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Directed Alumination

Aluminum Bases for the Highly Chemoselective Preparation of Aryl and Heteroaryl Aluminum Compounds**

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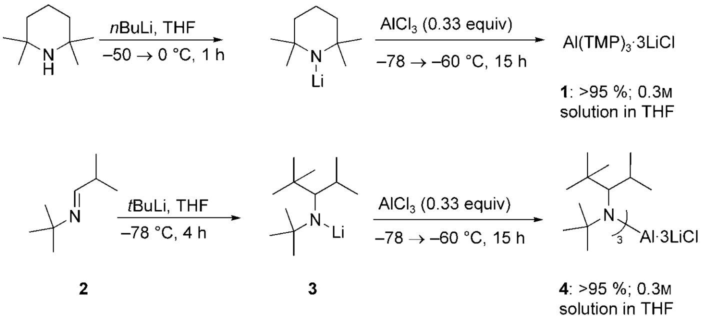
Organoaluminum reagents have found numerous applications in synthetic organic chemistry,[1] for example, in carbo- and hydroalumination reactions. The Lewis acidic character of the aluminum metal center enables reactions with unique chemo-, regio-, and enantioselectivity to be carried out.[2,3] In general, aryl aluminum species are generated by transmetalation of aryl lithium reagents with various aluminum(III) sources[4] or in some cases through aluminum–tin or aluminum–boron exchange reactions.[5] The deprotonation of aromatic rings with an aluminum base is a very convenient method for the preparation of unsaturated organoaluminum compounds. Recently, Uchiyama, Wheatley, and co-workers reported directed alumination reactions with the powerful aluminate base $i\mathrm{Bu_3Al(TMP)Li}$ (TMP = 2,2,6,6-tetramethylpiperidyl).[6] Owing to the ate character of this base, several aromatic and heteroaromatic compounds were metalated readily. Herein, we report new *neutral* aluminum trisamide bases inspired by recent structural investigations[7] that undergo highly regioselective metalation reactions.



Scheme 1. Preparation of the aluminum trisamide bases **1** and **4**.

Thus, the treatment of LiTMP with a solution of $\mathrm{AlCl_3}$ in THF (0.33 equiv)[8] at −78 °C leads to a solution of $\mathrm{Al(TMP)_3{\cdot}3LiCl}$ (**1**; Scheme 1). An additional sterically hindered aluminum base was prepared by treating the imine **2**[9] with *t*BuLi (1.0 equiv) in THF[10] at −78 °C to give the lithium amide **3**, followed by transmetalation with $\mathrm{AlCl_3}$ (0.33 equiv) in THF. The corresponding aluminum trisamide base **4** was obtained in quantitative yield (Scheme 1).[11] These bases display excellent reactivity and good solubility (0.3 M in THF).[12]

First, we investigated the alumination of various functionalized aromatic compounds, such as benzonitrile (**5a**), *tert*-butyl benzoate (**5b**), and *tert*-butyl 1-naphthoate (**5c**). These substrates all underwent complete metalation with $\mathrm{Al(TMP)_3{\cdot}3LiCl}$ (**1**, 1.0 equiv)[13] within 3–6 h at −5 to −10 °C. The resulting aryl aluminum compounds were transmetalated with $\mathrm{ZnCl_2}$ to give the corresponding zinc reagents, and after copper-mediated acylation[14] or a palladium-catalyzed cross-coupling reaction[15] with $[\mathrm{Pd(dba)_2}]$ (5 mol %) and P(*o*-furyl)$_3$ (10 mol %), the products **6a–c** were obtained in 70–79 % yield (Table 1, entries 1–3).

Similarly, complete alumination was observed with the aluminum trisamide **4** (1.0 equiv) within 3–5 h at −5 to −10 °C, and the biaryl compounds **6a–c** were isolated in 71–77 % yield (Table 1, entries 1–3). These results indicate that both bases, **1** and **4**, show similar metalation rates. However, the practical and economical synthesis of **4** led us to use this base for further experiments. The metalation of difluorobenzenes **5d–f** is especially challenging and requires a low reaction temperature.[16] However, with the aluminum base **4**, a smooth regioselective alumination proceeded at −40 °C within 1.5–3 h. After transmetalation to the corresponding zinc derivatives and Negishi cross-coupling, the functionalized biphenyls **6d–f** were obtained in 79–89 % yield (Table 1, entries 4–6). Moreover, the metalation of the corresponding dichlorobenzenes **5g–i** proceeded within 3–4.5 h under similar conditions at −60 °C to give the functionalized aromatic compounds **6g–i** in 78–85 % yield after transmetalation and cross-coupling (Table 1, entries 7–9).

