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A Convenient Alumination of Functionalized Aromatics by Using the Frustrated Lewis Pair Et_3Al and TMPMgCl·LiCl

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Abstract: A straightforward and efficient alumination of functionalized arenes by using the frustrated Lewis pair Et_3Al and TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidyl) has been developed. In particular, halogenated electron-rich aromatics can be smoothly functionalized by using the frustrated Lewis pair Et_3Al and TMPMgCl·LiCl. Compared with previously described alumination methods, this procedure avoids extensive cooling and the need for an excess of base. This in situ procedure has proven to be most practical and allows for regio- and chemoselective metalation of a wide range of aromatics with sensitive functional groups ($CONEt_2$, CO_2Me, CN, $OCONMe_2$) or halogens (F, Cl, Br, I). The resulting aromatic aluminates, which were characterized by using NMR spectroscopy, were subjected to allylations, acylations, and palladium-catalyzed cross-coupling reactions after transmetalation to zinc. It was shown that the nature of the Zn salt used for transmetalation is crucial. Thus, compared with $ZnCl_2$ (2 equiv), the use of $Zn(OPiv)_2$ (2 equiv; OPiv = pivalate) allows the subsequent quenching reactions to be performed with only a slight excess of electrophile (1.2 equiv) and provides interesting functionalized aromatics in good yields.

Keywords: aluminum · C–C coupling · Lewis pairs · metalation · regioselectivity

Introduction

Organoaluminum reagents are useful intermediates for the formation of new carbon–carbon bonds.[1] Compared with other main-group metals, aluminum is fairly inexpensive and nontoxic, and its recovery is possible through aluminum hydroxide precipitation.[2] Furthermore, aluminum exhibits useful reactivity due to its Lewis acid properties.[3] In particular, the alumination of electron-rich aromatics is of great synthetic interest because the corresponding lithiation can require extensive cooling, whereas the metalation with standard Mg and Zn bases is sluggish with such aromatics. However, for an efficient metalation of these scaffolds lithium bases or bimetallic bases are generally required.[4]

The pioneering work of Uchiyama has shown that aluminum ate bases[5] such as $iBu_3Al(TMP)Li$[6] (TMP = 2,2,6,6-tetramethylpiperidyl) proved to be very useful for the directed alumination of various aromatics and some heterocycles.[7] Nevertheless, an excess of base (2.2 equiv) was needed to achieve full conversion. Recently, we have prepared the related non-ate base $[(t\text{BuCH}(i\text{Pr}))(t\text{Bu})\text{N}]_3\text{Al}\cdot 3\,\text{LiCl}$, which proved to regioselectively aluminate a range of aromatic and heteroaromatic scaffolds.[8] Its metalation power and regioselectivity was complementary to other TMP bases, such as TMPMgCl·LiCl (**1**),[9] $TMP_2Mg\cdot 2\,LiCl$ (**2**),[10] TMPZnCl·LiCl,[11] $TMP_2Zn\cdot 2\,MgCl_2\cdot 2\,LiCl$[12] and $TMP_2Mn\cdot 2\,MgCl_2\cdot 4\,LiCl$.[13] Whereas most of these TMP-bases react readily with aromatics that have electron-withdrawing substituents, $[(t\text{BuCH}(i\text{Pr}))(t\text{Bu})\text{N}]_3\text{Al}\cdot 3\,\text{LiCl}$ is able to metalate electron-rich oxygen-substituted aromatics. Unfortunately, solutions of $[(t\text{BuCH}(i\text{Pr}))(t\text{Bu})\text{N}]_3\text{Al}\cdot 3\,\text{LiCl}$ in THF display only limited stability (2–3 d at −50 °C). Therefore, we looked for a more practical alternative, which is described herein. We report the use of the frustrated Lewis pair[14] Et_3Al–TMPMgCl·LiCl (**3**) for the alumination of various functionalized aromatics. The dual catalysis of the Lewis acid Et_3Al and the Lewis base TMPMgCl·LiCl has several preparative advantages. Also, Lewis pair **3** displays good metalating power and convenient practical handling. In contrast to previous reports, this new system and its in situ preparation avoids the problem of using an excess of the aluminum base in the metalation step. Furthermore, we reveal that the use of $Zn(OPiv)_2$ (OPiv = pivalate) allows the excess of electrophile to be minimized in subsequent reactions.

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Results and Discussion

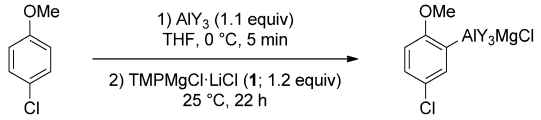
In the first optimization step of this new directed alumination procedure, we searched for the most convenient aluminum source. 4-Chloroanisole (**4a**), which was used as a model aromatic substrate, was treated at 0 °C with various aluminum(III) reagents (1.1 equiv) followed by the addition of TMPMgCl·LiCl (**1**; 1.2 equiv) and then warming to 25 °C.

When 4-chloroanisole (**4a**) was treated with **1** for 22 h at ambient temperature, 30% *ortho* metalatation was obtained. However, the reaction did not proceed further. In the presence of aluminum reagents $AlCl_3$, $MeAlCl_2$, and Me_2AlCl, conversion to corresponding *ortho*-metalated compound **5a** dropped to less than 5%. This was not surprising because a standard transmetalation of **1** to a tricoordinated aluminum compound is expected.[15a] The tentative structure of the resulting aluminum reagents is $Me_nCl_{2-n}Al$(TMP) ($n=0$–2), and no metalation activity is expected for these reagents. However, the use of trialkylaluminum reagents, such as Me_3Al, Et_3Al, and iBu$_3$Al, greatly increased the metalation rate of **4a**. The observed rates proved to be comparable, but the combination of **1** with Et_3Al led to more complete conversions (Table 1).

