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Introduction

The directed magnesiation of arenes and heteroarenes is an important synthetic tool for the preparation of polyfunctional aryl- and heteroaryl-magnesium organometallics.1 Mixed magnesium and lithium amides R2NMgX·LiCl are usually the most efficient reagents for such metalations.² Recently, we have examined the regioselective metalation of various pharmaceutically relevant aryl azoles such as 1.3 We found that standard metal amides such as LDA or TMPLi (TMP = 2,2,6,6-tetramethylpiperidyl) gave the lithiated products 2 with poor regioselectivity, due to a competitive deprotonation at the 5-position of the triazole ring of 1. The best result was achieved in toluene⁴ using the alkylmagnesium amide TMPMgBu⁵ prepared from commercial Bu₂Mg, which provided after cross-coupling with aryl bromides various products of type 3. Although this base was highly regioselective in toluene, an excess of ArBr was required to compensate the formation of the Ar-nBu side-product, originating from a faster cross-coupling of the nBu moiety compared to the metalated azole 2 (Scheme 1).

Directed regioselective *ortho*,*ortho*'-magnesiations of aromatics and heterocycles using sBu₂Mg in toluene[†]

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Aryl azoles are ubiquitous as bioactive compounds and their regioselective functionalization is of utmost synthetic importance. Here, we report the development of a toluene-soluble dialkylmagnesium base sBu₂Mg. This new reagent allows mild and regioselective *ortho*-magnesiations of various *N*-arylated pyrazoles and 1,2,3-triazoles as well as arenes bearing oxazoline, phosphorodiamidate or amide directing groups. The resulting diarylmagnesium reagents were further functionalized either by Pd-catalyzed arylation or by trapping reactions with a broad range of electrophiles (aldehydes, ketones, allylic halides, acyl chlorides, Weinreb amides, aryl halides, hydroxylamine benzoates, terminal alkynes). Furthermore, several double *ortho,ortho'*-magnesiations were realized in the case of aryl oxazolines, *N*-aryl pyrazoles as well as 2-aryl-2*H*-1,2,3-triazoles by simply repeating the magnesiation/electrophile trapping sequence allowing the preparation of valuable 1,2,3-functionalized arenes.

While commercially available Bu_2Mg contained a 60:40 mixture of nBu_2Mg and sBu_2Mg , we have found only small amounts of the branched coupling side-product Ar-sBu, suggesting that the secondary alkyl moiety was reacting much slower than the primary one.



E¹, E²: aldehydes, ketones, allylic halides, acyl chlorides, Weinreb amides, aryl halides (Negishi cross-coupling).

Scheme 1 (a) Regioselective magnesiation and subsequent Negishi cross-coupling of aryl azoles (1) using TMPMgBu in toluene/hexane. (b) Regioselective magnesiation and *ortho,ortho'*-functionalization of arenes and heteroarenes using sBu_2Mg in toluene.

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Herein, we report the preparation of sBu_2Mg ,⁶ which avoided these side reactions and significantly increased the metalation scope. Thus, we showed that sBu_2Mg was an improved magnesiation reagent, which allowed a highly *ortho*-regioselective magnesiation of arenes 4 bearing various directing groups (DG), leading after trapping of the resulting diarylmagnesium species 5 with various electrophiles E¹ to products of type 6. These polyfunctional arenes were in several cases magnesiated again using sBu_2Mg producing, after addition of a second different electrophile E², valuable 1,2,3-polyfunctional arenes of type 7.

Results and discussion

The reaction of *s*BuMgCl in diethyl ether with *s*BuLi (1.0 equiv.) in cyclohexane at 25 °C (2 h) gave, after solvent evaporation under vacuum, redissolution in toluene and filtration, a 0.43–0.48 M solution of *s*Bu₂Mg in 96% yield.^{7,8}

In preliminary experiments, we have observed a smooth magnesiation of oxazoline **8a** with a toluene solution of 0.6 equiv. of *s*Bu₂Mg leading to the diarylmagnesium **9a** (Table 1). A full conversion to the diarylmagnesium species was achieved within 1 hour and the iodolyzed product **10a** was isolated in 80% yield (entry 1). *s*Bu₂Mg gave also good results in cyclohexane or THF, albeit in lower yields (entries 2 and 3). *c*Hex₂Mg in toluene delivered the desired product **10a** in only 46% yield and other bases such as Ph₂Mg, (TMSCH₂)₂Mg and *t*Bu₂Mg or *s*BuMgCl⁹ did not give any conversion (entries 4–8).