Electron-rich aromatic compounds are generally difficult to metalate. Thus, aromatic ethers are poor *ortho*-directing groups for lithiation reactions.[17] Monometallic magnesium and zinc amides are unable to metalate such substrates at all.[18] However, aluminum amides are powerful reagents for the metalation of aromatic ethers, probably as a result of a strong coordination of the ether oxygen atom to the aluminum center. Thus, the metalation of anisole (**5j**) with **4** was complete within 9 h at 25 °C,[19] and a copper-mediated acylation gave the substituted benzophenone **6j** in 79 % yield (Table 1, entry 10). A substantially lower metalation rate was observed with **1** (11 h at 25 °C; Table 1, entry 10). Interestingly, the substituted anisoles **5k** and **5l**, as well as the naphthalene derivative **5m**, were also metalated regioselec-

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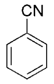
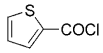
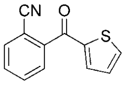
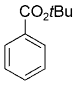
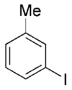
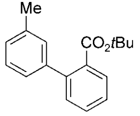
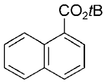
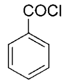
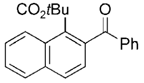
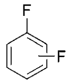
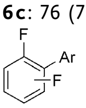
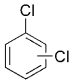
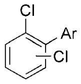
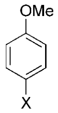
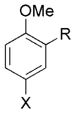
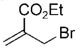
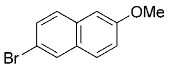
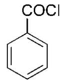
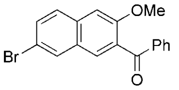
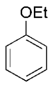
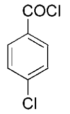
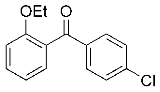
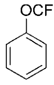
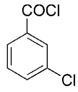
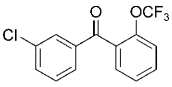
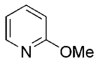
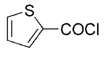
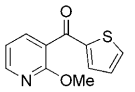
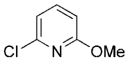
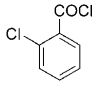
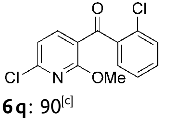
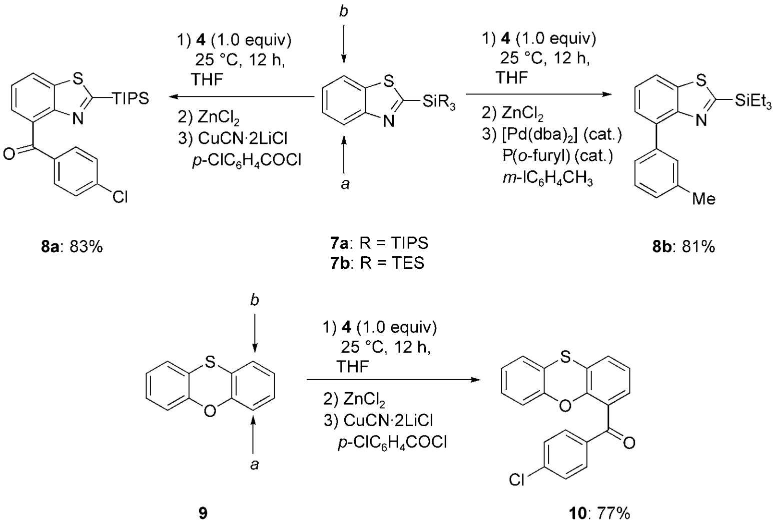
Table 1: Products of type **6** obtained by the alumination of aromatic and heteroaromatic compounds with **4**, transmetalation with ZnCl$_2$, and subsequent transformation with electrophiles (E$^+$).