One possible mechanism that could account for better conversion with R_3Al additives compared with R_2AlX additives is the initial formation of the aluminate species Et_3Al(TMP)MgCl·LiCl, similar to iBu$_3$Al(TMP)Li as reported by Uchiyama et el.[4c] This species could effectively deprotonate anisole **4a**. However, seminal studies by the groups of Hevia, García-Álvarez, Robertson, and Mulvey demonstrated that solvent-separated ion-pair species and a dismutation process have to be considered for such aluminates. In addition, ligand exchanges have been observed on such aluminates.[5] This prompted us to perform a multinuclear NMR spectroscopy study to clarify the nature of the species formed from **3**. Thus, mixing equimolar amounts of Et_3Al with **1** at 25 °C in THF (0.5 M) gave approximately 80% unchanged **1** along with two new species (Figure 1).

One of these species was identified as $Et_4Al(MgCl)$ by using ^{1}H, ^{13}C, and ^{27}Al NMR spectroscopy,[15] whereas the second species clearly contains at least one TMP moiety (Figure 1). The formation of $Et_4Al(MgCl)$ along with a new TMP-containing compound in solution proves that an equilibration process took place. Furthermore, the existence of only one new TMP-containing compound in solution implies that there is no Et_3Al(TMP)MgCl·LiCl species present because the observed formation of $Et_4Al(MgCl)$ can only be explained in connection with the two Et_2Al(TMP)·THF or $Et_2Al(TMP)_2MgCl$·LiCl[16] species (Scheme 1).

Table 1. Conversion of **4a** to aluminate species **5a** in the course of the metalation with in situ prepared bases, using various aluminum sources.[a]



4a **5a**

Entry	AlY_3	Conversion [%] 1 h	2 h	3 h	4 h	7 h	10 h	22 h
1	–	17	19	20	21	23	25	30
2	$AlCl_3$	<5	<5	<5	<5	<5	<5	<5
3	$MeAlCl_2$	<5	<5	<5	<5	<5	<5	<5
4	Me_2AlCl	<5	<5	<5	<5	<5	<5	<5
5	Me_3Al	32	44	58	61	69	74	76
6	Et_3Al	38	55	62	68	78	82	90
7	iBu$_3$Al	31	45	57	62	69	76	81

[a] The conversion to the corresponding metal species was monitored by using GC analysis of aliquots of the reaction mixture quenched with allyl bromide in the presence of CuCN·2 LiCl, with tetradecane as the internal standard.

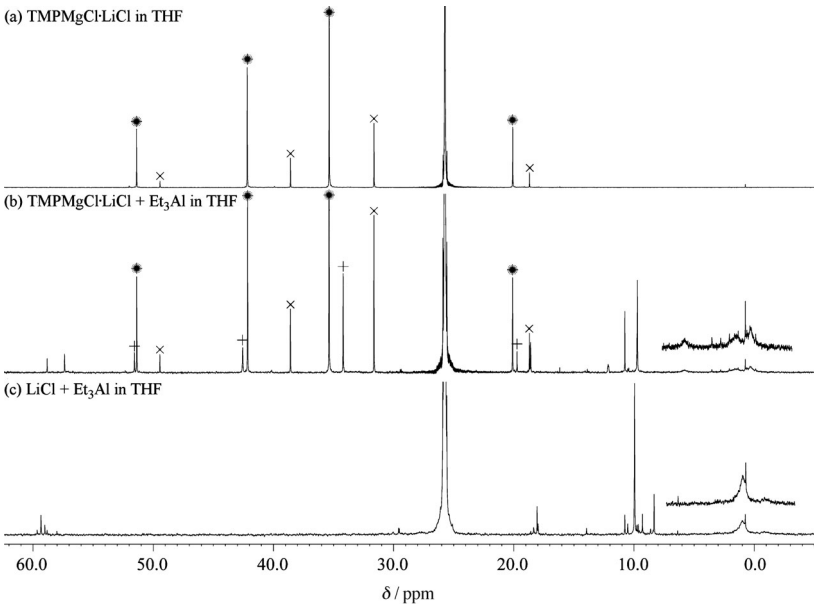
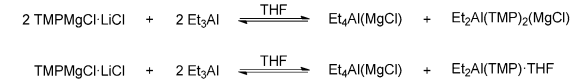


Figure 1. ^{13}C NMR spectra recorded in THF for TMPMgCl·LiCl (**1**), Et_3Al–TMPMgCl·LiCl (**3**), and Et_3Al with LiCl; *: TMPMgCl·LiCl, ×: TMPH, +: new species.



Scheme 1. Putative equilibria of **3** in THF.

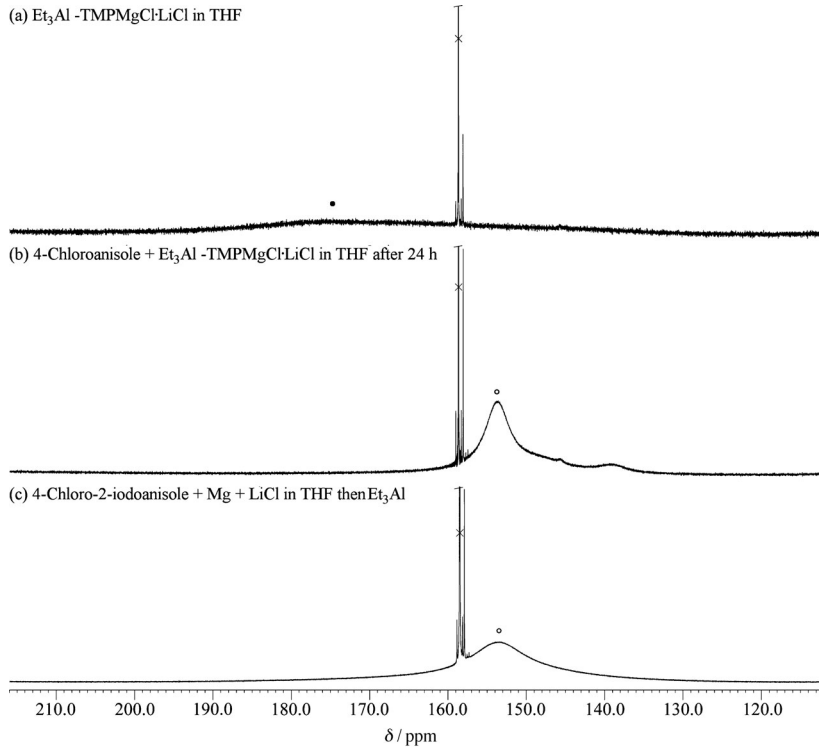


Figure 2. ^{27}Al NMR spectra recorded in THF for **3** and arylaluminate **5a** prepared by deprotonation or Mg insertion followed by transmetalation; ×: $Et_4Al(MgCl)$, ○: arylaluminates **5a** and **5aa**, ●: Et_3Al.

