## Ortho-directed functionalization of arenes using magnesate bases†

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*Ortho*-directed functionalisation of arenes using lithium alkylmagnesate bases were achieved, demonstrating the potential use of arylmagnesates as suitable arylanions, without a further transmetallation step, for challenging functionalizations such as fluorination, hydroxylation, arylation, vinylation and alkylation through epoxide ring-opening.

Deprotonative metallation of aromatics has been widely used as a powerful method for regioselective functionalization.<sup>1a,b</sup> *Ortho*-lithiation using alkyllithium and lithium amide bases has been extensively developed since lithiated species display a high reactivity towards many electrophiles, leading to various substitutions (*e.g.* halogenation, carboxylation, acylation, hydroxymethylation, aminomethylation, sulfuration, oxygenation). However aryllithiums can rarely be directly involved in transition metal cross-coupling reactions and are usually transformed in organometallic fragments suitable for standard Negishi, Stille, Suzuki-Miyaura and Hiyama reactions.<sup>1c</sup>

Over the past decade, two main complementary alternatives for ortho-directed functionalization of aromatics have started to grow through the development of transition metal-catalyzed chelated-assisted functionalization of aromatics methodologies,<sup>2</sup> and the use of a new class of metalating agent for regio and/or chemoselective deprotonative metallation of aromatics in smooth reaction conditions, e.g. at room temperature (Scheme 1). Indeed, since Eaton's pioneering chemoselective deprotonation of benzoate using magnesium amides (TMP<sub>2</sub>Mg; TMP = 2,2,6,6-tetramethylpiperidyl),<sup>3</sup> various combinations of organometallic compounds with alkali and/or N,N,N',N'-tetramethylenediamine (TMEDA) additives including -ate complexes<sup>4</sup> have been proposed such as  $R_2Zn(TMP)Li.TMEDA$  (R = <sup>t</sup>Bu, Et, Bu),<sup>4,5a-b</sup> <sup>i</sup>Bu<sub>3</sub>Al(TMP)Li,<sup>4,5c</sup> (Me<sub>3</sub>SiCH<sub>2</sub>)<sub>2</sub>Mn(TMP)-Li.TMEDA,<sup>5d</sup> (TMP)<sub>2</sub>Zn.2MgCl<sub>2</sub>.2LiCl,<sup>5e</sup> MeCu(TMP)(CN)-Li2,<sup>5f</sup> (TMP)3CdLi,<sup>5g</sup> Al(TMP)3·3LiCl,<sup>5h</sup> (TMP)2CuLi.<sup>5i</sup> We recently successfully investigated the magnesation of azines and azoles through the use of lithium tris- and tetra(alkyl)magnesates (Bu<sub>3</sub>MgLi and Bu<sub>4</sub>MgLi<sub>2</sub>), (alky)(amido)magnesates (Bu<sub>2</sub>(TMP)MgLi, Bu(TMP)<sub>2</sub>MgLi) and tris- and (tetra)amidomagnesate (TMP)<sub>3</sub>MgLi and (TMP)<sub>4</sub>MgLi<sub>2</sub>) bases,<sup>4,6</sup> thus demonstrating that heteroarylmagnesate complexes generated in smooth conditions display a high nucleophilic character in electrophilic trapping reactions and are suitable in nickel- and

palladium-catalyzed cross-coupling processes without an additional transmetallation step. We present here the *ortho*-magnesation of aromatics using lithium tris- and (tetra)butylmagnesate bases<sup>7</sup> and the evaluation of the suitability of (aryl)magnesate complexes for challenging functionalizations such as arylation, vinylation, epoxide ring-opening, oxygenation and fluorination.

Initial investigations were focused on *ortho*-magnesation of aromatics bearing electron-attractive *ortho*-directing groups. The (4',4'-dimethyloxazolin-2-yl)benzenes **1a–c** were first treated with **Bu**<sub>3</sub>MgLi (0.4 equiv.) at room temperature in THF over a 2 h period, and the complete magnesation was further indicated by a subsequent trapping with iodine leading to the *ortho*-iodo derivatives **2a–c** in fair to good yields (Table 1, entries 1–3). Therefore, the second order **Bu**<sub>4</sub>MgLi<sub>2</sub> (0.55 equiv.) was only suitable for magnesation of both *N-tert*-butylbenzamide **1d–f** and *N*-cumylbenzamide **1g–i** at room temperature and subsequent



