## Aluminum Reagents

## Diastereoselective Synthesis of Homoallylic Alcohols with Adjacent Tertiary and Quaternary Centers by Using Functionalized Allylic Aluminum Reagents\*\*

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Addition reactions of nucleophiles to carbonyl compounds are excellent ways of generating quaternary centers in a diastereoselective manner.<sup>[1]</sup> Especially the addition of allylic organometallic compounds to aldehydes or ketones proceeds with high diastereoselectivity in several cases.<sup>[2]</sup> Recently, we have shown that functionalized allylic zinc reagents can be prepared from allylic chlorides by the reaction of zinc powder in the presence of LiCl. Their addition to aldehydes and ketones proceeds with high diastereoselectivity.<sup>[3]</sup> Nevertheless, the preparation of allylic zinc reagents bearing sensitive functional groups (such as a cyano or an ester function) is limited by the high reactivity of such allylic organometallic compounds.<sup>[4]</sup> Besides zinc, aluminum is a metal which has many attractive features: it is of low toxicity, inexpensive, and because of the low ionic character of the carbon-aluminum bond, it may tolerate a number of important functional groups.<sup>[5]</sup> The preparation of unsaturated aluminum organometallic compounds from commercial aluminum powder is in general difficult, but a proper activation of the aluminum surface allows an effective insertion of aluminum into aryl halides.<sup>[6]</sup> Previously, allylic aluminum reagents were prepared from allylic bromides by the methods of Gaudemar et al.<sup>[7]</sup> and Miginiac et al.<sup>[8]</sup> using diethyl ether as the solvent and in the presence of a catalytic amount of HgCl<sub>2</sub>. Herein, we wish to report a practical synthesis of functionalized allylic aluminum reagents bearing an aryl, an ester, or a cyanide substituent by the insertion of commercial aluminum powder into various allylic chlorides or bromides in the presence of a catalytic amount of InCl<sub>3</sub>. In addition we report the diastereoselective addition of the resulting aluminum reagents to aldehydes and ketones.

Preliminary studies have shown that an appropriate activation of aluminum is essential for achieving a smooth insertion into organic halides.<sup>[9,10]</sup> Thus, 3-bromocyclohexene (**1a**) reacts with Al powder and  $InCl_3^{[11]}$  in THF at 0°C within 2 h and provides the corresponding allylic aluminum reagent

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**2a** in 82% yield.<sup>[12]</sup> Its reaction with 4'-bromoacetophenone (**3a**) leads to the *syn*-homoallylic alcohol (**4a**) in 97% yield as only diastereoisomer. This selectivity is best rationalized by a chair-like transition state **A** (Scheme 1).<sup>[13]</sup> Functional groups, such as an ester, are readily compatible with this procedure.



Scheme 1. Preparation of the allylic aluminum reagents 2a and 2b, and their addition to 4'-bromoacetophenone (3a).

Thus, starting from ethyl 6-chlorocyclohex-1-enecarboxylate<sup>[14]</sup> (**1b**), the functionalized allylic aluminum reagent (**2b**) is obtained in 77 % yield. Reagent **2b** also reacted well with 4'-bromoacetophenone (**3a**) affording the homoallylic lactone (**4e**) with excellent diastereoselectivity (Scheme 1). The relative stereoselectivity has been established by NOE NMR spectroscopic analysis (see Supporting Information).

The reaction scope of such additions has been studied and we have found that the allylic aluminum reagent 2a reacts well with variously substituted aromatic ketones. Thus, the addition to methyl 4-acetylbenzoate (**3b**) furnishes the homoallylic alcohol **4b** (Table 1, entry 1). Remarkably, despite the seemingly high nucleophilicity of the allylic aluminum reagent, the reagent **2a** adds perfectly to 1-(4nitrophenyl)ethanone (**3c**) without reacting with the nitro group and the homoallylic alcohol **4c** is isolated in 95% yield (Table 1; entry 2). An unprotected amino group is also compatible with the aluminum reagent under these reaction conditions and the addition of **2a** to 2-amino-5-chlorobenzal-

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Table 1:	Diastereoselective	preparation	of	homoallylic	alcohols	and
lactones	s of type <b>4</b> using al	lylic aluminum	rea	gents of type	2.	

