

New Preparation of Benzylic Aluminum and Zinc Organometallics by Direct Insertion of Aluminum Powder

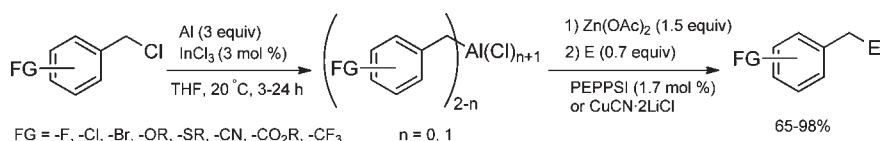
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ABSTRACT



The reaction of commercial Al-powder (3 equiv) and InCl₃ (1–5 mol %) with benzylic chlorides provides various functionalized benzylic aluminum sesquichlorides under mild conditions (THF, 20 °C, 3–24 h) without homocoupling (<5%). These new benzylic organometallics reacted smoothly with various electrophiles (Pd-catalyzed cross-couplings, or Cu-mediated acylations, allylations, or 1,4-addition reactions). Electron-poor benzylic chlorides or substrates prone to Wurtz coupling can be converted to benzylic zinc compounds by the reaction of Al-powder in the presence of ZnCl₂.

Benzylic organometallics are important intermediates in organic synthesis. They can be used to build up diaryl-methanes present in many natural products or pharmacologically active compounds.¹ Several methods are available for the preparation of benzylic organometallics.² Whereas benzylic lithium and magnesium organometallics do not

tolerate functional groups, benzylic zinc organometallics are compatible with numerous functionalities and are readily prepared by direct insertion of zinc dust in the presence of LiCl.² Like zinc, aluminum is also a cheap metal with low toxicity. By comparing the electronegativities of the metals (Mg, 1.32; Al, 1.61; Zn, 1.65)³ we anticipated that benzylic aluminum organometallics could also tolerate a number of functional groups.⁴ Generally, the preparation of organoaluminums from metal powder is difficult and requires a proper activation of the metal surface.^{4a,5} Reports on the reaction of aluminum powder with benzylic chlorides are scarce.^{4a,6} Recently, we found

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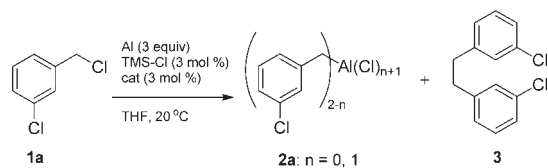
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that aluminum powder inserts readily into aromatic halides in the presence of LiCl and catalytic amounts of PbCl₂, InCl₃, TiCl₄, or BiCl₃.⁷ Inspired by these results, we have developed a general method for the preparation of benzylic aluminum reagents. Herein we report a mild synthesis of functionalized benzylic organoaluminums by the reaction of benzylic chlorides with Al-powder in the presence of InCl₃ (1–5 mol %) as well as their reactivity with various catalysts.

In preliminary experiments, 3-chlorobenzyl chloride (**1a**) was treated with Al-powder (3.0 equiv) and different metal salt additives (Table 1). No reaction was observed in the absence of the metal salts (Table 1, entry 1), whereas the addition of PbCl₂ (3 mol %) or BiCl₃ (3 mol %) lead to the formation of the 3-chlorobenzylaluminum reagent⁸ **2a** in 20% and 64% yield along with the homodimer **3** (entries 2 and 3).⁹

Table 1. Catalyst Screening for the Preparation of Benzylic Organoaluminums



entry	catalyst	time [h] ^a	yield [%] (2a) ^b	yield [%] (3) ^b
1	–	24	n.r. ^c	n.r. ^c
2	PbCl ₂	22	20	5
3	BiCl ₃	12	64	36
4	InCl ₃	3.5	90	0
5	TiCl ₄	24	n.r. ^c	n.r. ^c

^a Reaction time at 20 °C. ^b The yield was determined by iodolysis of reaction aliquots and subsequent GC analysis. ^c No reaction took place.

InCl₃ proved to be the best choice, and 3-chlorobenzyl chloride reacted with Al (3.0 equiv) in the presence of TMS-Cl (3 mol %)¹⁰ and InCl₃ (3 mol %) within 3.5 h at 20 °C furnishing the aluminum reagent **2a** in 90% yield without the formation of **3** (entry 4). Interestingly no reaction was observed when TiCl₄ was used as a catalyst although it is an effective additive for the preparation of arylaluminums (entry 5).⁷

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(8) An almost 1:1 mixture of RAlCl₂ and R₂AlCl is obtained as shown by NMR spectroscopy (see Supporting Information).

(9) The yield was determined by iodolysis of reaction aliquots and subsequent GC analysis. The use of LiCl leads to dimerization in almost quantitative yield.

(10) For the metal surface activation with TMS-Cl, see also: Takai, K.; Ueda, T.; Hayashi, T.; Moriwake, T. *Tetrahedron Lett.* **1996**, *37*, 7049.