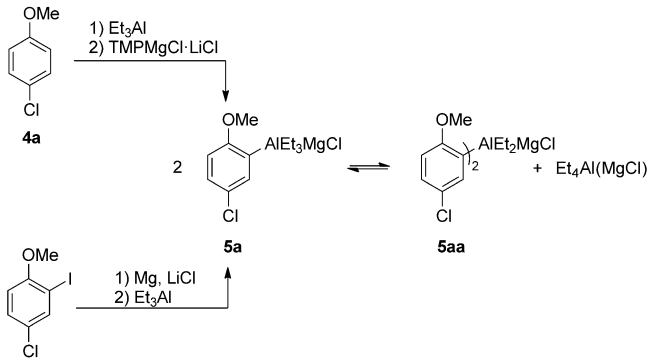
Unfortunately, ^{27}Al NMR spectroscopy does not allow these species to be distinguished between due to similar expected chemical shifts (Figure 2a).[17] However, comparison with control ^{27}Al NMR spectra proved that Figure 2a shows the expected broad signal for Et_3Al centered at $\delta = 175$ ppm along with the very sharp signal of $Et_4Al(MgCl)$ at $\delta = 159$ ppm.

Note that, as shown in Table 1, Me_2AlTMP is not active in the metalation of **4a**. A similar result is expected for Et_2AlTMP·THF (Scheme 1), whereas the formation of $Et_2Al(TMP)_2MgCl$·LiCl is less favored for steric reasons. Furthermore, the groups of Hevia, García-Álvarez, Robertson, and Mulvey have shown that iBu$_4$Al(Li) is not active in metalations.[5] Therefore, we conclude that the active species in our system must be Lewis pair **3**. In fact, **1** and Et_3Al represent 80% of the reaction mixture. This coexistence of Lewis acid Et_3Al and Lewis base **1** during the course of the reaction implies that **3** may be regarded as a frustrated Lewis pair. There is a very slow and incomplete reaction taking place between **1** and Et_3Al (Scheme 1 and Figure 1).

To shed some light on the organometallic species produced after metalation, we deprotonated **4a** with a stoichiometric mixture of **3** at ambient temperature. After a reaction time of 24 h, we investigated the reaction mixture by using ^{1}H, ^{13}C, ^{27}Al, and ^{7}Li NMR spectroscopy. The ^{13}C NMR spectrum recorded at 25 °C clearly shows the presence of three organoaluminum species, which are identified as **5a**, **5aa**, and $Et_4Al(MgCl)$ (Scheme 2 and Figure 3). The same three species are formed independently by transmetalation of the corresponding (5-chloro-2-methoxyphenyl)magnesium iodide Grignard reagent with Et_3Al (Figures 2 and 3).

The Grignard reagent was prepared through oxidative insertion of magnesium in the presence of LiCl in 4-chloro-2-iodo-1-methoxybenzene (Scheme 2).[18] Thus, it can be concluded that the alumination of **4a** proceeds through deprotonation by the TMP anion rather than by an alkyl ligand.

In particular, the absence of the ^{13}C NMR signals of the Grignard reagent and generation of the same species simply by adding Et_3Al to the Grignard reagent supports the identity of these organoaluminum species. Further evidence is provided by the ^{27}Al NMR spectrum (Figure 2). It shows a new broad signal at $\delta = 153$ ppm, which is attributed to



Scheme 2. Postulated equilibrium of arylaluminate **5a**.

two organoaluminum species **5a** and **5aa**. Due to the similar environment of Al in these compounds (surrounded by four carbon atoms) similar chemical shifts are anticipated, and due to the expected broadness of the signals they cannot be resolved. In all these reactions Li^+ obviously did not change its environment. All solutions in which Li^+ is present showed the same signal in ^{7}Li NMR spectroscopy, that is, a singlet at $\delta = 3.2$ ppm.

Further preliminary experiments proved that in situ generation of **3** was advantageous because **3** slowly decomposes in THF. Additionally, the conversion of **4a** to the aluminate species (**5a**) is slightly higher for the in situ preparation (Scheme 3 and Table 1).

In the next step, the stoichiometry of Et_3Al was optimized. Compound **4a** was treated with various amounts of

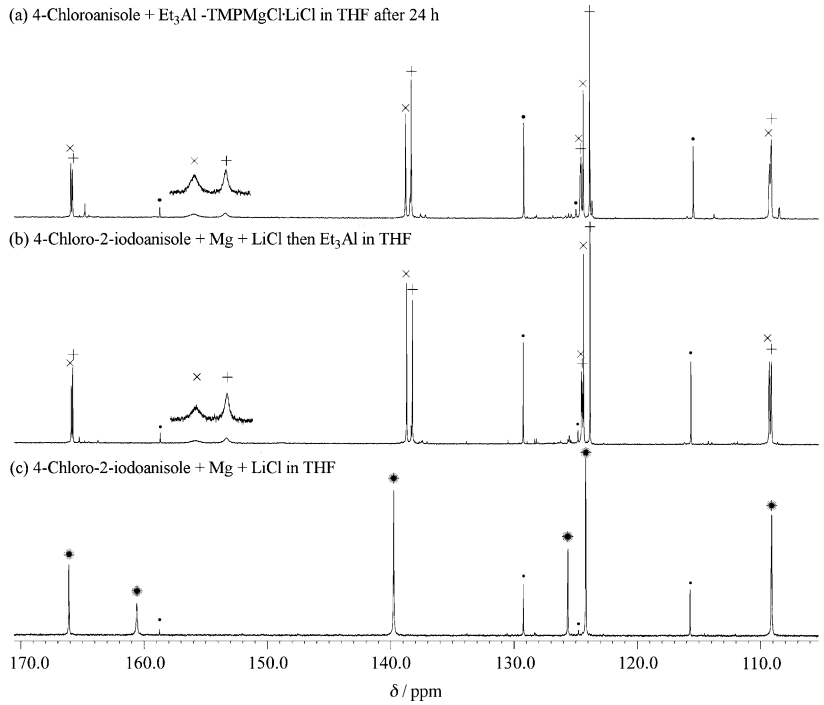
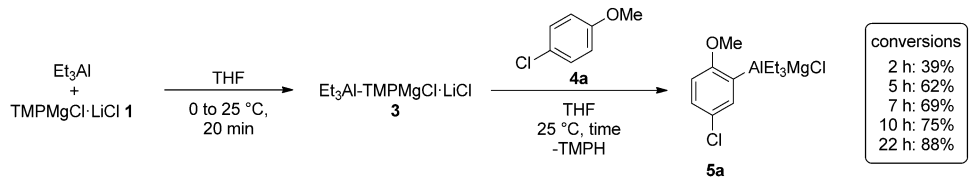