Therefore, a range of oxazolines (**8a–d**) were magnesiated selectively on the aryl ring and the resulting diarylmagnesiums (**9a–d**) underwent Negishi cross-couplings,¹⁰ copper-catalyzed allylation or acylation,¹¹ *in situ* Sonogashira cross-coupling¹² or trapping reactions with tetrachlorodibromoethane or dicyclopropylketone, leading to the *mono–ortho* substituted oxazolines **10b–j** in 68–98% yield (Scheme 2).

Most of the C–H activation methods currently available for the arylation of aryl azoles were performed by using transition

Table 1 Magnesiation of oxazoline 8a using various magnesium reagents in various solvents at 25 $^\circ\text{C}$



^a Calibrated GC-yield using undecane as internal standard. ^b 1.2 equiv. of *s*BuMgCl were used. ^c Isolated yield.

Toluene

Ether/toluene

0%

0%



Scheme 2 Regioselective magnesiation of oxazolines **8a–d** with sBu_2Mg leading, *via* diarylmagnesium species **9a–d**, to functionalized oxazolines **10b–j**. ^{*a*} All yields refer to isolated compounds. ^{*b*} Magnesiation conditions. ^{*c*} The reaction was catalyzed by CuCN·2LiCl (20 mol%). ^{*d*} Obtained after transmetalation with ZnCl₂ (1.1 equiv.) and a palladium-catalyzed cross-coupling with [PdCl₂(dppf]] (5 mol%, dppf = diphenylphosphinoferrocene) and an aryl halide (0.83 equiv.). ^{*e*} Obtained after transmetalation with ZnCl₂ (1.1 equiv.), subsequent iodine quench (1.1 equiv.) and Sonogashira cross-coupling with Cul (4 mol%), Pd(dba)₂ (3 mol%, dba = dibenzylideneacetone), tri-(2-furyl)-phosphine (6 mol%) and phenylacetylene (1.3 equiv.).

metal catalysts and suffered from the unwanted formation of symmetrical bis-arylated products and the selective preparation of unsymmetrical *ortho–ortho*[']-bis-functionalized¹³ aryl azoles remained challenging.¹⁴ We have found that various oxazolines **10g–j** were again magnesiated at 40–60 °C with *s*Bu₂Mg in toluene (Scheme 3).¹⁵ The intermediate diarylmagnesium species were further functionalized by a copper-catalyzed allylation, Negishi cross-coupling, cobalt-catalyzed electrophilic amination¹⁶ and iodolysis furnishing the desired products **11a–e** in 74–93% yield. Interestingly, magnesiation of **10j** followed by trapping with benzaldehyde and subsequent treatment with 6 M HCl provided lactone **11f** in 56% yield.¹⁷

To demonstrate the versatility of the oxazoline directing group, the strongly sterical hindered *ortho*,*ortho*'-functionalized oxazoline **11b** was successfully converted to the corresponding nitrile **11g** using thionyl chloride and DMF¹⁸ in 92% yield (Scheme 4).¹⁹

We then turned our attention to the magnesiation of various N-aryl pyrazoles (**12a–c**). sBu_2Mg proved also to be an excellent base for the regioselective magnesiation of N-aryl pyrazole **12a**, affording the corresponding bis-arylmagnesium species **13a**