The resulting benzylic reagent **2a** underwent a smooth Pd-catalyzed cross-coupling reaction¹¹ in the presence of Zn(OAc)₂ (1.5 equiv) and PEPPSI-*i*Pr (1.7 mol %)¹² with ethyl 3-iodobenzoate (**4a**, 0.7 equiv) furnishing the functionalized diarylmethane **5a** in 89% yield (Table 2, entry 1).¹³ Using the same conditions, 2-bromobenzyl chloride (**1b**) afforded the corresponding aluminum reagent (3 h, 20 °C) which reacted well with 4-chlorobenzoyl chloride (**2b**, 0.7 equiv) after transmetalation with Zn(OAc)₂ (1.5 equiv) and addition of CuCN·2LiCl, 20 mol %.¹⁴ The expected ketone **5b** was obtained in 83% yield (entry 2). Several fluorine-substituted benzylic chlorides (**1c–f**) could be readily converted to the aluminum reagents (20 °C, 6–24 h) and reacted with various unsaturated halides in Pd-catalyzed cross-couplings (Zn(OAc)₂ (1.5 equiv); PEPPSI-*i*Pr (1.7 mol %)) giving the functionalized diarylmethanes **5c–f** in 71–98% yields (entries 3–6). Besides electron-deficient benzylic chlorides, also electron-rich chlorides such as 4-methoxybenzyl chloride (**1g**) or 3-methoxybenzyl chloride (**1h**) reacted with Al-powder (3.0 equiv) in the presence of InCl₃ (3 mol %) within 5–12 h at 20 °C providing the expected intermediate aluminum reagents. Transmetalation with Zn(OAc)₂ (1.5 equiv) and subsequent cross-coupling reactions produced the diarylmethanes **5g–h** in 78% and 82% yields (entries 7, 8). Even 3,4,5-trimethoxybenzyl chloride (**1i**) or the thiomethyl substituted benzyl chloride **1j** could be readily used in this procedure, and after a Cu(I)-mediated allylation reaction (Zn(OAc)₂ (1.5 equiv), CuCN·2LiCl, –30 °C, 20 mol %) with ethyl (2-bromomethyl)acrylate¹⁵ (**4i**, 0.7 equiv) or 3-bromocyclohexene (**4j**, 0.7 equiv) the functionalized alkenes **5i** and **5j** were isolated in 75% and 92% yields (entries 9, 10).

In the case of benzylic chlorides bearing an ester or nitrile functionality, as well as secondary benzylic systems, the experimental procedure had to be modified. Although these benzylic chlorides reacted with Al-powder in the presence of InCl₃, the reaction resulted in low yields of the aluminum reagent, or dimerization. Nevertheless, the addition of ZnCl₂ proved to be beneficial.¹⁶ Thus,

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(13) In the absence of stoichiometric amounts of Zn(OAc)₂ almost no cross-coupling was observed. Both the acetate anion and the zinc cation seem to be important. We speculate that the acetate anion is reducing the Lewis acidity of the aluminum species whereas the zinc cation favors the transfer of the aryl group to palladium.

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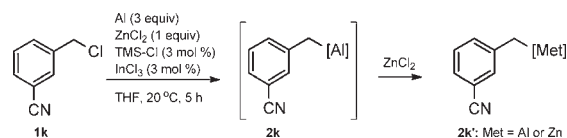
Table 2. InCl₃ Catalyzed Aluminum Insertion into Functionalized Benzyl Chlorides and Reaction with Various Electrophiles

entry	benzyl chloride	time ^a	electrophile ^b	product ^c
1		3.5		 5a: 89%
2		3		 5b: 83% ^d
3		22		 5c: 98%
4		6		 5d: 71%
5		6		 5e: 74%
6		24		 5f: 89%
7		5		 5g: 78%
8		12		 5h: 82%
9		7		 5i: 75% ^d
10		3		 5j: 92% ^d

^a Insertion time at 20 °C. ^b 0.7 equiv of electrophile was used; Cross-coupling conditions: PEPPSI-*i*Pr (1.7 mol %), THF/NMP (1:1), 50 °C, 2 h. ^c Isolated yields. ^d CuCN·2LiCl (20 mol %) was added.

3-cyanobenzyl chloride (**1k**) reacted with Al-powder (3.0 equiv), InCl₃ (3 mol %), and ZnCl₂ (1.0 equiv) within 5 h forming a mixture of the functionalized zinc

Scheme 1. *in Situ* Trapping of Aluminum Reagents with ZnCl₂



and aluminum reagent **2k'** (Scheme 1). This has been varied by ¹H, ¹³C, and ²⁷Al NMR studies (see Supporting Information).

This benzylic organometallic was allylated with ethyl (2-bromomethyl)acrylate¹⁵ (**4i**, 0.7 equiv) yielding the ester derivative **5k** in 93% yield (Table 3, entry 1). Interestingly, a cyano group in the *para* position is also compatible with these reaction conditions and 4-cyanobenzyl chloride (**1l**) is converted to the expected organometallic which reacted with *S*-4-fluorophenyl benzenesulfonylthioate (**4l**, 0.7 equiv) forming the thioether **5l** in 74% yield (entry 2).

