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Directed regioselective *ortho,ortho'*-magnesiations of aromatics and heterocycles using *s*Bu_2Mg in toluene†

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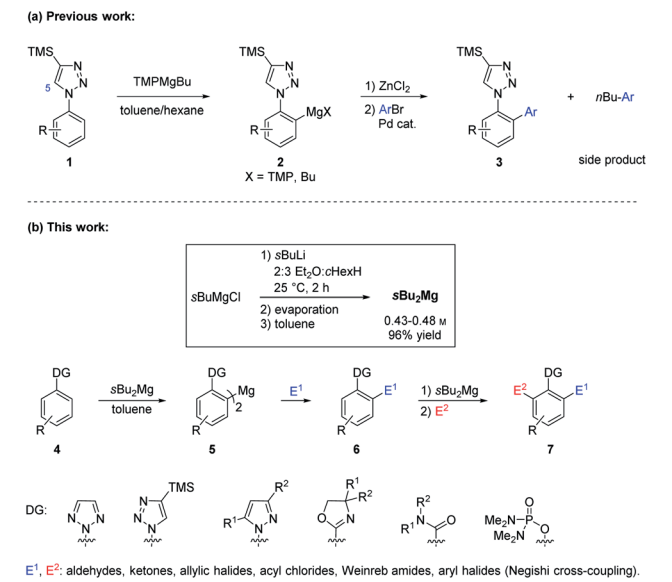
Aryl azoles are ubiquitous as bioactive compounds and their regioselective functionalization is of utmost synthetic importance. Here, we report the development of a toluene-soluble dialkylmagnesium base *s*Bu_2Mg. This new reagent allows mild and regioselective *ortho*-magnesiations of various *N*-arylated 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.

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 $R_2NMgX{\cdot}LiCl$ 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 toluene[4] using the alkylmagnesium amide TMPMgBu[5] prepared from commercial Bu_2Mg, 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-*n*Bu side-product, originating from a faster cross-coupling of the *n*Bu moiety compared to the metalated azole **2** (Scheme 1).

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



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 *s*Bu_2Mg in toluene.

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Herein, we report the preparation of sBu$_2$Mg,[6] which avoided these side reactions and significantly increased the metalation scope. Thus, we showed that sBu$_2$Mg 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 E^1 to products of type **6**. These polyfunctional arenes were in several cases magnesiated again using sBu$_2$Mg producing, after addition of a second different electrophile E^2, valuable 1,2,3-polyfunctional arenes of type **7**.

Results and discussion

The reaction of sBuMgCl in diethyl ether with sBuLi (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 sBu$_2$Mg in 96% yield.[7,8]

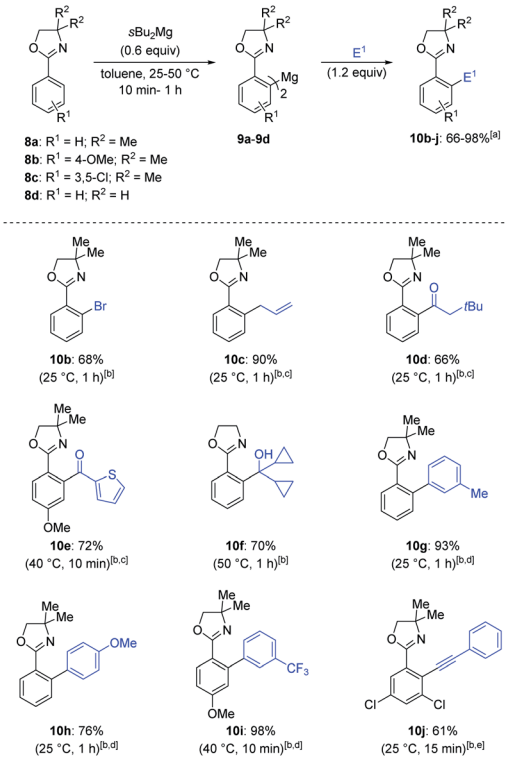
In preliminary experiments, we have observed a smooth magnesiation of oxazoline **8a** with a toluene solution of 0.6 equiv. of sBu$_2$Mg leading to the diarylmagnesium **9a** (Table 1). A full conversion to the diarylmagnesium species was achieved within 1 hour and the iodolyzed product **10a** was isolated in 80% yield (entry 1). sBu$_2$Mg gave also good results in cyclohexane or THF, albeit in lower yields (entries 2 and 3). cHex$_2$Mg in toluene delivered the desired product **10a** in only 46% yield and other bases such as Ph$_2$Mg, (TMSCH$_2$)$_2$Mg and tBu$_2$Mg or sBuMgCl[9] 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-coupling[12] 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 metal catalysts and suffered from the unwanted formation of symmetrical bis-arylated products and the selective preparation of unsymmetrical *ortho–ortho*′-bis-functionalized[13] aryl azoles remained challenging.[14] We have found that various oxazolines **10g–j** were again magnesiated at 40–60 °C with sBu$_2$Mg in toluene (Scheme 3).[15] The intermediate diarylmagnesium species were further functionalized by a copper-catalyzed allylation, Negishi cross-coupling, cobalt-catalyzed electrophilic amination[16] 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]