7

8

Ph₂Mg

sBuMgCl^b



Scheme 3 Regioselective magnesiation of mono-functionalized oxazolines **10g**–**j**, leading to *ortho,ortho'*-functionalized oxazolines **11a**–**f**. ^a All yields refer to isolated compounds. ^b Magnesiation conditions. ^c The reaction was catalyzed by CuCN·2LiCl (20 mol%). ^d Obtained after transmetalation with ZnCl₂ (1.1 equiv.) and a palladium-catalyzed cross-coupling with [PdCl₂(dppf)] (5 mol%) and an aryl iodide (0.83 equiv.). ^e Obtained after transmetalation with ZnCl₂ (1.1 equiv.) and a cobalt-catalyzed electrophilic amination with CoCl₂ (5 mol%) and morpholino benzoate (1.2 equiv.). ^f Obtained after addition of benzaldehyde (1.2 equiv.) followed by treatment with 6 M HCl.



Scheme 4 Transformation of *ortho,ortho'*-functionalized oxazoline **11b** to the corresponding nitrile **11g**. ^a Isolated yield.

after 0.5 h at 40 °C. After addition of benzaldehyde or Weinreb amide MeCON(OMe)Me, alcohol 14a and ketone 14b were obtained in 74-86% yield (Scheme 5). Copper-catalyzed allylation with 3-bromocyclohex-1-ene produced the pyrazole 14c (90% yield). Interestingly, N-aryl pyrazoles 12b and 12c although bearing relatively acidic protons at the heterocyclic ring were selectively magnesiated at the ortho-position of the phenyl ring. In particular, unsubstituted pyrazole 12c was metalated in 94% yield and >98 : 1 : 1 selectivity, as determined by deuterolysis of a reaction aliquot.²⁰ These results further confirm the key role of the coordination at the N(2)-atom of the pyrazole to direct the metalation selectively on the aryl ring in a non-polar solvent like toluene. Thus, the functionalized pyrazoles 14d-f were obtained after Negishi cross-coupling with 5-bromopyrimidine, 5-bromobenzo [d] [1,3] dioxole or addition of furfural in 64–90% yield. We also achieved an unsymmetrical ortho, ortho'-functionalization and mono-substituted pyrazole 14f was selectively magnesiated at 60 °C (0.5 h) and trapped by Negishi cross-coupling with 6-iodoquinoline and 4-iododibenzo[*b*,*d*]thiophene providing the products 15a-b in 67-84% yield (Scheme 6).



Scheme 5 Regioselective magnesiation of *N*-aryl pyrazoles 12a-c with sBu_2Mg leading, via diarylmagnesium species 13a-c, to functionalized *N*-aryl pyrazoles 14a-f. ^a All yields refer to isolated compounds. ^b Magnesiation conditions. ^c The reaction was catalyzed by CuCN-2LiCl (20 mol%). ^d Obtained after transmetalation with ZnCl₂ (1.1 equiv.) and a palladium-catalyzed cross coupling with [PdCl₂(dppf)] (5 mol%) and an aryl bromide (0.83 equiv.).

The functionalization of less common heterocycles is of key importance for pharmaceutical applications.²¹ Thus, the metalation of symmetrical 2-aryl-2H-1,2,3-triazoles 16a-b was then investigated (Scheme 7).22,23 After metalation of 16a with 0.6 equiv. of sBu2Mg for 15 min at 40 °C, the resulting bisarylmagnesium species 17a was then trapped with furfural, affording the functionalized 1,2,3-triazole 18a in a 68% yield. Further trapping reactions such as Negishi cross-coupling, copper-catalyzed allylation and oxidative alkynylation with (phenylethynyl)lithium²⁴ lead to 2-aryl-1,2,3-triazoles 18b-d in 52-66% yield. Similarly, 1,2,3-triazole 16b was readily magnesiated at 25 °C (0.5 h) as shown by the quantitative formation of a single regioisomer by NMR-analysis of a deuterolyzed reaction aliquot.20 Further quenching reactions of 17b like thiomethylation and allylation furnished triazoles 18e-f in 82-91% yield. A second functionalization was performed on N-aryl



Scheme 6 Regioselective magnesiation of mono-functionalized *N*-aryl pyrazole **14f** with sBu_2Mg leading to *ortho,ortho'*-functionalized *N*-aryl pyrazoles **15a–b**. ^a All yields refer to isolated compounds.