In the case of ester substituted benzylic chlorides (**1m–n**) the Al/ZnCl₂ method produced the expected benzylic organometallics which could be cross-coupled or allylated affording the functionalized ester derivatives (**5m–n**) in 83% and 75% yield (entries 3, 4). Piperonyl moieties are found in many pharmacologically active substances.¹⁷ Thus, the reaction of 5-chloro-6-(chloromethyl)benzo-*d*[[1,3]dioxole (**1o**) with Al-powder and InCl₃ was performed (20 °C, 10 h). Without the presence of ZnCl₂ the Wurtz-coupling product is formed almost quantitatively. However the use of a stoichiometric amount of ZnCl₂ allowed the formation of the intermediate organometallic within 8 h at 20 °C, and after a Cu(I)-mediated 1,4-addition with cyclohexenone (**4o**) in the presence of TMS-Cl (2.5 equiv), the ketone **5o** was isolated in 68% yield (entry 5).¹⁸ Secondary benzylic chlorides like **1p** or **1q** were also prone to dimerization during the insertion conditions, but the use of ZnCl₂ prevented the dimerization and within 22 h full conversion to the benzylic reagents was readily achieved. Quenching with ethyl (2-bromomethyl)acrylate¹⁵ (**4i**, 0.7 equiv) or *S*-methyl benzenesulfonylthioate (**4q**, 0.7 equiv) afforded the ester **5p** and the thioether **5q** in 76% and 65% yields (entries 6, 7).

Remarkably, using the same conditions it was also possible to generate benzylic bimetallic compounds. Only a few preparative methods of bimetallic species of this type are known. Usually high dilution (< 0.1 M) and dropwise addition of the benzylic substrate are needed to achieve a good yield of the organometallic.¹⁹ However, 1,2-bis(chloromethyl)benzene **1r** reacted readily with Al (3.0 equiv), InCl₃ (3 mol %), and ZnCl₂ (2.2 equiv) within

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Table 3. InCl₃ Catalyzed Aluminum Insertion into Functionalized Benzyl Chlorides and Subsequent Trapping with ZnCl₂ and Various Electrophiles

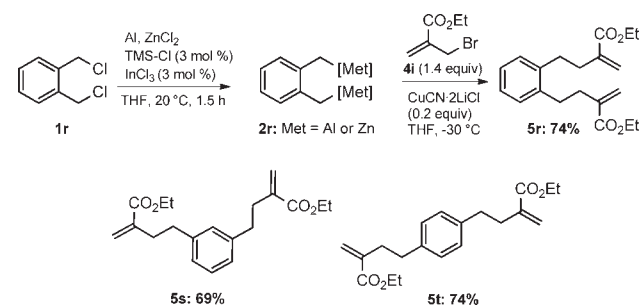
entry	benzyl chloride	time ^a	electrophile ^b	product ^c
1		5		
	1k		4i	5k: 93%^d
2		5		
	1l		4l	5l: 74%
3		10		
	1m		4m	5m: 83%
4		10		
	1n		4i	5n: 75%^d
5		8		
	1o		4o	5o: 68%^e
6		22		
	1p		4i	5p: 76%^d
7		22		
	1q		4q	5q: 65%

^a Insertion time at 20 °C. ^b 0.7 equiv of electrophile was used; Cross-coupling conditions: PEPPSI-*i*Pr (1.7 mol %), THF/NMP (1:1), 50 °C, 2 h. ^c Isolated yield. ^d CuCN·2LiCl (20 mol %) was used. ^e CuCN·2LiCl (1.0 equiv) and TMS-Cl (2.5 equiv) were used.

1.5 h at 20 °C (THF, 0.5 M) generating the bimetallic **2r** without the need for dropwise addition (Scheme 2).

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Scheme 2. Preparation of a Bimetallic and Subsequent Reaction with an Electrophile



Subsequent reaction with ethyl (2-bromomethyl)acrylate¹⁵ (**4i**, 0.7 equiv) furnished the bis-functionalized benzene derivative **5r** in 74% yield (Scheme 2). The substitution pattern is not important as 1,3- and 1,4-bis-(chloromethyl)-benzene reacted equally leading to **5s** and **5t** in 69% and 74% yields (Scheme 2).²⁰

In summary we have reported a mild and general method for the preparation of benzylic aluminum sesquichlorides starting from benzylic chlorides using commercially available aluminum powder and catalytic amounts of InCl₃. The aluminum reagents are obtained in good yields without formation of homocoupling byproducts. In the case of secondary benzylic chlorides or electron-poor benzylic substrates being prone to Wurtz coupling, the use of Al/ZnCl₂ for the insertion reaction proved to be advantageous. Extensions of this work are currently underway in our laboratories.

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Supporting Information Available. Experimental details and full spectroscopic data for all new compounds is given in the Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(20) We tried a number of metals in this reaction (Mg, Zn, In, and Al) under the same reaction conditions, and the best results were observed with Al, InCl₃, and ZnCl₂.