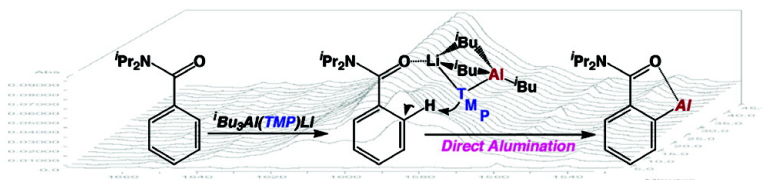## Communication

Regio- and Chemoselective Direct Generation of Functionalized Aromatic Aluminum Compounds Using Aluminum Ate Base

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Regio- and Chemoselective Direct Generation of Functionalized Aromatic Aluminum Compounds Using Aluminum Ate Base

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Organoaluminum compounds are widely used in organic synthesis, especially in aliphatic chemistry, to form carbon–carbon and carbon–heteroatom bonds.[1] Aromatic aluminum compounds should also be potentially attractive species as functional materials and synthetic building blocks.[2] However, aromatic aluminum chemistry has not been well developed, mainly due to the lack of efficient preparation methods compatible with various functional groups on aromatics. A common preparative method for aliphatic aluminum compounds is transmetalation of organolithiums or Grignard reagents to the corresponding aluminum compounds.[3] Unfortunately, application of this method for the preparation of functionalized aromatic aluminum compounds suffers from significant limitations. For instance, these common metalating reagents or the intermediary aromatic lithium or Grignard species are too highly reactive to coexist with various electrophilic functional groups, such as halogen, amide, and cyano groups, and π-deficient heterocycles.[4] Hydro- (or carbo)-alumination reaction at unsaturated bonds, which is another effective method for the preparation of aliphatic aluminum compounds, is also ineffective in aromatics.[5] Neither oxidative addition nor halogen–metal exchange reaction of aluminum on aromatic rings has been realized to date. Here we report a regio- and chemoselective direct alumination on functionalized aromatics using a newly designed aluminum ate base.

To develop the direct alumination reaction of aromatic compounds, we started our investigation from two directions, halogen–metal exchange and deprotonative metalation reactions. First, the halogen–aluminum exchange reactions of haloaromatics using various kinds of organoaluminum reagents were investigated. However, all attempts were unsuccessful. Then, we focused on the deprotonative alumination of functionalized benzenes, which would be more advantageous to generate (multi)functionalized aromatic aluminum compounds from the viewpoint of the availability of precursors.[6] After extensive experimentation using anisole (**1a**) as a model substrate, we found the best complex, lithium triisobutyl-(tetramethylpiperidino)aluminate ($^{i}Bu_3Al(TMP)Li$; aluminum ate base),[7] prepared by mixing triisobutylaluminum ($^{i}Bu_3Al$) and lithium tetramethylpiperide (LTMP) in THF,[8] to achieve the direct alumination under mild conditions (rt, 2 h). The resulting aryl aluminate (**2a**) was treated with D_2O or I_2 to give the desired *o*-deuterio- or *o*-iodoanisole, respectively, in high yields (Scheme 1). To obtain spectroscopic evidence for the intermediary formation of the aryl aluminate (**2a**), we next monitored the ^{13}C NMR spectrum of the reaction medium. The ^{13}C NMR chemical shifts (on **2a**, in Scheme 1) of the intermediary species (**2a**) generated by the reaction using $^{i}Bu_3Al(TMP)Li$ were reasonably consistent with those (in parentheses on **2a**) of the species prepared by the stepwise treatment of **1a** with $^{t}BuLi$ followed by complexation with $^{i}Bu_3Al$. This observation strongly supports the view that direct
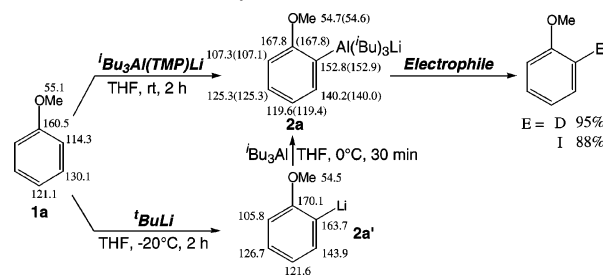
Scheme 1. ^{13}C NMR Study of Directed Ortho-Alumination

Table 1. Deprotonative Alumination of Functionalized Aromatics[a]

[a] Unless otherwise noted, the deprotonative alumination was carried out using $^{i}Bu_3Al(TMP)Li$ (2.2 equiv) and substrate (1 equiv) in THF. [b] Isolated yield. Items in parentheses are conditions of metalation. [c] Value in parentheses is the yield of the 2-deuteration (quenched with D_2O).

alumination occurred through the regioselective deprotonation of **1a** with $^{i}Bu_3Al(TMP)Li$ to form **2a**.