Scheme 1 Directed metal-assisted C-H bond transformation

**Table 1**Magnesation-iodination reactions from (oxazolinyl)<br/>benzene, N-protected benzamides, aniline and anisole

P DMG	1) Bu <sub>3</sub> MgLi or Bu <sub>4</sub> MgLi <sub>2</sub> THF, r. t., 2h	B			
1a-m	2) I <sub>2</sub>	2a-m			
R=H, CI, OMe					

Entry	Substrate	R		Base (equiv.)	Product		Yield $\%^b$ $(\%)^c$
1 2 3	R	H Cl OMe	1a 1b 1c	Bu <sub>3</sub> MgLi (0.4)	R	2a 2b 2c	75 (90) 68 (92) 71 (93)
4 5 6	R NH	H Cl OMe	1d 1e 1f	Bu <sub>4</sub> MgLi <sub>2</sub> (0.55)	R NH	2d 2e 2f	82 (95) 76 (97) 84 (100)
7 8 9	R Ph	H Cl OMe	1g 1h 1i	Bu <sub>4</sub> MgLi <sub>2</sub> (0.55)	R Ph	2g 2h 2i	88 (98) 82 (100) 87 (97)
10	R R R R R R R R R R R R R R R R R R R	Н	1k	Bu <sub>4</sub> MgLi <sub>2</sub> (1)		2k	$70^d (73)^d$
11 12	R	H OMe	11 1m	Bu <sub>4</sub> MgLi <sub>2</sub> (0.3)	OMe	21 2m	75 <sup>d</sup> 91 <sup>d</sup>

<sup>*a*</sup> Conditions: substrate (1 equiv.),  $Bu_3MgLi$  or  $Bu_4MgLi_2$ , r.t, 2 h then I<sub>2</sub>, (1.1–4 equiv.), 2 h. <sup>*b*</sup> Yield of isolated product. <sup>*c*</sup> NMR yield of deuteration with D<sub>2</sub>O. <sup>*d*</sup> Reflux, 2 h.

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Table 2 Evaluation of arylmagnesate complexes generated by deprotonation towards unusual electrophiles and in cross-coupling reactions<sup>4</sup>



Entry	Product		Yield $(\%)^b$	Entry	Product		Yield $(\%)^b$	Entry	Product		Yield (%) <sup>b</sup>
1	OH C C C C C C C C C C C C C C C C C C C	3a	55	11		5b	52	21	OH O NH Ph	8c	23
2		5a	52	12	Meo H	4d	41	22	F O NH Ph	9d	69
3		4a	40	13		6b	42	23	OH	3d	57
4		4b	53	14	NH NH	7b	67	24	OMe	5d	51
5		6a	62	15	F O NH	9b	59	25	OMe	7d	66
6	J NJ	7a	66 <sup>c</sup>	16	MeO H	9c	65	26	OH OMe	8d	38
7	F ON	9a	43 <sup><i>d</i></sup>	17		8b	37	27	F OMe	9e	15
8	OH ON	8a	55	18	OH OH NH Ph	3c	61	28	OH HZ N N N N N	3e	50
9	OH OH NH	3b	42	19	O NH Ph	5c	58	29		8e	42
10		4c	36	20	O NH Ph	7c	67	30		9f	n.r.

<sup>*a*</sup> Conditions: preliminary *ortho*-magnesation step was achieved by treatment with magnesate bases under the optimized conditions depicted in Table 1 and subsequent *ortho*-functionalization was carried out through the following treatments: **Exp. A**: Methyloxirane (1.1–1.25 equiv.), 2 h, r.t.; **Exp. B**: PdCl<sub>2</sub>dppf (5 mol%), iodopyridine or bromoquinoline (1.1–1.25 equiv.). **Exp. C**: PdCl<sub>2</sub>dppf (5 mol%), 1-methylbromoethene (1.1–1.25 equiv.). **Exp. D**: Dry O<sub>2</sub> bubbling, 15 min. **Exp. E**: NFSi (2 equiv.). <sup>*b*</sup> Isolated yield. <sup>*c*</sup> NMR yield. <sup>*d*</sup> The 2-Bromo(oxazolin-2-yl)benzene was also isolated (<10%).

