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Generation of functionalized aryl and heteroaryl aluminum reagents by halogen–lithium exchange†

Thomas Klatt, Klaus Groll and Paul Knochel*

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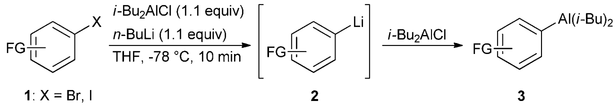
Various functionalized aryl and heteroaryl aluminum reagents were obtained by performing I–Li or Br–Li exchange reactions with the corresponding unsaturated organic halides in the presence of i-Bu$_2$AlCl. By means of an appropriate catalyst, the resulting new aluminum species were directly acylated, allylated or arylated. 1,4-Michael additions to enones have also been achieved.

In addition to its low toxicity and price, aluminum is a metal with many other attractive features. Especially owing to its broad functional group tolerance, efforts have been made over the past years to develop general preparation methods for arylaluminum compounds.[1] Recently, we have reported for the first time a convenient generation of functionalized arylaluminum sesquihalides by catalyzed direct insertion of Al powder into aryl halides.[2] In addition, cross-coupling reactions of these new aryl and heteroaryl organometallics obtained by direct alumination could be achieved very efficiently.[3]

Although this novel aluminum insertion is quite atom-economical,[4] its functional group tolerance is rather limited, and long reaction times are usually required. Therefore, we decided to prepare arylaluminums by Br–Li exchange followed by transmetalation with an aluminum halide.

However, the generation of functionalized aryllithiums is only possible at very low temperature (-100 °C)[5,6] unless Barbier-type conditions are used. Thus, Vedsø has developed a practical preparation method for arylboronic esters by *in situ* trapping of unstable lithio intermediates, which were obtained by *ortho*-metalation of the corresponding arenes.[7] In a similar manner, we decided to examine a reaction involving Br–Li exchange in the presence of i-Bu$_2$AlCl (Scheme 1).[8–10]

Herein, we report the new general synthesis of aryl and heteroaryl aluminum reagents at -78 °C, as well as their direct reactions with various electrophiles without the need for further transmetalation.[11,12]



Scheme 1 Hal–Li exchange–Li–Al–transmetalation sequence.

Thus, a mixture of i-Bu$_2$AlCl (1.1 equiv.) and 3-bromobenzonitrile (**1a**) reacted at -78 °C with *n*-BuLi (1.1 equiv., 10 min), furnishing the expected aluminum reagent **3a** in 81% yield.[13] This arylaluminum reagent readily underwent a cross-coupling reaction with ethyl 4-iodobenzoate (**4a**) in the presence of 2.5% Pd$_2$dba$_3$ and 10% P(*t*-Bu)$_3$, affording the biaryl **5a** in 65% yield (Table 1, entry 1).[14] The *ortho*-substituted 2-bromobenzonitrile (**1b**) provided the corresponding arylaluminum reagent **3b**, which was smoothly acylated (10% CuCN·2LiCl),[15] leading to the ketone **5b** (Table 1, entry 2). Similarly, 4-bromobenzonitrile (**1c**) was converted into the corresponding aluminum reagent **3c** in 80% yield, and, after Cu(I)-mediated 1,4-addition with cyclohexenone (**4c**) in the presence of TMSCl (2.5 equiv.), the ketone **5c** was isolated in 51% yield (Table 1, entry 3).

Benzamide **1d** was transformed into aluminum reagent **3d** in 75% yield. Reagent **3d** was then reacted with 3-bromocyclohexene (**4d**) to furnish product **5d** in 73% yield (Table 1, entry 4).

