Organoaluminum Reagents

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Direct Pd-Catalyzed Cross-Coupling of Functionalized Organoaluminum Reagents**

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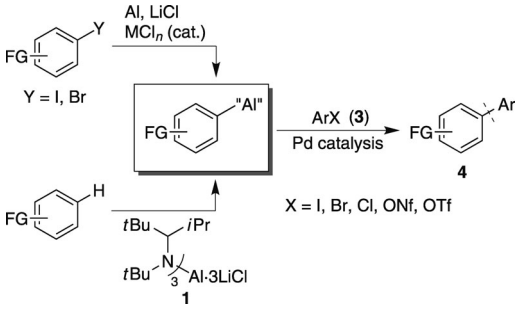
Transition-metal-catalyzed cross-couplings of organic halides with organometallic reagents are among the most important C–C bond-forming reactions in organic synthesis.[1] The great impact of these synthetic transformations was recognized in 2010 with the Nobel Prize in Chemistry awarded to Heck,[2] Suzuki,[3] and Negishi.[4] Because of the low cost and toxicity of aluminum, along with its exceptional chemoselectivity and Lewis acidity,[5] a direct cross-coupling of its organometallic compounds would be important. Whereas B,[6] Zn,[7] Sn,[8] and Mg[9] reagents have been thoroughly elaborated, cross-coupling reactions of organoaluminum compounds are rare, although alkenylalanes were used early on.[4a,b] In general, the cross-coupling of aluminum compounds was restricted to triorganoalanes such as $AlPh_3$[10] and $AlEt_3$,[11] in which case only one organic residue was transferred. However, the coupling of mixed organoalanes like $RAlEt_2$ and $RAl(iBu)_2$ (R = Ar, alkenyl, alkynyl) as well as organoaluminates, for example $RAl(iBu)_3Li$, have been reported recently.[12] In these reactions, the unsaturated R group was always transferred selectively. The cross-coupling of alkyl, vinyl, and allyl groups is also possible by using appropriate amino- and oxygen-containing ligands.[13] Alternatively, the organoalanes had to undergo transmetalation with zinc salts to ensure efficient cross-coupling.[4c–g]

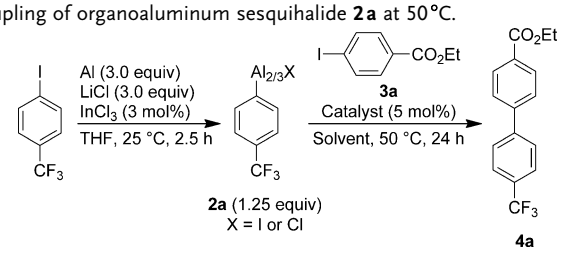
Recently, we reported a new and general preparation of functionalized organoaluminum compounds by direct insertion with Al powder, leading to organoaluminum halides of the type R_2AlX and $RAlX_2$, abbreviated as $RAl_{2/3}X$.[14,15] We have also developed an efficient directed alumination of aromatic and heterocyclic substrates using the hindered aluminum amide $[(tBuCH(iPr))(tBu)]N_3Al{\cdot}3\,LiCl$ (**1**; Scheme 1).[16] These Al reagents were reluctant to undergo directly C–C bond formation and a transmetalation to the corresponding zinc species was always required for cross-coupling. Herein, we report a new practical, direct procedure for the cross-coupling of these aluminum reagents with various unsaturated halides and pseudohalides.

Preliminary experiments for the direct cross-coupling of the organoaluminum sesquihalide **2a**[14a] were conducted using PEPPSI-*i*Pr[17] as the catalyst in THF/NMP (2:1)[18] at 50 °C; in the absence of a zinc salt biphenyl **4a** was obtained in



Scheme 1. Direct cross-coupling of organoaluminum reagents obtained by Al insertion or directed alumination. FG = functional group, Nf = nonaflate, Tf = triflate.

Table 1: Screening of catalysts and solvent systems for the direct cross-coupling of organoaluminum sesquihalide **2a** at 50 °C.