Figure 3. ^{13}C NMR spectra of arylaluminate **5a** prepared by deprotonation or Mg insertion followed by transmetalation and the corresponding Grignard reagent; +: arylaluminate **1**, ×: arylaluminate **2**, *: Grignard reagent, ●: hydrolysis (**4a**).



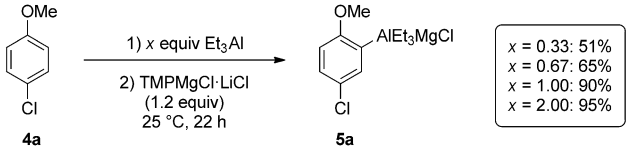
Scheme 3. Alumination of 4-chloroanisole (**4a**) with preformed **3**.

Et_3Al and reacted with 1.1 equivalents of **1** for 22 h at 25 °C. If Et_3Al was used in substoichiometric amounts, only low conversions (51–65 %) were obtained, whereas an excess of Et_3Al did not further improve the metalation rate (Scheme 4). Thus, the best conditions require the use of stoichiometric amounts of Et_3Al.

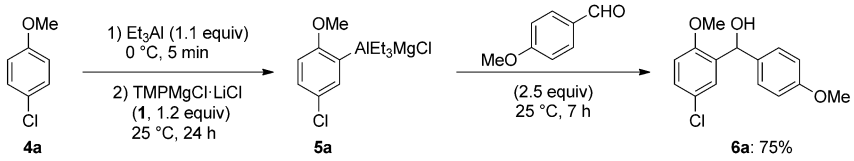
With these optimized reaction conditions, we were able to aluminate a broad range of electron-rich and -poor aromatics and reacted the resulting aluminates with various electrophiles, for example, addition to aldehydes, acylations, allylations, and cross-couplings with aryl iodides (Table 2). Thus, **4a** was smoothly metalated within 24 h at 25 °C. Resulting aryltriethylaluminate **5a** subsequently reacted with *p*-anisaldehyde to give desired alcohol **6a** in 75 % yield (Scheme 5).

This new procedure proved to be quite general. By treating a variety of aromatics of type **4** with Et_3Al followed by **1**, a range of functionalized aluminates was prepared in a convenient temperature range (−5–25 °C). After quenching with typical electrophiles, expected products of type **6** were isolated in 70 to 83 % yield (Table 2).

Accordingly, aluminate **5a** could also be smoothly transmetalated to zinc by using $ZnCl_2$, and underwent a Pd-catalyzed Negishi cross-coupling[19] with 2-chloro-4-iodobenzonitrile (2.5 equiv) with 2 % [Pd(dba)$_2$] (dba = dibenzylideneacetone) and 4 % TFP (TFP = tri(2-furyl)phosphine),[20] which led to desired biphenyl **6b** in 70 % yield (Table 2, entry 1). 4-Fluoroanisole (**4b**) and 4-bromoanisole (**4c**) were also completely metalated within 15 and 28 h, respectively, at 25 °C. After transmetalation with $ZnCl_2$ (2.2 equiv), the corresponding organometallics reacted with ethyl 4-iodobenzoate (2.5 equiv) under Pd catalysis or with 4-chlorobenzoyl chloride (2.5 equiv) mediated by CuCN·2 LiCl[21] (1.1 equiv) to give biphenyl **6c** and ketone **6d** in 77 to 79 % yield (Table 2, entries 2 and 3). Because 3-fluoroanisole (**4d**) is prone to undergoing β-elimination, it is metalated at lower temperature (−5 °C). Under these conditions, full metalation is achieved within 20 min. Following transmetalation to zinc, a copper-catalyzed allylation with 3-

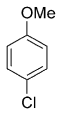
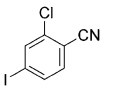
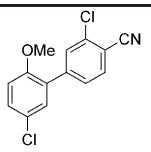
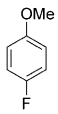
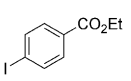
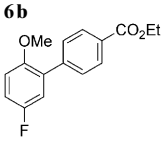
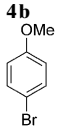
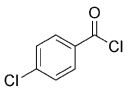
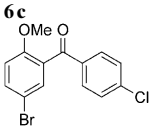
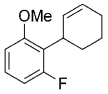
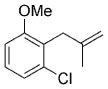
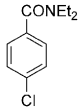
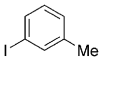
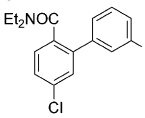
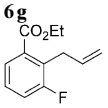
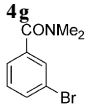
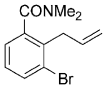
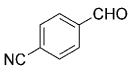
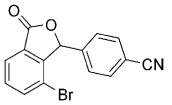


Scheme 4. Metalation of **4a** by using various amounts of Et_3Al.



Scheme 5. Regioselective functionalization of **4a** by alumination.

Table 2. Alumination of aromatics and subsequent quenching with electrophiles (2.5 equiv).