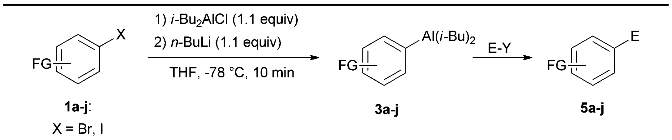
Although aldehydes were not tolerated under the insertion conditions, the corresponding acetal **1e** reacted well in the Br–Li exchange reaction and led to the aluminum reagent **3e** in 71% yield. A Cu-catalyzed acylation with cyclohexanecarbonyl chloride **4e** provided the ketone **5e** in 78% yield (Table 1, entry 5). Using the same conditions, several other aryl bromides (**1f–h**) carrying substituents such as an acetal-, silyl ether- or trifluoromethyl group could be converted to highly functionalized products (**5f–h**) in good yields (Table 1, entries 6–8).

However, for aryl bromides bearing a sensitive ester function, the Br–Li exchange was unsatisfactory as the respective butylketone was formed as the major reaction product. Nevertheless, by performing the halogen–lithium exchange on aryl iodides (**1i-j**), the corresponding arylaluminum reagents (**3i-j**)

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, 81377 München, Germany. E-mail: Paul.Knochel@cup.uni-muenchen.de

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cc43356k

Table 1 Preparation of arylaluminum reagents and subsequent reactions with electrophiles



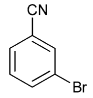
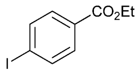
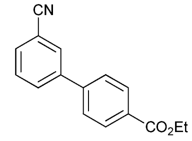
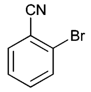
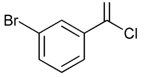
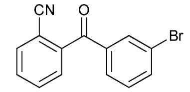
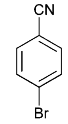
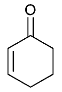
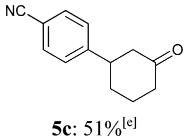
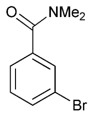
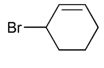
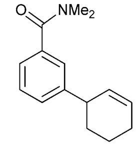
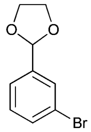
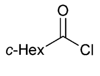
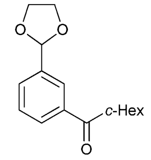
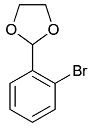
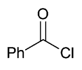
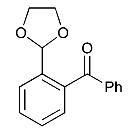
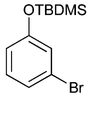
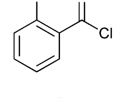
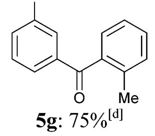
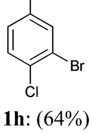
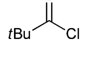
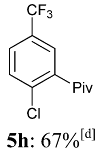
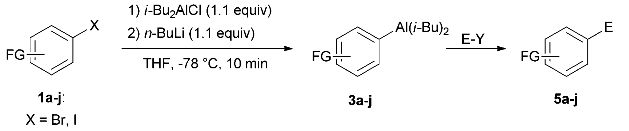
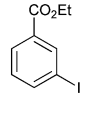
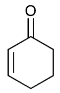
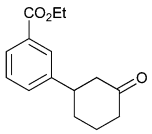
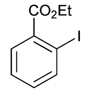
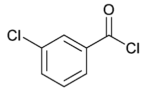
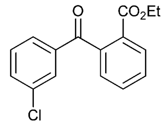
Entry	Substrate[a]	Electrophile	Product, yield[b]
1	 **1a**: (81%)	 **4a**	 **5a**: 65%[c]
2	 **1b**: (64%)	 **4b**	 **5b**: 72%[d]
3	 **1c**: (80%)	 **4c**	 **5c**: 51%[e]
4	 **1d**: (75%)	 **4d**	 **5d**: 73%[c]
5	 **1e**: (71%)	 **4e**	 **5e**: 78%[d]
6	 **1f**: (83%)	 **4f**	 **5f**: 73%[d]
7	 **1g**: (81%)	 **4g**	 **5g**: 75%[d]
8	 **1h**: (64%)	 **4h**	 **5h**: 67%[d]

Table 1 (*continued*)



Entry	Substrate[a]	Electrophile	Product, yield[b]
9	 **1i**: (65%)	 **4c**	 **5i**: 73%[e]
10	 **1j**: (72%)	 **4j**	 **5j**: 81%[d]

[a] Yield of the aluminum reagent in parentheses was determined by GC-analysis of iodolyzed reaction aliquots. [b] Yield of isolated analytically pure compounds. [c] 2.5% Pd_2dba_3 was used. [d] 20% CuCN·2LiCl was added. [e] 1.0 equivalent of CuCN·2LiCl was added.