Entry	Catalyst	Solvent[a]	Conversion [%] (Yield [%])[b]
1	PEPPSI-*i*Pr	A	16 (9)
2	$Pd(OAc)_2 + PCy_3$	A	12 (10)
3	$[Pd(PPh_3)_2Cl_2]$	A	11 (8)
4	$[Pd(PPh_3)_4]$	A	25 (21)
5	$Pd(OAc)_2$ + S-Phos	A	49 (10)
6	$[Pd(dba)_2]$ + RuPhos	A	72 (48)
7	$PdCl_2 + iPr{\cdot}HCl$	A	100 (25)
8	$[Pd(PhCN)_2Cl_2]$	A	100 (20)
9	$[Pd(tmpp)_2Cl_2]$	A	100 (69)[c]
10	$[Pd(tmpp)_2Cl_2]$	B	100 (71)
11	$[Pd(tmpp)_2Cl_2]$	C	100 (79)
12	$[Pd(tmpp)_2Cl_2]$	D	64 (61)
13	$[Pd(tmpp)_2Cl_2]$	E	81 (73)
14	$[Pd(tmpp)_2Cl_2]$	F	100 (89, 83[d])

[a] Solvents systems: A: THF/NMP (2:1); B: THF/NMP (1:1); C: THF/NMP (1:2), D: THF/NEP (1:2); E: THF/DMPU (1:2); F: THF/DMF (1:2). DMF = *N*,*N*-dimethylformamide, DMPU = *N*,*N*′-dimethylpropyleneurea, NEP = *N*-ethyl-2-pyrrolidone, NMP = *N*-methyl-2-pyrrolidone, THF = tetrahydrofuran. [b] Conversion of electrophile and GC yield were determined by GC analysis with tetradecane as the internal standard. [c] After 6 h at 50 °C more than 95% conversion of the electrophile was achieved. [d] Yield of isolated product after 2 h at 50 °C.

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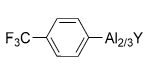
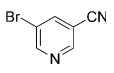
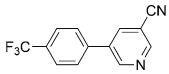
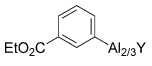
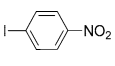
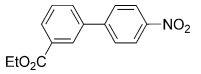
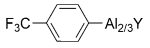
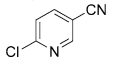
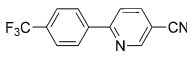
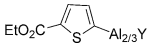
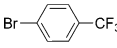
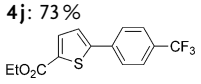
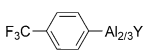
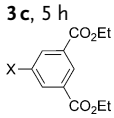
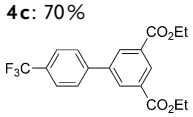
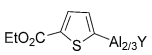
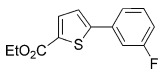
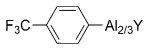
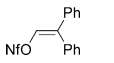
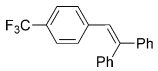
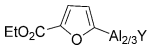
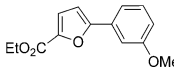
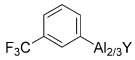
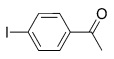
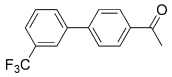
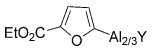
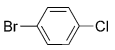
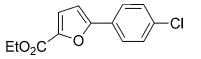
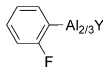
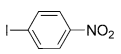
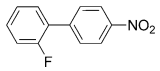
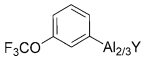
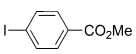
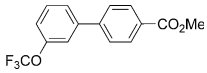
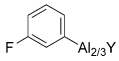
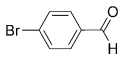
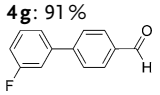
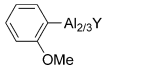
Table 2: Direct cross-coupling of arylaluminum sesquihalides of type **2** (1.25 equiv) with various electrophiles **3** in the presence of $[Pd(tmpp)_2Cl_2]$ (3 mol%) in THF/DMF (1:2) at 50°C.

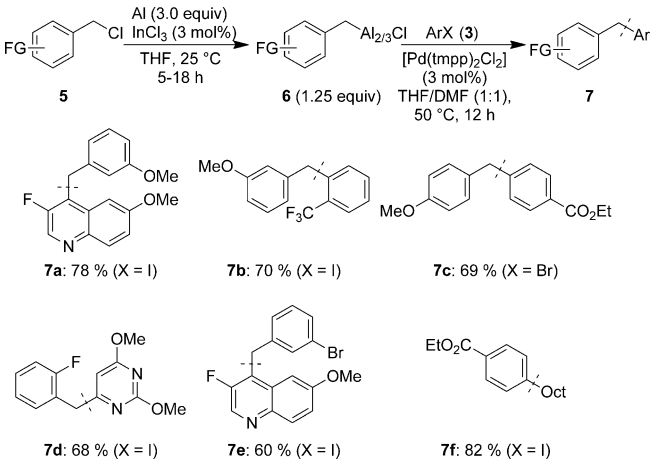
Entry	Nucleophile	Electrophile, Reaction time	Product Yield[a]	Entry	Nucleophile	Electrophile, Reaction time	Product Yield[a]
							