Entry	Substrate	T [°C], t [h][a]	E$^+$	Product/Yield [%][b]
1	 **5a**	−10, 4 (4)		 **6a**: 71 (70)[c]
2	 **5b**	−5, 3 (3)		 **6b**: 77 (79)[d]
3	 **5c**	−5, 5 (6)		 **6c**: 76 (78)[c]
4	 **5d**: p	−40, 2	p-$\mathrm{IC_6H_4CO_2Et}$	 **6d**: p; Ar = p-$\mathrm{CO_2EtC_6H_4}$: 79[d]
5	**5e**: m	−40, 1.5	m-$\mathrm{IC_6H_4NO_2}$	**6e**: m; Ar = m-$\mathrm{NO_2C_6H_4}$: 88[d]
6	**5f**: o	−40, 3	o-$\mathrm{IC_6H_4Cl}$	**6f**: o; Ar = o-$\mathrm{ClC_6H_4}$: 89[d]
7	 **5g**: p	−60, 3	p-$\mathrm{IC_6H_4Me}$	 **6g**: p; Ar = p-$\mathrm{MeC_6H_4}$: 85[d]
8	**5h**: m	−60, 4.5	o-$\mathrm{IC_6H_4OMe}$	**6h**: m; Ar = o-$\mathrm{OMeC_6H_4}$: 78[d]
9	**5i**: o	−60, 4.5	m-$\mathrm{IC_6H_4Me}$	**6i**: o; Ar = m-$\mathrm{MeC_6H_4}$: 81[d]
10	 **5j**: X = H	25, 9 (11)	p-$\mathrm{ClC_6H_4COCl}$	 **6j**: X = H; R = COC$_6$H$_4$-p-Cl: 79 (74)[c]
11	**5k**: X = Cl	25, 4	p-$\mathrm{IC_6H_4CN}$	**6k**: X = Cl; R = p-$\mathrm{CNC_6H_4}$: 78[d]
12	**5l**: X = I	25, 8		**6l**: X = I; R = (2-EtO$_2$C)allyl: 73[e]
13	 **5m**	25, 8		 **6m**: 77[c]
14	 **5n**	25, 10		 **6n**: 85[c]
15	 **5o**	0, 3		 **6o**: 81[c]
16	 **5p**	25, 3 (3.5)		 **6p**: 85 (81)[c]
17	 **5q**	0, 3		 **6q**: 90[c]

[a] The metalation times with TMP$_3$Al·3 LiCl (**1**) are given in parentheses. [b] Yield of the analytically pure isolated product. Yields in brackets are for the use of **1** in place of **4**. [c] The organozinc intermediate was transmetalated with CuCN·2 LiCl (1.1 equiv). [d] The product was obtained by palladium-catalyzed cross-coupling with [Pd(dba)$_2$] (5 mol%) and P(o-furyl)$_3$ (10 mol%). In products **6d–6f** and **6g–6i**, the aryl substituent is located between the two halogen atoms. [e] CuCN·2 LiCl (0.25 equiv) was used.

tively at the *ortho* position to the methoxy group. Copper-mediated trapping reactions or a palladium-catalyzed cross-coupling reaction then furnished the products **6k–m** in 73–78% yield (Table 1, entries 11–13). Additionally, phenetole (**5n**) was aluminated within 10 h at 25 °C, whereas the metalation of trifluoromethoxybenzene (**5o**) proceeded within 3 h at 0 °C. The subsequent reactions with chlorobenzoyl chlorides in the presence of CuCN·2 LiCl (1.1 equiv) led to the benzophenones **6n** and **6o** in 85 and 81% yield, respectively (Table 1, entries 14 and 15). Furthermore, 2-methoxypyridine (**5p**) and 6-chloro-2-methoxypyridine (**5q**) were aluminated within 3 h at 25 and 0 °C, respectively. After CuCN·2 LiCl-mediated acylation reactions, the ketones **6p** and **6q** were obtained in 85 and 90% yield (Table 1, entries 16 and 7). Interestingly, the use of aromatic or heteroaromatic ethers as substrates enables the alumination reactions to be carried out at very convenient temperatures (0 or 25 °C), possibly as a consequence of the complexation of the aluminum center with the ether oxygen atom.

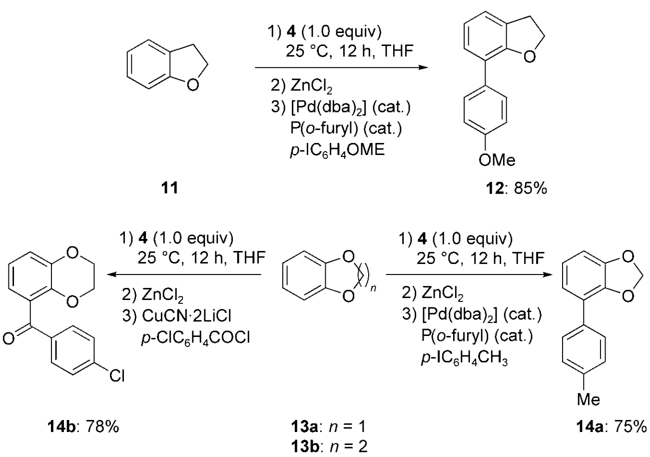
The highly regioselective alumination can be used to create unusual substitution patterns on heteroaromatic compounds. Thus, 2-(triisopropylsilyl)benzothiazole (**7a**) and 2-(triethylsilyl)benzothiazole (**7b**) may be metalated either at the *ortho* position to the nitrogen atom (position *a*) or at the *ortho* position to the sulfur atom (position *b*; Scheme 2). Interestingly, both substrates were aluminated exclusively at position *a* with the base **4** (1.0 equiv; 25 °C, 12 h). After transmetalation to form a zinc compound, followed by a copper-mediated acylation or palladium-catalyzed cross-coupling reaction, the functionalized benzothiazoles **8a** and **8b** were isolated in 83 and 81% yield, respectively. Similar regioselectivity is observed when metalation both α to an oxygen atom and α to a sulfur atom is possible. Thus, phenoxathiine (**9**) underwent a smooth regioselective