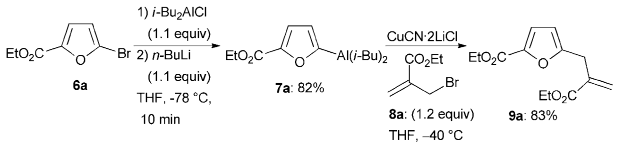
bearing an ethyl ester could be produced in 65–72% yield. Subsequent Cu(I)-mediated 1,4-addition or acylation reaction could be carried out in 73–81% yield (Table 1, entries 9 and 10).

Remarkably, in the case of electron-rich heteroaryl bromides bearing a furan or a thiophene moiety, sensitive ester functions could be tolerated, and the corresponding bromides (**6a-b**) were smoothly converted to the functionalized aluminum reagents (**7a-b**) (Scheme 2).

The hereby obtained heteroaryl aluminum reagents **7a-b** provided the corresponding products (**9a-b**) after subsequent Cu(I)-mediated allylation or acylation reaction in 68–83% yield (Scheme 2; Table 2, entry 1). The trisubstituted bromothiophene, **6c**, was converted to the aluminum species **7c** in 93% yield, and after acylation, the ketone **9c** was obtained in 85% yield (Table 2, entry 2).

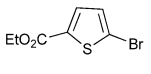
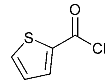
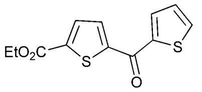
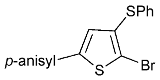
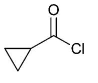
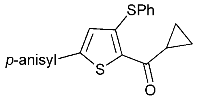
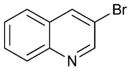
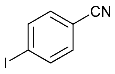
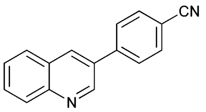
N-Heterocycles have been proven to be good substrates for an alumination reaction. Thus, starting from 3-bromoquinoline (**6d**), Br–Li exchange and subsequent transmetalation afforded the aluminum compound **7d**. Pd-catalyzed cross-coupling with 4-iodobenzonitrile (**8d**) furnished **9d** in 73% yield (Table 2, entry 3).

In addition, the generation of aluminum reagent **3f** was performed on a 10 mmol scale in 84% yield. Cu(I)-mediated acylation with 4-chlorobenzoyl chloride afforded the ketone **10** in 75% yield (Scheme 3). Starting from acetal **10**, the substituted phthalazine **11** could be obtained after treatment with

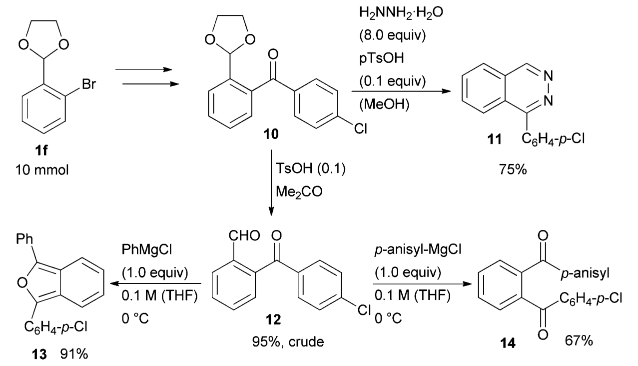


Scheme 2 Preparation of aluminum reagent **7a** and subsequent allylation reaction.