1	**2a** 	**3b**, 6 h 	**4b**: 96% 	9	**2f** 	**3g**, 2 h 	**4j**: 73% 
2	**2a** 	**3c**, 5 h 	**4c**: 70% 	10	**2g** 	**3j**, 6 h 	**4k**: 89% 
3	**2a** 	**3d** (X = ONf), **3d′** (X = OTf), 4 h 	**4d**: 93% (X = ONf), 84% (X = OTf) 	11	**2g** 	**3k**, 6 h 	**4l**: 86% 
4	**2a** 	**3e**, 6 h 	**4e**: 76% 	12	**2h** 	**3l**, 2 h 	**4m**: 91% 
5	**2b** 	**3f**, 2 h 	**4f**: 86% 	13	**2h** 	**3m**, 5 h 	**4n**: 65% 
6	**2c** 	**3g**, 3 h 	**4g**: 91% 	14	**2i** 	**3n**, 6 h	**4o**: 72%
7	**2d**	**3h**, 3 h	**4h**: 62%[b]	15	**2j**	**3o**, 1 h	**4p**: 78%
8	**2e**	**3i**, 2 h	**4i**: 96%	16	**2k**	**3p**, 8 h	**4q**: 74%
				17	**2l**	**3q**, 6 h	**4r**: 63%

[a] Yield of isolated, analytically pure product. [b] 1.43 equiv of nucleophile was used.

only 9% yield (Table 1, entry 1). Other catalyst systems such as $Pd(OAc)_2$ and PCy_3, which was used for the coupling of $ArAlEt_2(THF)$,[12d] gave only a low conversion of 12% (Table 1, entry 2). Similarly, the preformed Pd catalysts $[Pd(PPh_3)_2Cl_2]$ and $[Pd(PPh_3)_4]$ provided unsatisfactory results (Table 1, entries 3 and 4). The use of Buchwald's phosphine ligands S-Phos and RuPhos[19] with various palladium salts also resulted in incomplete cross-coupling (Table 1, entries 5 and 6). Although, the NHC precursor (N-heterocyclic carbene), *i*Pr·HCl,[20] and $[Pd(PhCN)_2Cl_2]$ led to complete conversion, product **4a** formed in only 20–25% yield because of several side reactions (e.g. homo-coupling, reduction; Table 1, entries 7 and 8). In contrast, the complex $[Pd(tmpp)_2Cl_2]$[21] gave full conversion of ethyl 4-iodobenzoate (**3a**) after 6 h at 50°C and the biphenyl **4a** was obtained in 69% yield (Table 1, entry 9).[22] After further optimization by increasing the proportion of NMP (Table 1, entries 10 and 11) and testing several other polar cosolvents (NEP, DMPU, DMF; Table 1, entries 12–14), we determined the best solvent system, THF/DMF (1:2), which provided after 2 h at 50°C the desired product **4a** in 89% GC yield and 83% yield of isolated product (Table 1, entry 14).[23]

To estimate the scope of this catalyst system, we performed the cross-coupling of **2a** with heteroaryl bromide **3b** and chloride **3c** (Table 2, entries 1 and 2). To our delight, these reactions gave the corresponding cyanopyridine derivatives **4b** and **4c** in respective yields of 96 and 70%. Extension to the cross-coupling with aryl nonaflate **3d** and aryl triflate **3d′** afforded biphenyl **4d** in respective yields of 93 and 84% (Table 2, entry 3). Interestingly, also an alkenyl nonaflate[24] reacted within 6 h to give the styrene derivative **4e** in a yield of 76% (Table 2, entry 4).

Moreover, the aluminum reagent **2b** (1.25 equiv), prepared by a $TiCl_4$-catalyzed (3 mol%) Al insertion in the presence of LiCl,[14a,25] underwent a cross-coupling with the sensitive aryl iodide **3f** bearing a relative acidic acetyl group to afford the expected product **4f** in 86% yield (Table 2, entry 5). Also, the *o*-fluorophenylaluminum sesquihalide **2c**