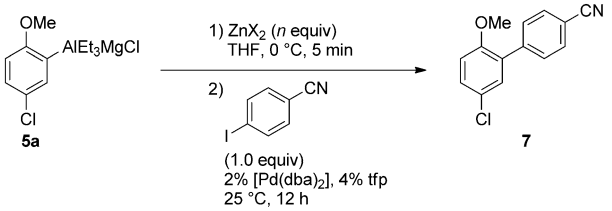
Entry	Substrate	t [°C], T [h]	Electrophile	Product	Yield[a] [%]
1	 **4a**	25, 24		 **6b**	70[b]
2	 **4b**	25, 15		 **6c**	77[b]
3	 **4c**	25, 28		 **6d**	79[c]
4	 **4d**	−5, 0.3		 **6e**	87[d]
5	 **4e**	25, 1		 **6f**	85
6	 **4f**	0, 3		 **6g**	73
7	 **4g**	0, 1		 **6h**	81
8	 **4h**	0, 1		 **6i**	74
9	 **4h**	0, 1		 **6j**	83

[a] Isolated yield of analytically pure product. [b] Obtained after transmetalation with $ZnCl_2$ (2.2 equiv) by palladium-catalyzed cross-coupling with 2% $[Pd(dba)_2]$ and 4% TFP. [c] A transmetalation with $ZnCl_2$ (2.2 equiv) and CuCN·2 LiCl (1.1 equiv) was performed. [d] Obtained after transmetalation with $ZnCl_2$ (2.2 equiv) and allylation catalyzed by 5% CuCN·2 LiCl.

bromocyclohexene provided desired product **6e** in 87% yield (Table 2, entry 4). In contrast, 3-chloroanisole (**4e**) was metalated at 25 °C within 1 h, and subsequent allylation with methallyl bromide gave anisole derivative **6f** in 85% yield (Table 2, entry 5). Electron-poor arenes **4f–h** were metalated at slightly lower temperatures. *para*-Substituted amide **4f** was aluminated within 3 h at 0 °C, and after Negishi cross-coupling with 3-iodotoluene (2.5 equiv), biphenyl **6g** was obtained in 73% yield (Table 2, entry 6). *meta*-Substituted ester **4g** and amide **4h** were metalated within 1 h at 0 °C, and the resulting arylaluminates were allylated or reacted with 4-cyanobenzaldehyde to give 2-allylated products **6h** and **6i** and lactone **6j** in 74 to 83% yield (Table 2, entries 7–9).

However, this smooth alumination still has a drawback. To achieve high yields, it was necessary to use an excess of the electrophile (2.5 equiv). Preliminary results showed that a direct cross-coupling of the intermediate aluminates by using $[Pd(tmpp)_2Cl_2]$ (tmpp = tris(2,4,6-trimethoxyphenyl)-phosphine) leads only to low yields of the desired biphenyl (15%). Therefore, we screened the nature and amount of zinc reagent used for the transmetalation (Table 3). If two

Table 3. Screening of various Zn-salts for the transmetalation step.



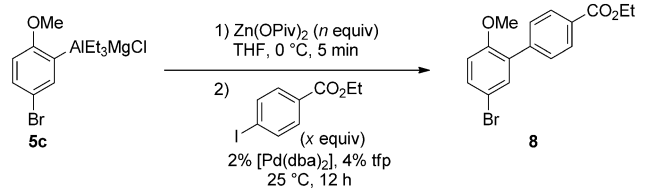
Entry	ZnX_2	n [equiv]	Yield of **7** [%]
1	$ZnCl_2$	2	38
2	$ZnCl_2$	5	58
3	$ZnCl_2$·2 LiCl	2	<5
4	$ZnCl_2$·2 LiCl	5	<5
5	$Zn(OPiv)_2$	2	70
6	$Zn(OPiv)_2$	5	67

equivalents of $ZnCl_2$ were used for the transmetalation, biphenyl **7** was isolated in 38% yield, whereas with five equivalents of $ZnCl_2$, the yield increased to 58% (Table 3, entries 1 and 2). In contrast, the use of two or five equivalents of $ZnCl_2$·2 LiCl[22] gave mainly 4-ethylbenzonitrile and only small amounts of **7** (Table 3, entries 3 and 4). Lastly, $Zn(OPiv)_2$ provided the best results; remarkably, two equivalents of $Zn(OPiv)_2$ were sufficient to provide **7** in 70% yield, whereas the use of five equivalents did not further improve the yield of **7** (Table 3, entries 5 and 6)

In the next step, we further optimized the stoichiometry of $Zn(OPiv)_2$ and the electrophile. We attempted to reduce the amount of $Zn(OPiv)_2$ used and investigated whether the use of an excess of electrophile still had an impact on the reaction yield (Table 4). Interestingly, a large excess of ethyl 4-iodobenzoate did not significantly improve the yield of **8** in the Negishi cross-coupling, whereas the amount of $Zn(OPiv)_2$ greatly influenced the reaction yield. The best results were obtained with 2.2 equiv of $Zn(OPiv)_2$ and 1.2 equiv of the electrophile (Table 4, entry 3).

With these optimized conditions in hand, metalations of various electron-rich substrates were carried out and gave products **9a–k** in yields of 51 to 91% (Table 5). Under these conditions, **4a** was metalated within 24 h at 25 °C. After transmetalation with $Zn(OPiv)_2$ a Negishi cross-coupling

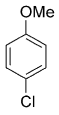
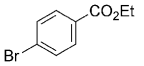
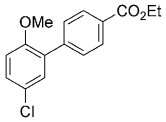
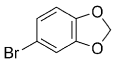
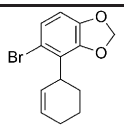
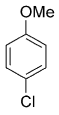
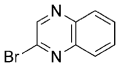
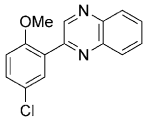
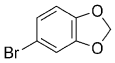
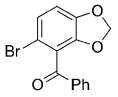
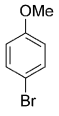
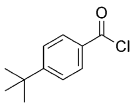
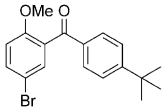
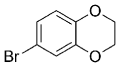
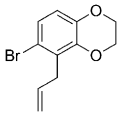
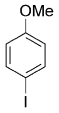
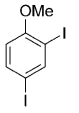
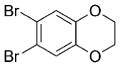
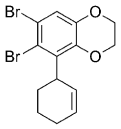
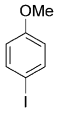
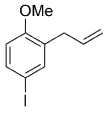
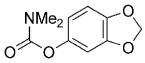
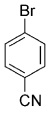
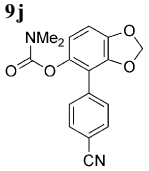
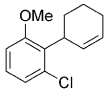
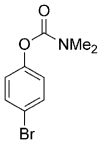
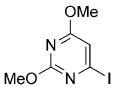
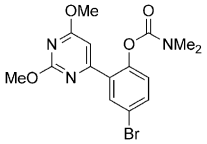
Table 4. Influence of the stoichiometry of $Zn(OPiv)_2$ and the electrophile.



