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Preparation of functionalized organoaluminiums by direct insertion of aluminium to unsaturated halides

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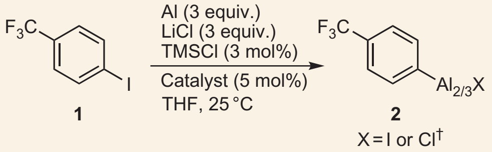
The preparation of polyfunctional organometallics is important in organic synthesis as these reagents are very popular nucleophiles. The preparation of functionalized aluminium reagents by direct insertion of aluminium powder is in general not possible. Such a reaction would be of special importance owing to the low price of aluminium compared with magnesium (it is half the price), the low toxicity of this metal and the chemoselectivity of the resultant organoaluminium reagents. We have now found that by adding catalytic amounts of selected metallic chlorides ($TiCl_4$, $BiCl_3$, $InCl_3$ or $PbCl_2$) in the presence of LiCl, aluminium powder inserts into various unsaturated iodides and bromides under mild conditions. These resulting new organoaluminium reagents undergo smooth Pd-catalysed cross-coupling and acylation reactions, as well as copper-catalysed allylic substitutions, affording various interesting products for pharmaceutical and material science applications.

Organometallic compounds, which are molecules containing a carbon–metal bond, are widely adopted for carbon–carbon bond-forming reactions. The insertion of metals to unsaturated halides is the most straightforward method to prepare aromatic and heteroaromatic organometallics[1]. For example, the preparation of organomagnesium reagents (Grignard reagents) is conducted by adding an organic halide to a suspension of magnesium turnings in a polar nonprotic solvent such as THF or diethyl ether[2]. However, many unsaturated organometallic reagents (for example, from zinc, indium, manganese or aluminium) are difficult to generate from commercial metal powders. The surface layers of the metals mostly consist of hydroxides and oxides (that is, they are passivated), thus making the metal unreactive towards the organic halide. In particular, the highly oxophilic aluminium is passivated very easily[3]. Metal activation is therefore essential for the success of such direct insertions, and several procedures including the use of Rieke-metals[4–6] have been developed[7–9]. However, preparation methods of arylaluminium reagents are scarce[10]. A recent directed alumination[11–14] using an aluminium base allows the generation of arylaluminium compounds by a deprotonation reaction. The transmetallation[15–18] of organolithium and organomagnesium reagents using aluminium salts also provides a convenient route to arylaluminium derivatives.

Although the reaction of metallic aluminium with organic halides has been known since the pioneering work of Hallwachs[19] and Schaferik in 1859 only very few examples of aromatic halides undergo this reaction[20,21]. In recent years, we have shown that several metals such as zinc[22–24], indium[25,26] and magnesium[27,28] can be activated in the presence of stoichiometric amounts of LiCl, which solubilizes and removes the resulting organometallic species from the metal surface, therefore allowing a further insertion to occur on the clean metal surface. Extensions of such an inexpensive activation to aluminium powder would be highly desirable owing to the low toxicity, very low price and potential high chemoselectivity of the organoaluminium reagents[29–32]. Herein, we report a new preparation of various unsaturated organoaluminium reagents by a direct metal insertion in the presence of LiCl and catalytic amounts of selected metallic salts.

Preliminary results showed that aluminium powder did not insert into various organic halides in the presence of LiCl or other lithium salts. We envisaged that additional metallic salts could be beneficial as the preparation of allylic aluminium reagents is accelerated by the addition of $InCl_3$ (refs 33–36). We therefore screened the influence of several additives on the insertion rate of aluminium powder (3 equivalents) in the presence of LiCl (3 equivalents) to a typical

Table 1 | Catalyst screening for the preparation of arylaluminium reagent from aryl iodide*.