Scheme 7 Regioselective magnesiation of 2-aryl-2*H*-1,2,3-triazoles **16a–b** with sBu₂Mg leading, *via* diarylmagnesium species **17a–b**, to functionalized 2-aryl-2*H*-1,2,3-triazoles **18a–f**. ^a All yields refer to isolated compounds. ^b Magnesiation conditions. ^c Obtained after transmetalation with ZnCl₂ (1.1 equiv.) and a palladium-catalyzed cross-coupling with [PdCl₂(dppf)] (5 mol%) and an aryl halide (0.83 equiv.). ^d Obtained after transmetalation with CuCN·2LiCl (1.2 equiv.) and subsequent addition of (phenylethynyl)lithium (2.0 equiv.), followed by addition of chloranil (1.3 equiv.). ^e The reaction was catalyzed by CuCN·2LiCl (20 mol%).

triazoles **18d–f** using again sBu_2Mg in toluene, followed by quench with a different electrophile (E²) (Scheme 8). We observed a complete magnesiation of **18d** with sBu_2Mg within 15 min at 40 °C and a subsequent reaction with benzaldehyde produced the mixed bis-functionalized 1,2,3-triazole **19a** in 42% yield. Similarly, **18e** and **18f** were magnesiated under the standard conditions and the resulting bis-arylmagnesium species were trapped with a different electrophile (E^2) leading to a range of unsymmetrical functionalized 1,2,3-triazoles **19b–f** in 70–88% yield.

Finally, we examined the metalation of 1-aryl-1*H*-1,2,3-triazoles such as **20a–e** and found that sBu_2Mg led to a highly regioselective magnesiation at the *ortho*-position of the aryl ring in toluene (25–40 °C, 0.5–1 h), affording the bis-aryl-magnesium species **21a** in 75% yield and 97 : 3 regioselectivity (Scheme 9).²⁰

This new metalation procedure occurred twice as fast as the previously reported TMPMgBu base.³ 1,2,3-Triazoles **22a** and **22b** were isolated in 93% and 67% yields respectively after Negishi cross-couplings with only 0.83 equiv. of aryl bromide.³ Copper-catalyzed acylation¹¹ with benzoyl chloride lead to products **22c** and **22d** in 55–58% yield and quenching with various aldehydes afforded compounds **22e–h** in 69–80% yield.

Remarkably, sBu₂Mg was also an excellent base for the magnesiation of various arenes bearing directing groups such as a tertiary amide or phosphorodiamidate (23a-j; Scheme 10).25 The addition of sBu₂Mg to the aromatic amide 23a in toluene led to a clean magnesiation within 0.5 h at room temperature. The resulting diarylmagnesium species 24a was then further allylated with allyl and cyclohexenyl bromides, leading to 25a and 25b in 62% and 71% yield respectively. Copper-catalyzed acylation of 23a with thiophene-2-carbonyl chloride or trapping with furfural furnished the ketone 25c (64% yield) and the lactone 25d (76% yield).26 Similarly, the amides 23b-f afforded with the same magnesiation/trapping sequence the polyfunctional amides (25e-i) in 61-72% vield. Various



Scheme 8 Regioselective magnesiation of mono-functionalized 2aryl-2*H*-1,2,3-triazoles **18d**–**f** with sBu₂Mg leading to *ortho,ortho'*functionalized 2-aryl-2*H*-1,2,3-triazoles **19a–f**. ^a All yields refer to isolated compounds. ^b Magnesiation conditions. ^c The regioselectivity was determined by crystal structure analysis, see ESI.† ^d The reaction was catalyzed by CuCN·2LiCl (20 mol%). ^e The reaction was catalyzed by Cul (10 mol%). ^f Obtained after transmetalation with ZnCl₂ (1.1 equiv.) and a palladium-catalyzed cross-coupling with [PdCl₂(dppf)] (5 mol%) and an aryl bromide (0.83 equiv.).