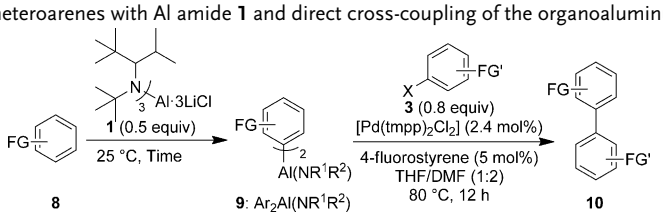


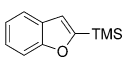
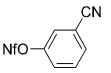
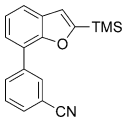
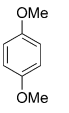
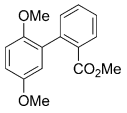
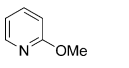
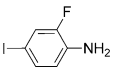
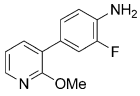
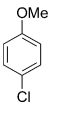
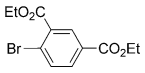
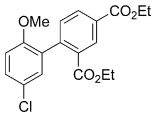
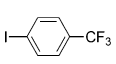
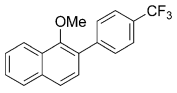
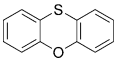
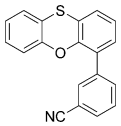
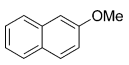
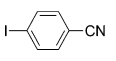
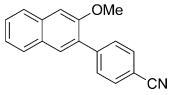
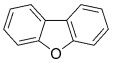
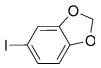
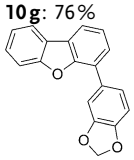
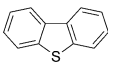
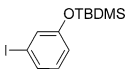
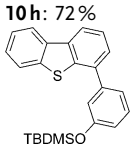
Scheme 2. Pd-catalyzed cross-coupling of benzylic (and alkyl) aluminum reagents **6** with unsaturated halides **3**.

underwent an efficient cross-coupling with the nitro-substituted electrophile **3g** to give **4g** in 91% yield (Table 2, entry 6). The high functional-group tolerance of the cross-coupling is also shown in the reaction of **2d** with the sensitive 4-bromobenzaldehyde (**3h**) which provided biphenyl **4h** in 62% yield (Table 2, entry 7). Aryl and heteroaryl aluminum reagents **2e–h** bearing an ester group, readily prepared by Al insertion in the presence of LiCl using 3 mol% $PbCl_2$,[14a,25] reacted smoothly with various aryl iodides, bromides, and nonaflates (50 °C, 2–6 h) leading to the cross-coupling products **4i–n** (65–96% yield; Table 2, entries 8–13). Furthermore, electron-rich Al reagents **2i–l** (obtained by Al insertion with 3 mol% $InCl_3$ or $TiCl_4$)[25] also underwent cross-coupling, providing the polyfunctional products **4o–r** in 63–78% yield (Table 2, entries 14–17).

Benzylic aluminum sesquichlorides of type **6** (1.25 equiv), prepared by Al insertion (in the presence of 3 mol% $InCl_3$) into the corresponding benzylic chlorides **5**,[14d,25] similarly underwent cross-coupling with various aryl and heteroaryl iodides and bromides to give the expected products **7a–e** (Scheme 2).[26] Interestingly, Oct-$Al_{2/3}X$ obtained by Al insertion (3.0 equiv LiCl, 3 mol% $InCl_3$, THF, 50 °C, 2.5 h, 81% yield)[25] also underwent cross-coupling with ethyl 4-iodobenzoate (**3a**) to furnish product **7f** in 82% yield (Scheme 2).

Table 3: Alumination of arenes and heteroarenes with Al amide **1** and direct cross-coupling of the organoaluminum reagents **9** using $[Pd(tmpp)_2Cl_2]$.



Entry	Substrate, Reaction time	Electrophile	Product Yield[a]	Entry	Substrate, Reaction time	Electrophile	Product Yield[a]
							
1	**8a**, 1 h	**3r**	**10a**: 71%	5	**8e**, 1 h	**3u**	**10e**: 74%
							
2	**8b**, 0.5 h	**3s**	**10b**: 73%	6	**8f**, 1 h	**3v**	**10f**: 86%
							
3	**8c**, 12 h[b]	**3t**	**10c**: 89%	7	**8g**, 1 h	**3i**	**10g**: 76%
							
4	**8d**, 1 h	**3o**	**10d**: 88%	8	**8h**, 1 h	**3w**	**10h**: 72%
							
				9	**8i**, 2 h	**3x**	**10i**: 63%

[a] Yield of isolated, analytically pure product. [b] 1.25 equiv of aluminum base **1** was used for the metalation.