1 **2**

X = I or Cl[†]

Entry	Catalyst	Insertion time (h)	Yield (%)[‡]
1	$ZnCl_2$	8	Traces[§]
2	$FeCl_3$	8	Traces[§]
3	$MnCl_2$	8	Traces[§]
4	$ZrCl_4$	8	Traces[§]
5	Cp_2ZrCl_2	8	Traces[§]
6	$HfCl_4$	8	Traces[§]
7	$PbCl_2$	4	77[‖,¶]
8	VCl_4	4	47
9	$NiCl_2$	5	0[#]
10	$InCl_3$	2.5	87
11	$SnCl_2$	8	85
12	$BiCl_3$	4.5	85
13	$TiCl_4$	0.5	62[**]

[*] The reactions were carried out with 1-iodo-4-(trifluoromethyl)benzene (2 mmol) and THF (4 ml). [†] The arylaluminum reagents prepared by oxidative addition of metallic aluminum exist in a complex equilibrium. The sesquihalide structure ($Ar_3Al_2X_3 = ArAl_{2/3}X$, **2**)[3] is one possibility among others; there may also be structures such as $Li[ArAlX_3]$ present in solution. [‡] Yield was determined by iodolysis in THF. [§] Below 3%. [‖] Without activation with TMSCl the yield dropped to 60%. [¶] In the absence of LiCl no insertion was observed. [#] Homodimer was formed quantitatively. [**] More than 20% of homodimer was found.

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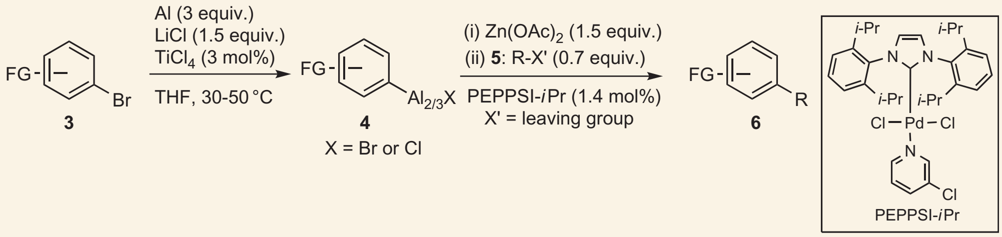
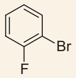
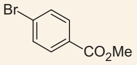
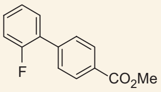
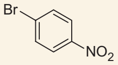
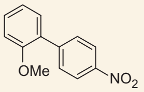
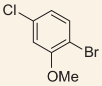
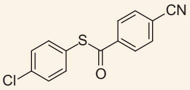
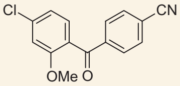
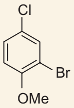
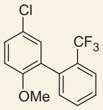
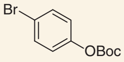
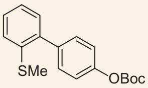
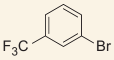
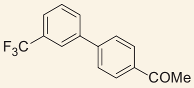
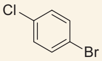
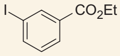
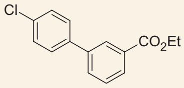
Table 2 | $TiCl_4$-catalysed insertion of aluminium to aryl bromides and subsequent cross coupling reaction.



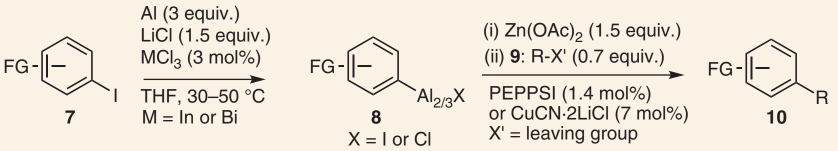
Entry	Substrate	Conditions (Temperature, time)	Electrophile	Product (Yield, %)*
1	 **3a**	30 °C 3.5 h	 **5a**	 **6a** (93)
2	 **3b**	50 °C 20 h	 **5b**	 **6b** (80)
3	 **3c**	50 °C 6 h	 **5c**	 **6c** (70)
4	 **3d**	50 °C 5 h	 **5d**	 **6d** (79)†
5	 **3e**	50 °C 16 h	 **5e**	 **6e** (68)†
6	 **3f**	50 °C 4 h	 **5f**	 **6f** (82)
7	 **3g**	50 °C 14 h	 **5g**	 **6g** (91)†