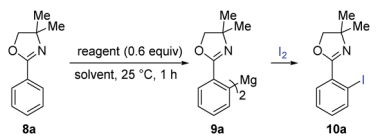
To demonstrate the versatility of the oxazoline directing group, the strongly sterical hindered *ortho*,*ortho*′-functionalized oxazoline **11b** was successfully converted to the corresponding nitrile **11g** using thionyl chloride and DMF[18] in 92% yield (Scheme 4).[19]

We then turned our attention to the magnesiation of various *N*-aryl pyrazoles (**12a–c**). sBu$_2$Mg proved also to be an excellent base for the regioselective magnesiation of *N*-aryl pyrazole **12a**, affording the corresponding bis-arylmagnesium species **13a**



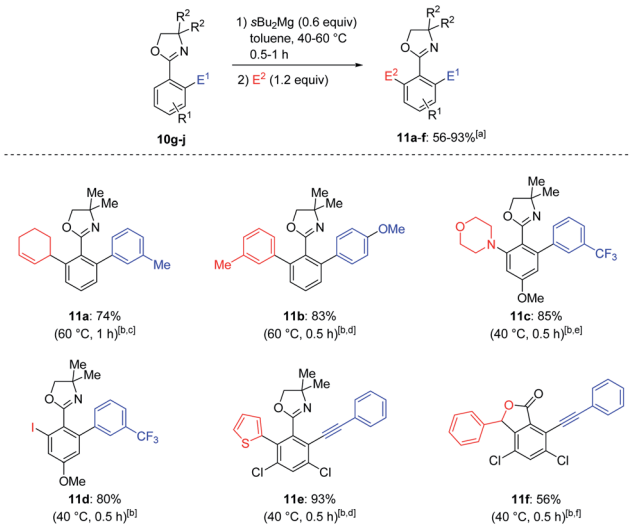
Scheme 2 Regioselective magnesiation of oxazolines **8a–d** with sBu$_2$Mg leading, *via* diarylmagnesium species **9a–d**, to functionalized oxazolines **10b–j**. [a] All yields refer to isolated compounds. [b] Magnesiation conditions. [c] The reaction was catalyzed by CuCN·2LiCl (20 mol%). [d] Obtained after transmetalation with ZnCl$_2$ (1.1 equiv.) and a palladium-catalyzed cross-coupling with [PdCl$_2$(dppf)] (5 mol%, dppf = diphenylphosphinoferrocene) and an aryl halide (0.83 equiv.). [e] Obtained after transmetalation with ZnCl$_2$ (1.1 equiv.), subsequent iodine quench (1.1 equiv.) and Sonogashira cross-coupling with CuI (4 mol%), Pd(dba)$_2$ (3 mol%, dba = dibenzylideneacetone), tri-(2-furyl)-phosphine (6 mol%) and phenylacetylene (1.3 equiv.).