trapping with iodine afforded the *ortho*-iodo derivatives **2d–i** in high yields (entries 4–9). Interestingly, the magnesation of the electron-rich *N*-pivaloylaniline **1k** could also be achieved, but it required the use of a large excess of  $Bu_4MgLi_2$  (1 equiv.) along with a 2 h refluxing period of the mixture, and the subsequent

treatment with iodine afforded the iodopivaloylaniline 2k, albeit in a more moderate 66% yield (entry 10). Similarly, the electronrich anisoles **11–m** were also magnesated over a 2 h refluxing period by treatment with Bu<sub>4</sub>MgLi<sub>2</sub> (0.3 equiv.) and the subsequent trapping with iodine thus provided the iodoanisoles **21–m**  in slightly better 75% and 91% yields. With magnesation procedures under control, we next evaluated arylmagnesate intermediates as arylanions for the preparation of functionalized arenes through magnesation-trapping or cross-coupling reactions (Table 2, experiences A-E). Lewis acid- and copper-mediated processes are generally employed for clean epoxide ring-opening arylithiums and Grignards reagents respectively.8 Interestingly all magnesation-trapping sequences using 1-methyldioxirane as electrophile from oxazolinylbenzene 1a, N-tert-butyl and cumylbenzamide 1d, 1g, pivaloylaniline 1k and anisole 1l led to the isolation of the corresponding alcohols (3a-e), formed exclusively from the selective opening at the less steric hindered site, in fair 42 to 55% yields (Table 2, entries 1,9,18,23,28). The oxidation of monometallic aryl lithium and aryl magnesium reagents is especially challenging, notably when using molecular oxygen.9 When the arylmagnesate intermediates generated from the orthomagnesation of oxazolinylbenzene 1a, N-tert-butyl 1d, pivaloylaniline 1k and anisole 1l were exposed to molecular oxygen, the phenols 8a-e were isolated in fair yields (entries 8,17,21,26,29). Only the cumylbenzamide 1g was oxidized in a slightly moderate 23% yield (entry 21). This procedure represents one of the most versatile routes toward functionalized phenols.<sup>10</sup> In spite of the latent metal-exchange reaction between the arylmagnesate and electrophile which represents the most competitive side-reaction, representative ortho-heteroarylations (entries 2-5,10-13, 19, 24) of four arene-class were next successfully executed through a magnesation-cross-coupling sequence with 2-bromo- and 3-iodopyridines or 3-bromoquinoline as electrophiles affording the corresponding arylated heterocycles 4a-d, 5a-d, 6a-b in moderate to good yields (36-67%). The reaction failed only when starting with the pivaloylaniline 1k, mainly due to the excessive amount of base used for the magnesation. The orthovinvlation reactions (entries 6,14,20,25) with 1-methylbromoethene were also achieved, providing vinylated arenes 7a-d in good yields. At the last stage of the study, the orthomagnesates arenes were trapped at room temperature with N-fluorobenzenesulfonimide (NFSi) reagent which displays a fair reactivity towards highly reactive aryllithiums.<sup>11</sup> Except for anisole 11 and pivalolyaniline 1k, the ortho-magnesation-NFSi trapping sequence of arenes (entries 7, 15, 16, 22) were successfully realized leading to fluoroarenes 9a-d in a range of 43-69% yields. To our knowledge we described here the first examples of fluorination of arylate intermediates and this new procedure gives a novel convenient synthesis of fluoroarenes.

In summary, we report here a highly efficient novel procedure for the *ortho*-magnesation of the five main arene classes using readily available and safe Bu<sub>3</sub>MgLi and Bu<sub>4</sub>MgLi<sub>2</sub> magnesate bases. The generated arylcomplexes are suitable for general access to a wide variety of functionalized arenes, thus giving a particular interest in this procedure by contrast to chelated-assisted direct C–H catalytic functionalization methodologies that are focused on one type of substitution. Notably, the lithium arylmagnesate intermediates react in challenging electrophile-trapping as well as in cross-coupling reactions without any further transmetallationassisted enhanced reactivity steps, thus allowing the introduction of hydroxy, fluoro, hydroxyethyl, aryl and vinyl groups on the arenes. Challenging structural determinations of generated arylamagnesates complexes<sup>4,12</sup> are under progress to highlight the important variation of reactivity sometimes observed.

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