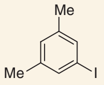
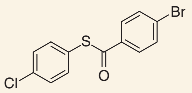
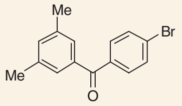
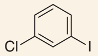
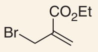
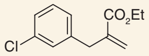
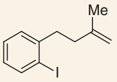
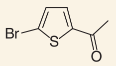
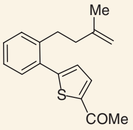
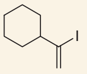
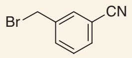
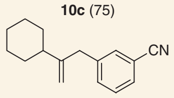
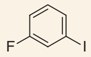
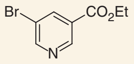
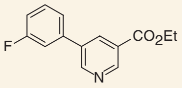
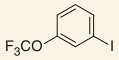
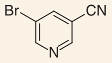
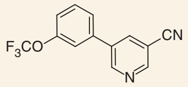
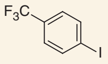
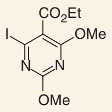
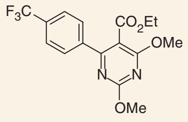
*Isolated yield of analytically pure product (>95% pure). †0.6 equivalents of electrophile used.

substrate like 1-iodo-4-(trifluoromethyl)benzene (**1**) in THF. A number of metallic salts such as $ZnCl_2$, $FeCl_3$, $MnCl_2$, $ZrCl_4$, Cp_2ZrCl_2 and $HfCl_4$ have proved ineffective, affording less than 3% of the desired arylaluminium reagent (**2**) (Table 1, entries 1–6); however, some metal chlorides dramatically accelerated the aluminium insertion (Table 1, entries 7–13). The addition of $PbCl_2$ (5 mol%)[37] along with LiCl led to the desired aluminium reagent **2** in 60% yield after 3 h at 30 °C, whereas no product was obtained in the absence of LiCl. Additional activation of the aluminium suspension in THF with Me_3SiCl (3 mol%)[38–40] yielded **2** in 77% (Table 1, entry 7). The addition of VCl_4 (5 mol%) afforded the desired aluminium reagent **2** at 30 °C in 4 h in 47% yield, but the addition of $NiCl_2$ provided only a homodimer (Table 1, entries 8–9). Interestingly other chlorides such as $InCl_3$ (refs 41–43), $SnCl_2$ and $BiCl_3$ were quite effective and provided **2** in 85–87% yield. In addition, inexpensive $TiCl_4$ (5 mol%) led to the aluminium reagent **2** in 62% yield within 30 min (Table 1, entry 13). In this case, dimerization of **1**, which led to 4,4′-ditrifluoromethylbiphenyl, was responsible for the lower yield.

These preliminary experiments have demonstrated that several additives ($PbCl_2$, VCl_4, $InCl_3$, $SnCl_2$, $BiCl_3$, $TiCl_4$) allow the direct insertion of aluminium powder in the presence of Me_3SiCl (3 mol%) and LiCl (3 equivalents). Further experimentation has shown that the choice of the appropriate additive depends on the structure and the nature of the organic halide. Thus, for the preparation of arylaluminium reagents starting from aryl bromides, the addition of $TiCl_4$ (3 mol%) was found to be optimum. The treatment of 1-bromo-2-fluorobenzene (**3a**) with Al powder (3 equivalents),

Table 3 | $InCl_3$- and $BiCl_3$-catalysed insertion of aluminium to unsaturated iodides and subsequent reaction with electrophiles.