Table 1 Magnesiation of oxazoline **8a** using various magnesium reagents in various solvents at 25 °C

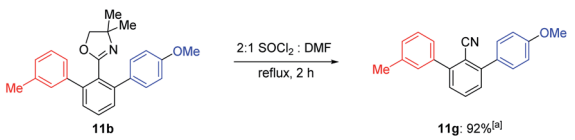


Entry	Reagent	Solvent	Yield[a]
1	sBu$_2$Mg	Toluene	91% (80)[c]
2	sBu$_2$Mg	THF	73%
3	sBu$_2$Mg	Cyclohexane	64%
4	cHex$_2$Mg	Toluene	46%
5	tBu$_2$Mg	Toluene	0%
6	(TMSCH$_2$)$_2$Mg	Toluene	0%
7	Ph$_2$Mg	Toluene	0%
8	sBuMgCl[b]	Ether/toluene	0%

[a] Calibrated GC-yield using undecane as internal standard. [b] 1.2 equiv. of sBuMgCl were used. [c] Isolated yield.

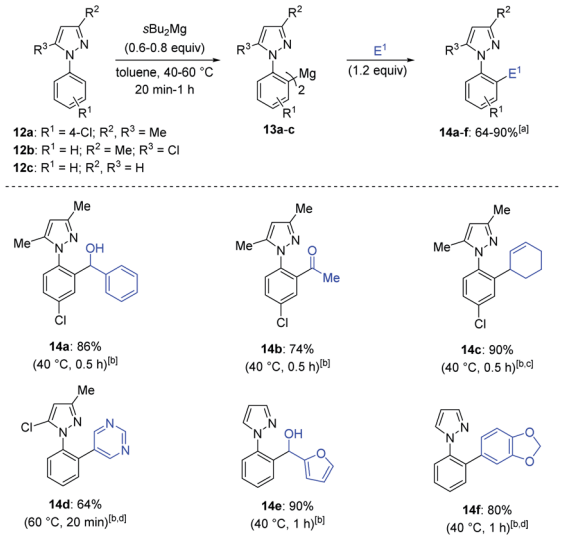


Scheme 3 Regioselective magnesiation of mono-functionalized oxazolines **10g–j**, leading to *ortho,ortho'*-functionalized oxazolines **11a–f**. [a] All yields refer to isolated compounds. [b] Magnesiation conditions. [c] The reaction was catalyzed by CuCN·2LiCl (20 mol%). [d] Obtained after transmetalation with $ZnCl_2$ (1.1 equiv.) and a palladium-catalyzed cross-coupling with [$PdCl_2$(dppf)] (5 mol%) and an aryl iodide (0.83 equiv.). [e] Obtained after transmetalation with $ZnCl_2$ (1.1 equiv.) and a cobalt-catalyzed electrophilic amination with $CoCl_2$ (5 mol%) and morpholino benzoate (1.2 equiv.). [f] Obtained after addition of benzaldehyde (1.2 equiv.) followed by treatment with 6 M HCl.



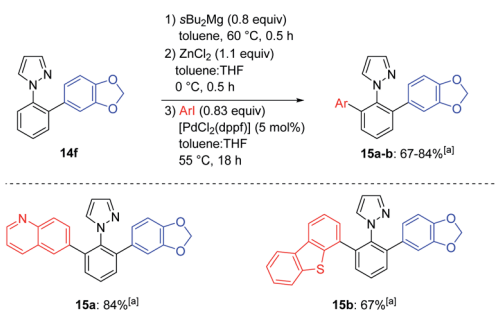
Scheme 4 Transformation of *ortho,ortho'*-functionalized oxazoline **11b** to the corresponding nitrile **11g**. [a] Isolated yield.

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).