Table 2 Preparation of functionalized heteroarylaluminum reagents and subsequent reaction with electrophiles

Entry	Substrate[a]	Electrophile	Product, yield[b]
1	 **6b**: (72%)	 **8b**	 **9b**: 68%[c]
2	 **6c**: (93%)	 **8c**	 **9c**: 85%[c]
3	 **6d**: (63%.)	 **8d**	 **9d**: 73%[d]

[a] Yield of the aluminum reagent in parentheses was determined by GC-analysis of iodolyzed reaction aliquots. [b] Yield of isolated analytically pure compounds. [c] 20% CuCN·2LiCl was added. [d] 2.5% Pd_2dba_3 was used.



Scheme 3 Synthesis of the substituted phthalazine **11**, isobenzofuran **13** and diketone **14** starting from the acylation product **10**.

hydrazine in the presence of catalytic amounts of *p*-toluenesulfonic acid in 75% yield. After deprotection and aqueous workup, the crude aldehyde **12** reacted smoothly with PhMgCl affording the isobenzofuran **13** in 91% yield.[16] Interestingly, under the same reaction conditions, addition of an electron-rich anisyl Grignard reagent to the aldehyde **12** furnished the diketone **14** in 67% yield (Scheme 3).

In summary, we have shown that aryl aluminum reagents bearing functional groups such as nitriles or benzamides, as well as heteroaryl aluminum reagents bearing an ester group, can be readily prepared by Br–Li exchange reactions in the presence of i-Bu_2AlCl. Complementary to this, arylaluminum reagents bearing a sensitive ester group can be prepared by performing I–Li exchange with the corresponding aryl iodides. These new reagents undergo Pd-catalyzed cross-coupling reactions or Cu-catalyzed allylations, acylations and 1,4-Michael additions without further transmetalation. Further synthetic extensions of this method are currently underway in our laboratories.

Notes and references

1 (*a*) C. Hawner, D. Müller, L. Gremaud, A. Felouat, S. Woodward and A. Alexakis, *Angew. Chem.*, 2010, **122**, 7935 (*Angew. Chem., Int. Ed.*, 2010, **49**, 7769); (*b*) L. Gremaud and A. Alexakis, *Angew. Chem.*, 2012, **124**, 818 (*Angew. Chem., Int. Ed.*, 2012, **51**, 794); (*c*) X. Tang, D. Rawson and S. Woodward, *Synlett*, 2010, 636; (*d*) Y. Zhou, T. Lecourt and L. Micouin, *Angew. Chem.*, 2010, **122**, 2661 (*Angew. Chem., Int. Ed.*, 2010, **49**, 2607); See also: (*e*) Preparation of organoalanes for organic synthesis, P. Knochel, T. D. Blümke, K. Groll, Y.-H. Chen, Topics in Organometallic Chemistry, in *Modern Organoaluminum Reagents*, ed. S. Woodward, S. Dagorne, Springer-Verlag, Berlin, Heidelberg, 2012, vol. 41, Kap. 36 (in press), DOI: 10.1007/3418_2012_36.

2 (*a*) T. D. Blümke, Y.-H. Chen, Z. Peng and P. Knochel, *Nat. Chem.*, 2010, **2**, 313; See also: (*b*) L.-N. Guo, H. Gao, P. Mayer and P. Knochel, *Chem.–Eur. J.*, 2010, **16**, 9829; (*c*) Z. Peng, T. D. Blümke, P. Mayer and P. Knochel, *Angew. Chem.*, 2010, **122**, 8695 (*Angew. Chem., Int. Ed.*, 2010, **49**, 8516); (*d*) T. D. Blümke, K. Groll, K. Karaghiosoff and P. Knochel, *Org. Lett.*, 2011, **13**, 6440; (*e*) T. D. Blümke, T. Klatt, K. Koszinowski and P. Knochel, *Angew. Chem.*, 2012, **124**, 10064 (*Angew. Chem., Int. Ed.*, 2012, **51**, 9926).

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