Entry	Substrate	Conditions (Catalyst, temperature, time)	Electrophile	Product (Yield, %)*
1	 **7a**	$InCl_3$ 50 °C 24 h	 **9a**	 **10a** (89)
2	 **7b**	$InCl_3$ 50 °C 3 h	 **9b**	 **10b** (91)
3	 **7c**	$InCl_3$ 50 °C 24 h	 **9c**	 **10c** (75)
4	 **7d**	$InCl_3$ 50 °C 24 h	 **9d**	 **10d** (54)
5	 **7e**	$BiCl_3$ 50 °C 3 h	 **9e**	 **10e** (82)
6	 **7f**	$BiCl_3$ 50 °C 12 h	 **9f**	 **10f** (75)
7	 **1**	$BiCl_3$ 30 °C 4.5 h	 **9g**	 **10g** (73)

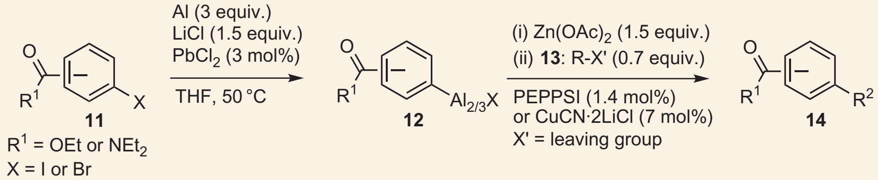
*Isolated yield of analytically pure product (>95% pure).

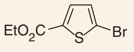
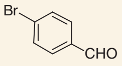
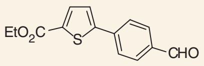
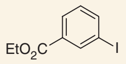
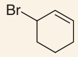
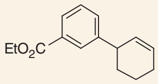
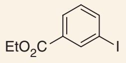
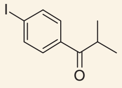
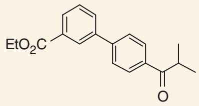
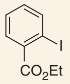
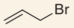
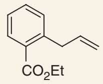
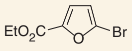
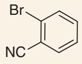
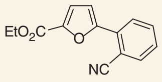
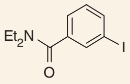
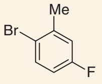
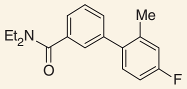
LiCl (1.5 equivalents) and $TiCl_4$ (3 mol%) at 30 °C for 3.5 h furnished the corresponding aluminium reagent (**4a**), which underwent a smooth Pd-catalysed cross-coupling in the presence of $Zn(OAc)_2$ (1.5 equivalents) and PEPPSI-*i*Pr (=[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride; 1.4 mol%)[44,45] with methyl 4-bromobenzoate (**5a**, 0.7 equivalents) leading to the biphenyl ester **6a** in 93% yield (Table 2, entry 1). Remarkably, the intermediate 2-fluoroarylaluminium reagent (**4a**) did not undergo elimination to an aryne under the preparation and cross-coupling conditions.

It is not only electron-poor arylaluminium reagents that can be prepared; electron-rich aryl bromides also reacted smoothly. Aluminium inserted into 1-bromo-2-methoxybenzene (**3b**) at 50 °C within 20 h to give the aluminium reagent **4b**, which was converted to the biphenyl derivative **6b** in 80% yield by a cross-coupling as described above (Table 2, entry 2). Similarly, the 4-chloro-2-bromoanisole (**3c**) was converted to the corresponding organoaluminium reagent (**4c**), which after transmetallation with $Zn(OAc)_2$ (1.5 equivalents) readily underwent a Liebeskind-Srogl[46,47] cross-coupling with the thioester **5c** to afford the functionalized benzophenone derivative **6c** in 70% yield (Table 2, entry 3). Variously substituted aryl bromides such as **3d**–**g**, bearing substituents such as a chloride, trifluoromethyl or thiomethyl group, were readily converted to the intermediate aluminium reagents at 50 °C within 4–16 h. Subsequent transmetallation and highly chemoselective Pd-catalysed cross-coupling with various aryl bromides or iodides bearing a carbonate, an acetyl or an ester furnished the expected polyfunctional biphenyl adducts in 68–91% yield (Table 2, entries 4–7).