Scheme 9 Regioselective magnesiation of 1-aryl-2*H*-1,2,3-triazoles **20a**–**e** with sBu₂Mg leading, *via* diarylmagnesium species **21a**–**e**, to functionalized 1-aryl-2*H*-1,2,3-triazoles **22a**–**h**. ^a All yields refer to isolated compounds. ^b Magnesiation conditions. ^c Obtained after transmetalation with ZnCl₂ (1.1 equiv.) and a palladium-catalyzed cross-coupling with [PdCl₂(dppf)] (5 mol%) and an aryl halide (0.83 equiv.).^d The reaction was catalyzed by CuCN·2LiCl (20 mol%). ^e The regioselectivity was determined by crystal structure analysis, see ESI.†



Scheme 10 Regioselective magnesiation of various arenes bearing an amide or a phosphorodiamidate directing group as well as 1-propyl-1,2,4-triazole 23a-k with sBu₂Mg leading, *via* diarylmagnesium species 24a-k, to functionalized arenes 25a-o. ^a All yields refer to isolated compounds. ^b Magnesiation conditions. ^c The reaction was catalyzed by CuCN·2LiCl (20 mol%). ^d R = P(O)(NMe₂)₂. ^e Obtained after treating 25m with 2 M HCl in dioxane (105 °C, 1 h).



Scheme 11 Synthetic transformations of magnesiated product 25b. ^a All yields refer to isolated compounds.

phosphorodiamidates (**23g-j**) were also metalated with sBu_2Mg at 40–60 °C (0.5–1 h) providing the diarylmagnesiums **24g-j**, which were trapped with a range of electrophiles (MeSSO₂Me, I₂, cHexCHO and (BrCCl₂)₂) furnishing the phenol derivatives **25j-m** in 68–98% yield. Removal of the phosphorodiamidate group²⁷ in **25m** was achieved with a 2 M HCl treatment in dioxane (105 °C, 1 h) leading to phenol **25n** in 88% yield. Interestingly, 1-propyl-1,2,4-triazole (**23k**) was magnesiated with sBu_2Mg and allylated with cinnamyl bromide providing the *N*-heterocycle **250** in 86% yield.²⁸

We performed some further transformations leading to polyfunctionalized 1,2,3-trisubstituted arenes to show the utility of these magnesiations. The newly prepared amide **25b** was thus selectively reduced with $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}^{29}$ (25 °C, 15 min) to

the aldehyde **26a** in 90% yield. A two-step transformation consisting of a reduction with the complex borohydride LiH_3 -BPyrr (Pyrr = pyrrolidino)³⁰ followed by a treatment with ethyl chloroformate³¹ provided the benzylic chloride **26b** in 85% overall yield (Scheme 11).

Conclusions

In summary, we have developed a new preparation of *s*Bu₂Mg in toluene and showed its utility for the directed magnesiation of various aromatic and heterocyclic systems including pharmaceutically relevant *N*-arylated pyrazoles as well as *N*-arylated 1,2,3-triazoles. This method provides a unique access to varius diarylmagnesium reagents in toluene. Furthermore, a range of arenes bearing various directing groups such as an oxazoline, phosphorodiamidate or an amide were magnesiated with *s*Bu₂Mg. Remarkably, a second unsymmetrical *ortho,ortho'*functionalization was achieved in the case of aryl oxazolines, *N*aryl pyrazoles as well as *N*-aryl triazoles, leading to valuable synthetic intermediates of potential pharmaceutical relevance. Further investigations of the use of *s*Bu₂Mg as metalating agent are currently underway in our laboratory.

Author contributions

A. H., J. P. P, S. B. D., F. T. and K. K. performed and analyzed the experiments. A. H., F. H. L., S. L., S. W. and P. K. designed the experiments. A. H., S. L., S. W., and P. K. prepared the manuscript with contributions of all authors.

Conflicts of interest

There are no conflicts to declare.

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