Scheme 2. Regioselective alumination of the benzothiazoles **7a** and **7b** and phenoxathiine (**9**) with the aluminum base **4** and subsequent transmetalation with ZnCl$_2$, followed by copper-mediated acylation or palladium-catalyzed cross-coupling. dba = dibenzylideneacetone, TES = triethylsilyl, TIPS = triisopropylsilyl.

alumination within 12 h at 25 °C at the *ortho* position to the oxygen atom. Subsequent transmetalation and a copper-mediated acylation with *p*-chlorobenzoyl chloride (1.0 equiv) provided the ketone **10** in 77 % yield (Scheme 2).

Few examples of the metalation of substrates containing partly saturated rings have been described.[20] However, the metalation of 2,3-dihydrobenzofuran (**11**) with **4** proceeded smoothly within 12 h at 25 °C, and a palladium-catalyzed cross-coupling reaction furnished the compound **12** in 85 % yield (Scheme 3). Furthermore, the treatment of benzo[1,3]dioxole (**13a**) or benzo[1,4]dioxane (**13b**) with **4** (1.0 equiv) led to an aluminated intermediate within 12 h at 25 °C. A subsequent transmetalation with ZnCl$_2$ and palladium-catalyzed cross-coupling or copper-mediated acylation provided the products **14a** and **14b** in 75 and 78 % yield, respectively (Scheme 3).



Scheme 3. Alumination of substrates with annelated oxygen-containing rings and subsequent transmetalation with ZnCl$_2$, followed by copper-mediated acylation or palladium-catalyzed cross-coupling.

In conclusion, we have reported a new directed alumination that enables the regioselective functionalization of various aromatic and heteroaromatic compounds. A number of functional groups are tolerated, including ester and cyano groups, as well as halogen atoms. Owing to the strong Lewis acidic character of aluminum, remarkable regioselectivity was observed with oxygen-substituted aromatic substrates. These substrates are difficult to metalate with other amide bases. The high regioselectivity enables the preparation of compounds with uncommon substitution patterns. We are currently investigating the scope of application of these new aluminum bases.

Experimental Section

Preparation of ($C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**4**): *tert*-Butylisobutylideneamine[10] (**2**; 7.63 g, 60.0 mmol) was dissolved in THF (60 mL) in an argon-flushed Schlenk flask. This solution was cooled to −78 °C, *t*BuLi (1.5 M in pentane, 40 mL, 60.0 mmol) was added dropwise, and the resulting mixture was stirred at this temperature for 4 h. A freshly prepared solution of AlCl$_3$ (20 mmol, 2.67 g) in THF was then added, and the mixture was stirred at −60 °C for 15 h. The solvents were then reduced in vacuo. The fresh solution of **4** was titrated prior to use at 0 °C with menthol[21] or 2-propanol, and with 4-(phenylazo)diphenylamine[18] as an indicator. A concentration of 0.3 M in THF was found.

Synthesis of **12**: $(C_{12}H_{26}N)_3Al{\cdot}3LiCl$ (**4**; 0.3 M solution in THF, 7 mL, 2 mmol) was added dropwise to a solution of 2,3-dihydrobenzofuran (**11**; 240 mg, 2.0 mmol) in dry THF (2 mL) under argon in a 50 mL Schlenk tube equipped with a magnetic stirring bar, and the resulting mixture was stirred at 25 °C for 12 h. After transmetalation with ZnCl$_2$, a palladium-catalyzed cross-coupling reaction with 4-iodoanisole was carried out at 25 °C for 2 h. After aqueous workup and purification by column chromatography, **12** (385 mg, 85 %) was obtained as a colorless solid.

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[20] No directed metalation of substrates **11** and **13a**,**b** has been reported previously. When previously reported bases[18] were used, no metalation of these substrates or of substrates **7a**,**b** and **9** was observed. For an alternative Br/Mg exchange, see: S. Ravi Kanth, G. Venkat Reddy, T. Yakaiah, B. Narsaiah, P. Shanthan Rao, *Synth. Commun.* **2006**, *36*, 3079.

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