In the case of aryl iodides as substrates, $InCl_3$ and $BiCl_3$ were used as additives (3 mol%) and led to the best conversions and yields. Thus, the reaction of 1-iodo-3,5-dimethylbenzene (**7a**) with Al powder (3 equivalents) in the presence of LiCl (1.5

Table 4 | $PbCl_2$-catalysed insertion of aluminium to aryl and heteroaryl halides bearing ester and amide functionalities and subsequent reaction with electrophiles.



Entry	Substrate	Conditions (Temperature, time)	Electrophile	Product (Yield %)*
1	 **11a**	50 °C 6 h	 **13a**	 **14a** (92)
2	 **11b**	50 °C 25 h	 **13b**	 **14b** (88)
3	 **11b**	50 °C 25 h	 **13c**	 **14c** (78)
4	 **11c**	30 °C 4 h	 **13d**	 **14d** (80)
5	 **11d**	50 °C 24 h	 **13e**	 **14e** (83)
6	 **11e**	50 °C 30 h	 **13f**	 **14f** (91)

*Isolated yield of analytically pure product (>95% pure).

equivalents) and $InCl_3$ (3 mol%) afforded the arylaluminium halide **8a** within a 24 h reaction time at 50 °C. After treatment with $Zn(OAc)_2$ (1.5 equivalents), a Pd-catalysed acylation with a bromo-substituted thioester (**9a**, 0.7 equivalents)[48] provided the benzophenone **10a** in 89% yield with excellent chemoselectivity (Table 3, entry 1). A similar reaction of 3-chloro-1-iodobenzene (**7b**) with Al powder (3 equivalents), LiCl (1.5 equivalents) and $InCl_3$ (3 mol%) led to the aluminium organometallic **8b** within 3 h at 50 °C. After the successful transmetallation with $Zn(OAc)_2$ (1.5 equivalents) a copper(I)-catalysed allylation with ethyl (2-bromomethyl)acrylate (**9b**)[49] in the presence of CuCN·2LiCl (ref. 50) at 0 °C furnished the acrylate **10b** in 91% yield after 30 min (Table 3, entry 2). Several functionalized unsaturated substrates (**1**,**7c–f**) including a cycloalkenyl iodide (**7d**) readily underwent an Al insertion with $InCl_3$ or $BiCl_3$ as a catalyst, followed by transmetallation and Pd-catalysed cross-coupling, to generate the desired products **10c–g** in 54–82% yield (Table 3, entries 3–7).

The aluminium insertion in the presence of an ester or an amide functional group did not lead to satisfactory yields with $TiCl_4$, $InCl_3$ or $BiCl_3$. However in the presence of $PbCl_2$ (3 mol%) a smooth insertion proceeds at 50 °C allowing for the first time the direct preparation of ester- or amide-functionalized aryl and heteroarylaluminium halides. Thus, the reaction of 5-bromo-thiophene-2-carboxylic acid ethyl ester (**11a**) with Al powder in the presence of LiCl (1.5 equivalents) and $PbCl_2$ (3 mol%) after 6 h at 50 °C led to the corresponding aluminium reagent (**12a**). A Pd-catalysed cross-coupling with 4-bromobenzaldehyde (**13a**, 0.7 equivalents) produced the 2,5-disubstituted thiophene **14a** in 92% yield after prior transmetallation with $Zn(OAc)_2$ (1.5 equivalents) (Table 4, entry 1). Remarkably, the sensitive formyl functionality was perfectly compatible with the cross-coupling conditions. Ethyl 3-iodobenzoate (**11b**) was also converted to the corresponding aluminium reagent **12b** (50 °C, 25 h). After the preceding transmetallation with $Zn(OAc)_2$ (1.5 equivalents), the copper-catalysed allylation with 3-bromocyclohexene (**13b**, 0.7 equivalents) with catalytic amounts of CuCN·2LiCl (7 mol%) at 0 °C over 30 min generated the allylated product **14b** in 88% yield (Table 4, entry 2). In addition, a Pd-catalysed cross-coupling with 1-(4-iodophenyl)-2-methylpropan-1-one (**13c**, 0.7 equivalents) afforded the biphenyl **14c** in 78%