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Entry	Aluminum reagent <sup>[a]</sup>	Carbonyl elec- trophile <sup>[b]</sup>	Product <sup>[c,d]</sup>
	Al <sub>2/3</sub> Br	R Me	R HO <sup>'</sup> Me
1 2	2a 2a	<b>3 b</b> : $R = CO_2Me$ <b>3 c</b> : $R = NO_2$ Cl	4b: 98%; 99:1 4c: 95%; 99:1 Cl
		СНО	NH <sub>2</sub> OH
3	2a	3 d	<b>4d</b> : 95%; 99:1
	EtO <sub>2</sub> C	R	
4 5	2b 2b	<b>3 e</b> : R = CO <sub>2</sub> Me <b>3 f</b> : R = CN	R 4 f: 78%; 99:1 <sup>[e]</sup> 4g: 87%; 99:1 ○
		NC Me	
6	<b>2b</b> CO <sub>2</sub> Et	3 g U Me	4h: 79%; 98:2
7	2c	$\mathbf{R}^{\mathbf{H}}$ <b>3b</b> : $\mathbf{R} = \mathbf{CO}_{2}\mathbf{M}\mathbf{e}$	HO` <sup>•</sup> Me <sub>CO2</sub> Et <b>4i</b> : 70%: 98:2
8	2c	3a: R=Br	<b>4j</b> : 71%; 98:2 <sup>[e]</sup>
	Pn Al <sub>2/3</sub> Ci	R	HOME
9 10 11	2d 2d 2d	<b>3 a</b> : $R = Br$ <b>3 b</b> : $R = CO_2Me$ <b>3 g</b> : $R = CN$	4k: 99%; 98:2 4l: 99%; 96:4 4m: 98%; 94:6
	MeO Al <sub>2/3</sub> Cl	-	NC OMe
12	2e	3 f	OH 4n: 95%; 97:3 <sup>[e]</sup>
			Br Jan Ma
13	2e	3a 0	<b>4o</b> : 74%; 92:8
	Ph Al <sub>2/3</sub> OP(O)(OEt) <sub>2</sub>	Ме	HO
14	2 f	3h	4p: 62%; 97:3
15	2 f	0 3i	HO' Me 4q: 90%; 98:2

[a] All reactions were carried out on a 1–4 mmol scale. [b] 0.6–0.7 equivalents were used. [c] Yield of isolated analytically pure products. [d] The diastereoselectivities were determined by <sup>1</sup>H NMR spectroscopy. [e] The structures were established by X-ray analysis.<sup>[18]</sup>

dehyde (**3d**) affords the aminoalcohol **4d** in 95% yield (Table 1, entry 3). Various aromatic aldehydes and ketones (**3e–g**) react with the functionalized allylic aluminum reagent **2b**, leading to the corresponding lactones (**4f–h**) in 77–87% yield (Table 1, entries 4–6). The structure of the bicyclic lactone **4f** has been confirmed by X-ray analysis.<sup>[18]</sup>

Also, ethyl 5-chlorocyclopent-1-enecarboxylate (1c) reacted with Al powder (3 equiv) and  $InCl_3$  (5 mol%) in THF affording the aluminum reagent 2c within 16 h at 25 °C (60% yield). However, in contrast to the six-membered analogue (2b), a lactone formation is disfavored and the reaction with 4-acetylbenzoate (3b) or 4'-bromoacetophenone (3a) yields the ester-substituted uncyclized homoallylic alcohols (4i–j) in 70–71% (Table 1, entries 7–8). Again, Xray analysis of 4j has been used to establish its structure.<sup>[18]</sup>

