $I_2$ provided the aryl iodide **13** in 91 % yield.

The magnesiation of electron-rich aromatic rings is especially difficult. However, such metalations can be performed successfully with the highly active bases of type **3**. For example, dimethyl-1,3-benzodioxan-4-one (**14**)[10] was converted to the corresponding magnesium reagent **15** within 10 min at −40 °C. After a transmetalation with $ZnCl_2$ and Pd-catalyzed cross-coupling with (*E*)-1-hexenyl iodide[11] (**16**) (1.5 equiv, 25 °C, 12 h), the 6-substituted benzodioxane (**17**) was isolated in 77 % yield. Hydrogenation of the double bond followed by cleavage of the dioxanone with excess of KOH



*Scheme 2.* Chemoselective directed magnesiation using **3a**.

provided the 6-hexylsalicylic acid (**18**), a natural product found in the essential oil of *Pelargonium sidoides* DC,[12] in 89% yield (Scheme 3).



*Scheme 3.* Preparation of 6-hexylsalicylic acid (**18**), a compound found in the essential oil of *Pelargonium sidoides* DC.

In summary, we have reported a new class of mixed magnesium bisamides complexed with two equivalents of LiCl. These reagents of type $(R_2N)_2Mg\cdot 2LiCl$ **3** display superior magnesiation capability, allowing access to new polyfunctional aromatic or heteroaromatic reagents bearing functional groups such as an ester, a nitrile, or a ketone. $(tmp)_2Mg\cdot 2LiCl$ (**3a**) proves to be an especially efficient magnesium base. Both the OBoc group and the $OP(O)(NMe_2)_2$ function serve as excellent directing groups and lead to complementary regioselectivities. The scope of this methodology is currently being studied in our laboratories.

## Experimental Section

**3a:** In an argon-flushed Schlenk flask equipped with a magnetic stirring bar, 2,2,6,6-tetramethylpiperidine (5.07 mL, 30 mmol) was dissolved in THF (30 mL). This solution was cooled to −40°C and *n*BuLi (2.4 M in Hexane, 12.5 mL, 30 mmol) was added dropwise. After the addition was complete, the reaction mixture was warmed to 0°C and stirred at this temperature for 30 min. Freshly titrated **1**[4] (1.0 M in THF, 30 mL, 30 mmol) was then added dropwise to the reaction mixture. The reaction mixture was stirred at 0°C for 30 min, warmed to 25°C, and stirred for 1 h. The solvents were then removed under vacuum affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the salts were completely dissolved. The resulting solution of **3a** solution was titrated[13] prior to use at 0°C with benzoic acid using 4-(phenylazo)diphenylamine as the indicator. A concentration of 0.7 M in THF was obtained.

**4c**: A dry and nitrogen-flushed 10 mL Schlenk flask equipped with a magnetic stirring bar and a septum was charged with a solution of **2a** (0.178 g, 1.0 mmol) in dry THF (1 mL). Freshly prepared **3a** (0.70 M in THF, 1.57 mL, 1.1 mmol) was added dropwise, and the reaction mixture was stirred at this temperature for 1 h. The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a solution of $I_2$ in anhydrous ether. The mixture was then cooled to −40°C, $ZnCl_2$ (1 M solution in THF, 1.2 mL, 1.2 mmol) was added, and the reaction mixture stirred for 15 min. $[Pd(dba)_2]$ (11 mg, 2 mol%) and P(*o*-furyl)$_3$ (9 mg, 4 mol%) dissolved in THF (0.5 mL) were then transferred by cannula to the reaction mixture, and then ethyl 4-iodobenzoate (0.414 g, 1.5 mmol) dissolved in THF (0.5 mL) was added. The reaction mixture was slowly warmed to 25°C and stirred for 12 h. The reaction mixture was quenched with sat. aq. $NH_4Cl$ solution, extracted with diethyl ether (3 × 15 mL), and dried over anhydrous $Na_2SO_4$. After filtration, the solvent was removed in vacuo. Purification by flash chromatography (*n*-pentane/diethyl ether, 10:1) furnished compound **4c** (0.267 g, 82%) as a colorless oil.

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