yield (Table 4, entry 3). Related iodo- and bromo-unsaturated substrates bearing an ester (**11c–d**) or an amide (**11e**) were smoothly converted to the corresponding aluminium reagents. After Cu-catalysed allylation or Pd-catalysed cross-coupling in the presence of $Zn(OAc)_2$ the expected adducts **14d–f** were obtained in 80–91% yield (Table 4, entries 4–6).

The mechanism of aluminium powder activation by the additives MX_n (Table 1) is certainly complex. It seems that the combination of catalytic amounts of MX_n (whose role may be to activate the aluminium by forming new reactive M–Al entities) and stoichiometric amounts of LiCl (whose role is to solubilize the resulting organometallic) results in continuous activation of the aluminium. Interestingly Pb and Bi did not insert into **1** under the standard reaction conditions. Also, the addition of a stoichiometric amount of $PbCl_2$ or low-valent salts like $TiCl_2$ or InCl to **1** did not lead to the formation of an organometallic species.

In summary, we have shown that metallic chlorides such as $TiCl_4$, $InCl_3$, $BiCl_3$ and $PbCl_2$ allow for the first time a convenient generation of functionalized arylaluminium halides, which undergo Pd-catalysed cross-coupling or Cu-catalysed allylations after successful transmetallation with Zn salts. The conversion of aryl bromides to the corresponding arylaluminium halides using Al powder may be of industrial relevance owing to the low price of aluminium and low toxicity of the aluminium hydroxides obtained after aqueous workup. Further studies of the reaction scope and mechanism are currently underway in our laboratories.

Methods

General procedure for aluminium insertion and subsequent cross-coupling: Preparation of 14a. LiCl (127 mg, 3 mmol, 1.5 equivalents) and $PbCl_2$ (17 mg, 0.06 mmol, 3 mol%) were placed in an argon-flushed flask and dried for 10 min at 380 °C (heat gun) on high vacuum (1 mbar). Aluminium powder (162 mg, 6 mmol, 3.0 equivalents) was added under argon and the flask was evacuated and refilled with argon three times. After the addition of THF (1.5 ml), aluminium powder was activated by treatment with Me_3SiCl (2 mol%). Ethyl 5-bromothiophene-2-carboxylate (**11a**, 470 mg, 2 mmol, 1.0 equivalents), along with heptadecane (0.12 ml) as an internal standard, was added in THF (1 ml) at 25 °C and the resulting solution was stirred at 50 °C for 5.5 h. Gas chromatography analysis of hydrolysed reaction aliquots showed full conversion. The organoaluminium solution was separated from the remaining aluminium powder and canulated to an argon-flushed flask containing anhydrous $Zn(OAc)_2$ (556 mg, 3 mmol, 1.5 equivalents). The resulting suspension was stirred for 20 min at 25 °C. 4-bromobenzaldehyde (**13a**, 262 mg, 1.4 mmol, 0.7 equivalents) was added as a solution in THF (2 ml) followed by the addition of PEPPSI-^{i}Pr (19 mg, 0.028 mmol, 1.4 mol%). The reaction mixture was then stirred at 30 °C for 2 h and quenched with saturated NH_4Cl solution (1 ml) and water (2 ml). The aqueous layer was extracted three times with ether. The combined organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (pentane/ether = 4:1) to afford **14a** as a colourless oil (335 mg, 92% yield).

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Author contributions

T.B. and Y.-H.C. contributed equally to this work. Z.P. assisted in conducting and analysing the chemical experiments. P.K. designed and directed the project and wrote the manuscript with contributions from Y.-H.C. and T.B. All authors contributed to discussions.

Additional information

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