Entry	*n* [equiv]	*x* [equiv]	Yield of **8** [%]
1	1.1	1.2	47
2	1.1	2.4	51
3	2.2	1.2	78
4	2.2	2.4	75

with ethyl 4-bromobenzoate and 2-bromoquinoxaline led to desired products **9a** and **9b** in 71 to 73% yield (Table 5, entries 1 and 2). Similarly, 4-bromoanisole (**4c**) was metalated within 28 h at 25°C and a subsequent CuCN·2LiCl-mediated acylation gave ketone **7c** in 68% (Table 5, entry 3). 4-Iodoanisole (**4i**) was iodolyzed and allylated after alumination to give diiodoarene **9d** and 2-allylated anisole **9e** in 83 to 89% yield (Table 5, entries 4 and 5). Furthermore, 3-chloroanisole (**4e**) was smoothly aluminated and allylated to give anisole derivative **9f** in 77% yield (Table 5, entry 6). Also, dioxygenated substrates were readily metalated by following this procedure. 5-Bromo-1,3-benzodioxole (**4j**) is aluminated within 30 min at 0°C. Subsequent allylation with 3-bromocyclohexene or benzoylation gave expected arenes **9g** and **9h** in 51 to 91% yield (Table 5, entries 7 and 8). Similarly, 6-bromo-2,3-dihydro-1,4-benzodioxine (**4k**) and 6,7-bromo-2,3-dihydro-1,4-benzodioxine (**4l**) were efficiently aluminated at 0°C and readily allylated under CuCN·2LiCl catalysis to give desired functionalized dihydrobenzodioxines **9i** and **9j** in 72 to 80% yield (Table 5, entries 9 and 10). Interestingly, dimethylcarbamate-protected phenols **4m** and **4n**

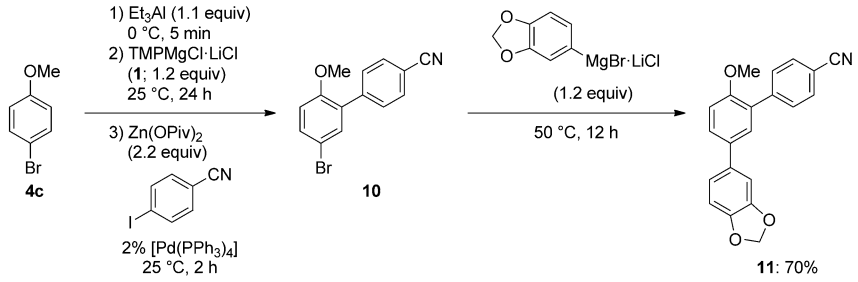
Table 5. Metalation of electron-rich aromatics and reaction with electrophiles (1.2 equiv) after transmetalation with $Zn(OPiv)_2$ (2.2 equiv).

Entry	Substrate	*t* [°C], *T* [h]	Electrophile	Product	Yield[a] [%]	Entry	Substrate	*t* [°C], *T* [h]	Electrophile	Product	Yield[a] [%]
1	 **4a**	25, 24		 **9a**	73[b]	7	 **4j**	0, 0.5		 **9g**	91[e]
2	 **4a**	25, 24		 **9b**	71[b]	8	 **4j**	0, 0.5	PhCOCl	 **9h**	51[e]
3	 **4c**	25, 28		 **9c**	69[c]	9	 **4k**	0, 0.5		 **9i**	80[d]
4	 **4i**	25, 30	I_2	 **9d**	83	10	 **4l**	0, 0.5		 **9j**	72[e]
5	 **4i**	25, 30		 **9e**	89[e]	11	 **4m**	0, 0.5		 **9k**	74[d]
6	 **4e**	25, 1		 **9f**	77[e]	12	 **4n**	0, 2		 **9l**	77[b]

[a] Isolated yield of analytically pure product. [b] Obtained after transmetalation with $Zn(OPiv)_2$ (2.2 equiv) by palladium-catalyzed cross-coupling by using 2% $[Pd(dba)_2]$ and 4% TFP. [c] Obtained after transmetalation with $Zn(OPiv)_2$ (2.2 equiv) by palladium-catalyzed cross-coupling with 2% $[Pd(PPh_3)_4]$. [d] Transmetalation with $Zn(OPiv)_2$ (2.2 equiv) and CuCN·2LiCl (1.1 equiv) was performed. [e] Obtained after transmetalation with $Zn(OPiv)_2$ (2.2 equiv) and allylation catalyzed by 5% CuCN·2LiCl.

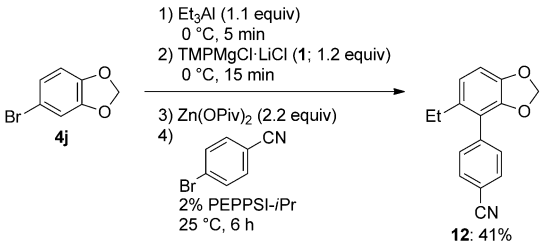
were smoothly aluminated without undergoing anionic *ortho*-Fries rearrangement[23] to give biphenyls **9k** and **9l** in 74 to 77%, respectively, after Pd-catalyzed cross-coupling (Table 5, entries 11 and 12).