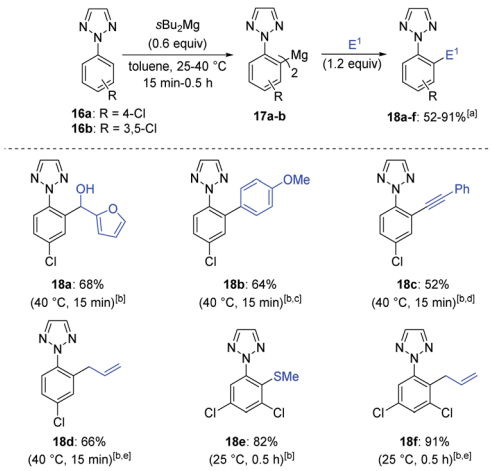


Scheme 5 Regioselective magnesiation of *N*-aryl pyrazoles **12a–c** with sBu_2Mg leading, *via* diarylmagnesium species **13a–c**, to functionalized *N*-aryl pyrazoles **14a–f**. [a] All yields refer to isolated compounds. [b] Magnesiation conditions. [c] The reaction was catalyzed by CuCN·2LiCl (20 mol%). [d] Obtained after transmetalation with $ZnCl_2$ (1.1 equiv.) and a palladium-catalyzed cross coupling with [$PdCl_2$(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-2*H*-1,2,3-triazoles **16a–b** was then investigated (Scheme 7).[22,23] After metalation of **16a** with 0.6 equiv. of sBu_2Mg 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)lithium[24] 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.



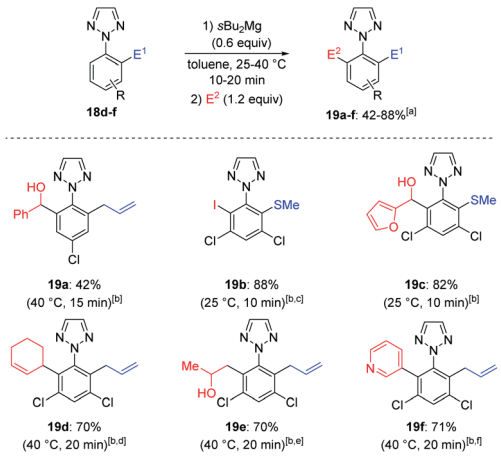
Scheme 7 Regioselective magnesiation of 2-aryl-2*H*-1,2,3-triazoles **16a–b** with sBu_2Mg leading, *via* diarylmagnesium species **17a–b**, to functionalized 2-aryl-2*H*-1,2,3-triazoles **18a–f**. [a] All yields refer to isolated compounds. [b] Magnesiation conditions. [c] Obtained after transmetalation with $ZnCl_2$ (1.1 equiv.) and a palladium-catalyzed cross-coupling with [$PdCl_2$(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 (E^2) (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.

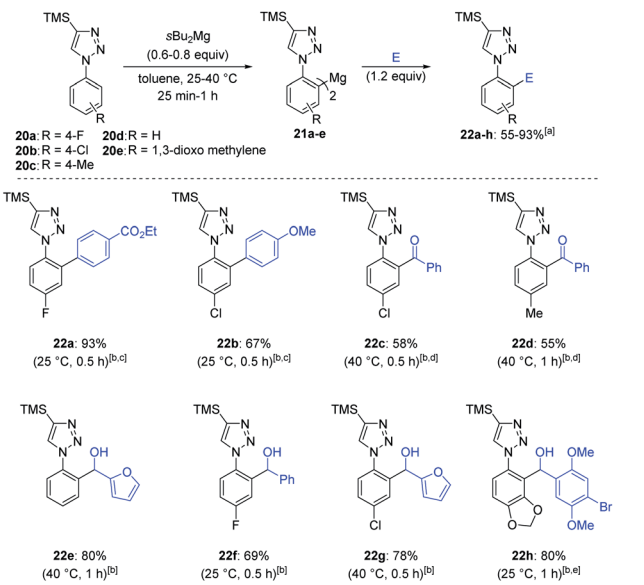
Finally, we examined the metalation of 1-aryl-1*H*-1,2,3-triazoles such as **20a–e** and found that sBu_2Mg led to a highly regioselective magnesiation at the *ortho*-position of the aryl ring in toluene (25–40 °C, 0.5–1 h), affording the bis-aryl-magnesium species **21a** in 75% yield and 97 : 3 regioselectivity (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 acylation[11] 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.