Recently, we have reported a directed alumination of arenes and heteroarenes (Ar-H) using 1.0 equiv of the new, hindered Al base [(*t*BuCH(*i*Pr))(*t*Bu)]N_3Al•3 LiCl (**1**, hereafter abbreviated as $(R^1R^2N)_3Al$) with an unique regioselectivity.[16] This metalation provides Al reagents of the type Ar-Al$(NR^1R^2)_2$. Although these organometallics undergo Pd-catalyzed cross-couplings, a transmetalation with $ZnCl_2$ (1.1 equiv) was required for achieving good cross-coupling yields, also two equivalents of HNR^1R^2 were wasted. We have considerably improved the atom economy of this reaction, as the alumination of unsaturated substrates **8** with only 0.5 equiv $(R^1R^2N)_3Al$ (**1**) proceeds equally well at 25 °C within 0.5–2 h to provide bis(organo)aluminum amides of type **9** ($Ar_2Al(NR^1R^2)$, Table 3). Moreover, these Al reagents smoothly reacted by direct cross-coupling in the presence of 2.4 mol % $[Pd(tmpp)_2Cl_2]$ at 80 °C for 12 h; 5 mol % 4-fluorostyrene served as the cocatalyst to promote the reductive elimination.[27]

Using those modified conditions, the 2-silylated benzofuran **8a** was metalated rapidly with Al amide **1** (0.5 equiv) and the resulting bis(organo)alane was then cross-coupled with the aryl nonaflate **3r** (80 °C, 12 h) to give the heterocycle **10a** in 71 % yield (Table 3, entry 1). Remarkably, a free NH_2 group is readily tolerated in these cross-couplings. Alumination of 2-methoxypyridine (**8b**) using base **1** (0.5 equiv, 25 °C, 0.5 h) followed by cross-coupling with the iodoaniline **3s** (0.8 equiv) provided the biphenyl **10b** in 73 % yield (Table 3, entry 2). No useful, regioselective metalation of 1-methoxynaphthalene (**8c**) in the 2-position has been reported so far;[12f,28] however, when the Al amide **1** (1.25 equiv, 25 °C, 12 h)[29] was used, a smooth alumination occured selectively at this position. The subsequent cross-coupling with aryl iodide **3t** gave the naphthalene **10c** in 89 % yield (Table 3, entry 3). The alumination of 2-methoxynaphthalene (**8d**) with amide **1** is equally selective and the 2,3-disubstituted naphthalene **10d** was obtained after direct cross-coupling with 4-iodobenzonitrile (**3o**) in 88 % yield (Table 3, entry 4). Other anisole derivatives such as 1,4-dimethoxybenzene (**8e**) and 4-chloroanisole (**8f**) are rapidly metalated and subsequent cross-coupling with iodide **3u** or bromide **3v** gave the products **10e** and **10f** in yields of 74 and 86 %, respectively (Table 3, entries 5 and 6). Alumination of phenoxathiine (**8g**) with the Al base **1** (0.5 equiv) occurs *ortho* to oxygen and after cross-coupling the heterocycle **10g** was obtained in 76 % yield (Table 3, entry 7). Furthermore, dibenzofuran (**8h**) and dibenzothiophene (**8i**) were used after alumination in the direct cross-coupling with iodides **3w** and **3x** leading to the arenes **10h** and **10i** in respective yields 72 and 63 % (Table 3, entries 8 and 9).

In summary, we have reported a new efficient, direct cross-coupling of functionalized organoaluminum reagents without the need for a transmetalation. This methodology allows a practical C–C bond formation starting from organoaluminum sesquihalides of type **2**, obtained by an Al insertion, or using bis(organo)aluminum amides **9**, prepared by a directed alumination with 0.5 equiv of the sterically hindered Al base **1**. We have shown that aryl and heteroaryl iodides, bromides, and nonaflates, and in special cases chlorides and triflates, are good electrophiles for such cross-couplings and that free NH_2 groups, aldehydes, ketones, esters and nitro functions are well tolerated.

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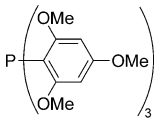
[21] tmpp = tris(2,4,6-trimethoxyphenyl)phosphine;



tmpp

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[22] We also tried the tmpp ligand with several other Pd, Ni and Fe salts (see the Supporting Information).

[23] In a further reaction, we found that with these conditions all three phenyl groups of $AlPh_3 \cdot 3\,LiCl$ can be transferred (see the Supporting Information).

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[25] See the Supporting Information.

[26] As the benzylaluminum sesquihalides are prepared as a 0.5 M solution in THF, we used a 1:1 mixture of THF/DMF instead of 1:2 to prevent further dilution.

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[29] In this case, 1.25 equiv of Al amide **1** was needed to achieve full conversion for the metalation.