Furthermore, selective cross-couplings can be performed. The choice of the Pd catalyst is essential for achieving a chemoselective reaction. Use of 2% $[Pd(PPh_3)_4]$ as the catalyst left the bromo substituent in the *para* position untouched during a cross-coupling with 4-iodobenzonitrile that gave biphenyl **10** at 25°C. On addition of 1.2 equivalents of (3,4-methylenedioxy)phenylmagnesium bromide to the same reaction vessel, a second cross-coupling took place at 50°C to give polyfunctional terphenyl **11** in 70% yield (Scheme 6).



Scheme 6. One-pot preparation of a polyfunctional terphenyl (**11**) through two consecutive selective cross-couplings.

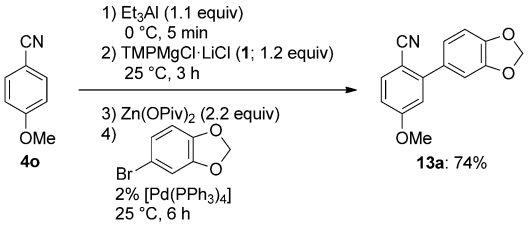
In contrast, use of [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI-*i*Pr)[24] led selectively first to the formation of the desired bromobiphenyl at 25°C, which directly underwent a second cross-coupling with an ethyl group from the aluminum reagent Et_3Al to give alkylated biphenyl **12** in 41% yield (Scheme 7).



Scheme 7. Selective one-pot arylation and alkylation.

This methodology was also applied to arenes with electron-withdrawing groups and heterocycles. 4-Methoxybenzonitrile (**4o**) was readily aluminated at 25°C, and subsequent cross-coupling with 5-bromo-1,3-benzodioxole afforded desired biphenyl **13a** in 74% yield (Scheme 8).

Under the same reaction sequence, alumination of **4o** and transmetalation with $Zn(OPiv)_2$ afforded 2-*z*incated 4-methoxybenzonitrile, which was acylated in the presence of CuCN·2LiCl to give functionalized ketone **13b** in 72% yield (Table 6, entry 1). Similarly, it underwent Pd-catalyzed



Scheme 8. Metalation of 4-methoxybenzonitrile (**4o**).

cross-couplings with ethyl 4-bromobenzoate or 4-bromophenyl dimethylcarbamate to give biphenyls **13c–d** in 67 to 75% yield (Table 6, entries 2 and 3). Isomeric 3-methoxybenzonitrile (**4o**) and ethyl 4-methoxybenzoate (**4p**) were correspondingly metalated and cross-coupled to give highly functionalized biphenyls **13e** and **13f** in 62 to 73% yield (Table 6, entries 4 and 5). Carbamate **4f**, ethyl ester **4q**, and methyl ester **4r** were smoothly aluminated at 0°C and after Pd-catalyzed cross-coupling gave arenes **13g–i** in 65 to 82% yield (Table 6, entries 6–9). This methodology is also applicable to heteroarenes. Benzothiophene (**4s**) was metalated within 1 h at 25°C and underwent Pd-catalyzed cross-coupling after transmetalation with $Zn(OPiv)_2$ with diethyl 4-bromoisophthalate to give 2-arylated benzothiophene **13j** in 74% yield (Table 6, entry 10).

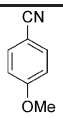
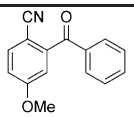
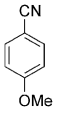
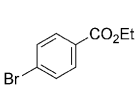
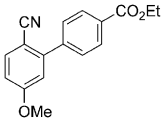
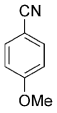
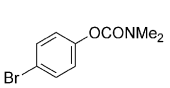
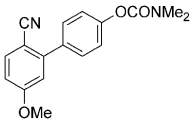
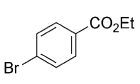
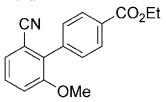
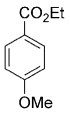
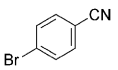
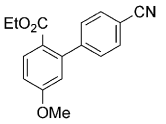
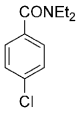
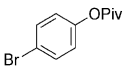
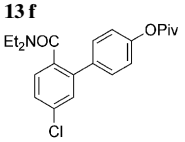
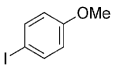
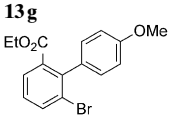
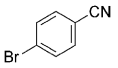
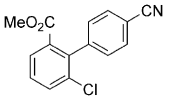
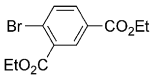
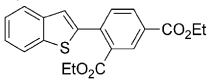
The method can also be extended to the alumination of more electron-rich arenes, such as 2-methoxynaphthalene (**14**), by replacing **1** with $TMP_2Mg{\cdot}2LiCl$ (**2**). In the metalation of **14** with in situ prepared **3**, only low conversions to the corresponding arylaluminate species were obtained. Thus, naphthalene derivative **14** was smoothly metalated by Et_3Al and **2** within 12 h at 25°C. Resulting aluminate **15** undergoes a Pd-catalyzed Negishi cross-coupling or acylation after transmetalation with $Zn(OPiv)_2$ to give desired products **16a** and **16b** in 57 to 62% yield (Scheme 9).

Finally, homocoupling[25] of the aluminate derived from 5-bromo-2,2-difluorobenzo[1,3]dioxole (**17**) proceeded readily in the presence of *p*-chloranil (2.4 equiv, −78°C, 2 h) to afford bis-naphthol **18**, a known precursor for Difluorphos,[26] the electron-deficient analogue of SEGPHOS[27] (Scheme 10).

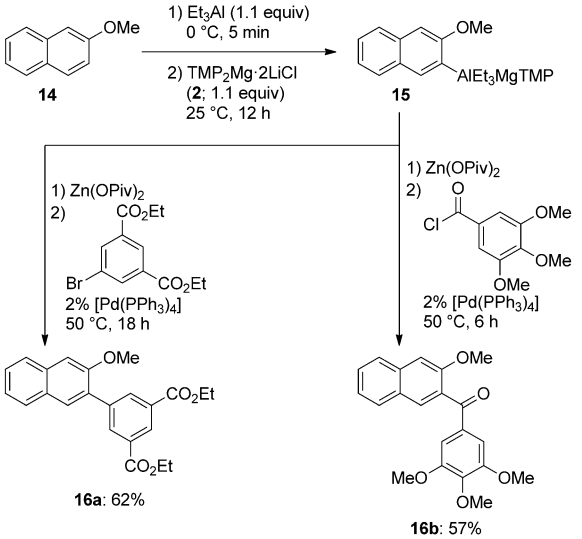
Conclusion

We have reported a new alumination procedure involving the in situ preparation of **3** through sequential addition of Et_3Al and TMPMgCl·LiCl. This method combines chemo- and regioselective metalation with good functional group tolerance and storable reagents, and overcomes the need for

Table 6. Metalation of electron poor substrates and reaction with electrophiles (1.2 equiv) after transmetalation with $Zn(OPiv)_2$ (2.2 equiv).