Similarly, the reaction of Al powder (1.5 equiv) and InCl<sub>3</sub> (1 mol%) with cinnamyl chloride (1d) provides the aluminum reagent 2d (73% yield) within 2 h at 25°C. Addition to methyl ketones, such as 4'-bromoacetophenone (3a), methyl-4-acetylbenzoate (3b), or 4-acetylbenzonitrile (3g), affords the corresponding alcohols 4k-m in almost quantitative yields, with high diastereoselectivities (Table 1, entries 9-11). Remarkably, in contrast to the preparation of the corresponding cinnamylzinc reagent,<sup>[15]</sup> little homocoupling of the allylic reagent is observed. Even a more electron-rich cinnamyl chloride (1e) bearing a methoxy group provides the corresponding aluminum reagent 2e under the same conditions (25°C, 11 h, 71% yield). It adds smoothly to 4-cyanobenzaldehyde (3f) or 4'-bromoacetophenone (3a) affording the polyfunctional anti-homoallyllic alcohols 4n and 4o in 95 and 74% yield, respectively (Table 1, entries 12, 13). Interestingly, a cinnamylaluminum phosphate (2 f) could be readily prepared by reacting the phosphoric cinnamyl ester (1 f) with Al powder (1.5 equiv)and InCl<sub>3</sub> (1 mol%) in THF (25°C, 12 h, 70% yield). Trapping this new organometallic reagent with aliphatic methyl ketones, such as 1-cyclohexylethanone (3h) or 3methylbutan-2-one (3i) furnishes the corresponding homoallylic alcohols bearing two adjacent stereocontrolled tertiary and quaternary centers **4p,q** in 62–90% yield (Table 1, entries 14, 15). The structures of all homoallylic alcohols resulting from the addition to ketones and aldehydes could be established either by literature comparison<sup>[3a, 13]</sup> or X-ray analysis in the case of 4 f, 4 j, and 4 n.<sup>[18]</sup>

Usually, cyano groups react rapidly with allylic organometallic compounds, such as zinc reagents (Blaise reaction).<sup>[16]</sup> Remarkably, a cyano function is well tolerated during the Al insertion reaction. Thus, the preparation of a cyano-substituted cyclopentylaluminum reagent (**2g**) is possible starting from 5-chlorocyclopent-1-enecarbonitrile<sup>[17]</sup> (**1g**) using Al powder and InCl<sub>3</sub> (Scheme 2). The addition of this aluminum reagent to a ketone or an aldehyde affords the homoallylic alcohols **4r** and **4s** in 89 and 70% yield, respectively. An X-ray analysis for **4s** has been performed.<sup>[18]</sup>

In the case of a  $\beta$ -silyl-substituted crotylaluminum reagent (**2h**), which was prepared starting from the  $\beta$ -silyl-substituted crotyl chloride **1h** (Scheme 3), the addition to benzaldehyde (**3j**) and 4'-bromoacetophenone (**3a**) was also

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## Communications



**Scheme 2.** Preparation of a cyano-substituted allylic aluminum reagent **(2g)** and its addition reactions.



Scheme 3. Preparation of a trimethylsilyl-substituted allylaluminum reagent (2h) and its addition reactions.

selective, and the *syn*-homoallylic alcohols 4t and 4u were obtained.

In summary, we have demonstrated that allylic aluminum reagents can be conveniently prepared using aluminum powder in the presence of catalytic amounts of InCl<sub>3</sub> from allylic chlorides or bromides under mild conditions. The addition to various functionalized aldehydes or ketones affords polyfunctionalized homoallylic alcohols, bearing adjacent tertiary and quaternary centers in good diastereoselectivity. Further extensions of this method as well as mechanistic studies are currently being investigated.

## **Experimental Section**

Typical procedure: Preparation of **4a**: Al powder (81 mg, 3 mmol) and InCl<sub>3</sub> (4.4 mg, 0.02 mmol) were placed in an argon-flushed dry flask. After THF (5 mL) was added, a solution of 3-bromocyclohexene (**1a**, 322 mg, 2 mmol) in THF (5 mL) was added with a syringe pump over 1 h at 0°C and the resulting solution was stirred at 0°C for 1 h. The insertion reaction was monitored by GC analysis of hydrolyzed reaction aliquots. The resulting allylic aluminum reagent (**2a**) was added to a solution of 4'-bromoacetophenone (**3a**, 279 mg, 1.4 mmol) in THF (1.5 mL) at -78°C and the resulting mixture was stirred at -78°C for 2 h. Standard work-up and purification by flash chromatography over silica (eluting with pentane:diethyl ether 1:10) yielded compound **4a** as colorless liquid (384 mg, 97% yield).

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