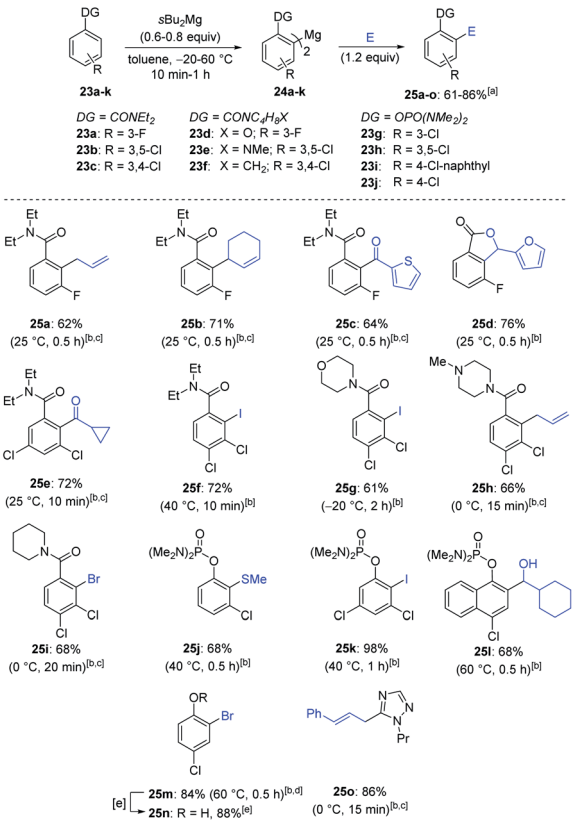
Remarkably, sBu_2Mg was also an excellent base for the magnesiation of various arenes bearing directing groups such as a tertiary amide or phosphorodiamidate (**23a–j**; Scheme 10).[25] The addition of sBu_2Mg to the aromatic amide **23a** in toluene led to a clean magnesiation within 0.5 h at room temperature. 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% yield. Various



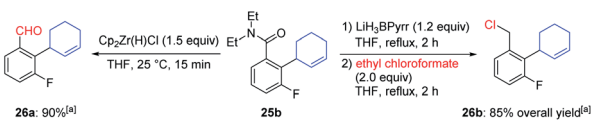
Scheme 8 Regioselective magnesiation of mono-functionalized 2-aryl-2*H*-1,2,3-triazoles **18d–f** with sBu_2Mg leading to *ortho*,*ortho*′-functionalized 2-aryl-2*H*-1,2,3-triazoles **19a–f**. [a] All yields refer to isolated compounds. [b] Magnesiation conditions. [c] The regioselectivity was determined by crystal structure analysis, see ESI.† [d] The reaction was catalyzed by CuCN·2LiCl (20 mol%). [e] The reaction was catalyzed by CuI (10 mol%). [f] Obtained after transmetalation with $ZnCl_2$ (1.1 equiv.) and a palladium-catalyzed cross-coupling with [$PdCl_2$(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 sBu_2Mg 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 $ZnCl_2$ (1.1 equiv.) and a palladium-catalyzed cross-coupling with [$PdCl_2$(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 sBu$_2$Mg 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)(NMe$_2$)$_2$. [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$_2$Mg at 40–60 °C (0.5–1 h) providing the diarylmagnesiums **24g–j**, which were trapped with a range of electrophiles (MeSSO$_2$Me, I$_2$, *c*HexCHO and (BrCCl$_2$)$_2$) furnishing the phenol derivatives **25j–m** in 68–98% yield. Removal of the phosphorodiamidate group[27] 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$_2$Mg and allylated with cinnamyl bromide providing the *N*-heterocycle **25o** 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 Cp$_2$Zr(H)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 chloroformate[31] provided the benzylic chloride **26b** in 85% overall yield (Scheme 11).

Conclusions

In summary, we have developed a new preparation of sBu$_2$Mg 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 sBu$_2$Mg. 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 sBu$_2$Mg 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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