Entry	Substrate	t [°C], T [h]	Electrophile	Product	Yield[a] [%]
1		25, 3	PhCOCl		72[b]
	4o			**13b**	
2		25, 3			67[c]
	4o			**13c**	
3		25, 3			75[c]
	4o			**13d**	
4		25, 2			62[c]
	4p			**13e**	
5		25, 2			73[c]
	4q			**13f**	
6		0, 3			82[c]
	4f			**13g**	
7		0, 1			65[d]
	4r			**13h**	
8		0, 1			73[c]
	4s			**13i**	
9		25, 1			74[c]
	4t			**13j**	

[a] Isolated yield of analytically pure product. [b] Transmetalation with $Zn(OPiv)_2$ (2.2 equiv) and CuCN·2LiCl (1.1 equiv) was performed. [c] Obtained after transmetalation with $Zn(OPiv)_2$ (2.2 equiv) by palladium-catalyzed cross-coupling with 2% $[Pd(PPh_3)_4]$. [d] Obtained after transmetalation with $Zn(OPiv)_2$ (2.2 equiv) by palladium-catalyzed cross-coupling with 2% $[Pd(dba)_2]$ and 4% TFP.

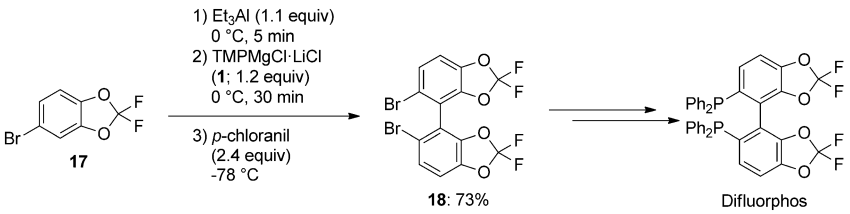


Scheme 9. Metalation of 2-methoxynaphthalene (**14**) by using Et_3Al and **2**.

an excess of base and electrophile. This practical procedure gives access to new organometallics not readily available by halogen/metal-exchange reactions or previously reported metalation procedures by using TMP bases. It allows alumination at a convenient temperature range and provides new efficiently functionalized aromatic building blocks in high yields. Extensions of this method are currently under investigation in our laboratories.

Experimental Section

4-(4-Cyanophenyl)benzo[1,3]dioxol-5-yl dimethylcarbamate (9k): A solution of benzo[1,3]dioxol-5-yl dimethylcarbamate (**4m**; 418 mg, 2.0 mmol) in dry THF (2 mL) was placed in a flame-dried and argon-flushed Schlenk tube equipped with a rubber septum and a magnetic stirring bar and tetradecane (internal standard for GC analysis; 50 μL) was added. The mixture was cooled to and maintained at 0°C, then Et_3Al (251 mg, 2.2 mmol, 1.1 equiv) was added and the mixture was stirred for 10 min. TMPMgCl·LiCl (**1**; 1.2 M in THF, 2.0 mL, 2.4 mmol) was then added dropwise at 0°C and the reaction mixture was stirred for 30 min. Complete metalation was detected by GC analysis of aliquots of the reaction mixture quenched with allyl bromide in the presence of CuCN·2LiCl in dry THF, with tetradecane as the internal standard. The reaction mixture was cooled to −20°C, then $Zn(OPiv)_2$ (1.18 g, 4.4 mmol) was added and the mixture was stirred for 15 min. The mixture was allowed to warm to 25°C, then a solution of $[Pd(PPh_3)_4]$ (46 mg, 2 mol%) in THF (2 mL) was added, followed by 4-bromobenzonitrile (437 mg, 2.4 mmol), and the mixture was stirred for 12 h. The reaction was quenched with a mixture of saturated aqueous NH_4Cl (30 mL) and aqueous HCl (2 M, 10 mL), extracted with diethyl ether (3×50 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated in vacuo. The crude product



Scheme 10. Preparation of a Difluorphos precursor by using in situ prepared **3**.

was purified by column chromatography (eluent: pentane/diethyl ether 2:1) to give **9k** as an off-white solid (460 mg, 74%).

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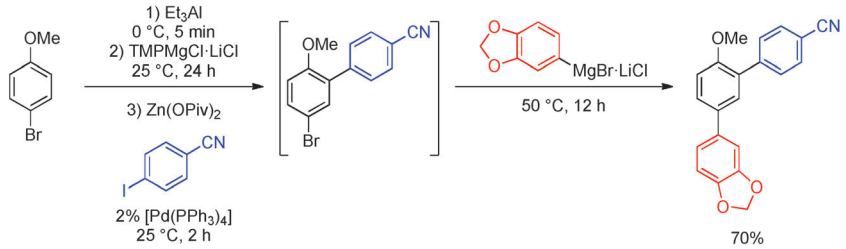

The power of frustration: A wide range of polyfunctional aryltriethylaluminate reagents were prepared at a convenient temperature range (−5 to 25 °C) by in situ preparation of the frustrated Lewis pair Et_3Al–TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidyl). The protocol tolerates a wide range of functional groups and an efficient alumination proceeds without a large excess of base (see scheme).

C–C Coupling

*A. Unsinn, S. H. Wunderlich, A. Jana, K. Karaghiosoff, P. Knochel** ..... ▮▮▮▮–▮▮▮▮

A Convenient Alumination of Functionalized Aromatics by Using the Frustrated Lewis Pair Et_3Al and TMPMgCl·LiCl