A variety of aromatic compounds with functional groups can be used in this direct alumination reaction (Table 1). This deprotonative alumination was found to be regioselective and tolerant of both electron-donating groups such as OMe, and electron-withdrawing groups such as CN and amide groups. In the reaction using typical bases such as alkyllithiums, Grignard reagents, and zincate bases,[9] it is well-known that the iodide group does not coexist, because the iodine–metal exchange reaction predominantly proceeds.[10] In the case of $^{i}Bu_3Al(TMP)Li$, the deprotonative ortho-alumination of *p*-iodoanisole and *p*-iodobenzonitrile occurred chemoselectively. The metalation of trifluoromethylbenzene with this aluminum ate base unexpectedly showed meta-orientation. The regioselective alumination is also applicable to ortho-/meta-disubstituted benzenes without any problems. Especially, in the cases of *o*-/*m*-dichlorobenzenes, the deprotonative alumination occurred regio- and chemoselectively *without the formation of benzyne* (vide infra). Therefore,

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Chart 1. Various Kinds of Electrophilic Trapping of the Functionalized Phenyl Aluminate Intermediate (**2c**)
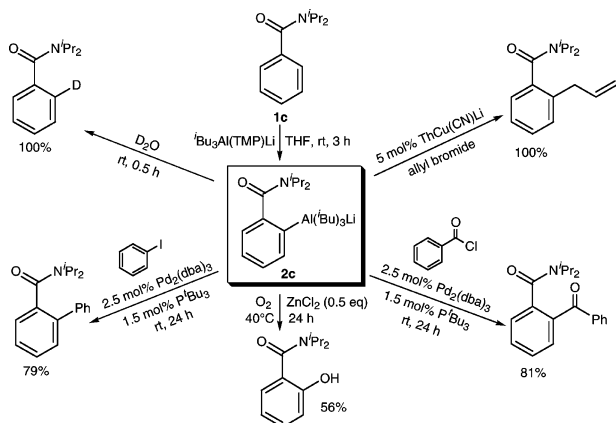
alumination with ^{i}Bu$_3$Al(TMP)Li, followed by electrophilic trapping (with I$_2$), proved to be a powerful tool for the preparation of 1,2,3-trisubstituted aromatic compounds. π-Deficient and π-rich heterocycles can be good substrates for this reaction, where the directed alumination proceeded smoothly.

We next demonstrated, as shown in Chart 1, that the functionalized arylaluminate intermediate **2c** (as a typical intermediate) can be utilized as an aryl anion equivalent. The intermediate **2c**, generated by the deprotonative alumination of **1c** using ^{i}Bu$_3$Al-(TMP)Li, was treated with D$_2$O to give the corresponding ortho-deuterated product in a quantitative yield. The intermediate **2c** also undergoes copper- and palladium-catalyzed C−C bond-forming reactions such as allylation, phenylation, and benzoylation in high yields and with high chemo- and regioselectivities.

A preliminary result aimed at the regioselective introduction of an OH moiety is also shown in Chart 1. When the intermediate **2c** was exposed to molecular oxygen in the presence of 0.5 equiv of ZnCl$_2$, the corresponding phenol was obtained in 56% yield. Since regio- and chemoselective direct introduction of a hydroxyl group on an aromatic ring is generally difficult,[3] the present procedure would provide a new, convenient one-pot synthesis of functionalized phenols.[11]

Recently, we reported that chemo- and regioselective zincation of meta-functionalized haloaromatics and generation of 3-substituted benzynes could be controlled by utilizing the drastic ligand effects in zincates.[12] In this case, with the aluminum ate base, generation of benzynes could be controlled by changing the reaction temperature. The intermediate **2m** generated by the deprotonative alumination of N,N-diisopropyl-3-bromo-2-iodobenzamide (**1m**) could be trapped with an electrophile (I$_2$) at low temperature (below 0 °C), whereas the generation of 3-functionalized benzyne proceeded smoothly at room temperature, and the resulting benzyne reacted with 1,3-diphenylisobenzofuran to give the corresponding Diels−Alder adduct in a quantitative yield (Scheme 2).

Finally, an in situ FT-IR study was performed by using **1c** as the substrate for monitoring this metalation (Supporting Information). The absorption (1585 cm^{-1}) due to the carbonyl group of

Scheme 2. Generation and Suppression of 3-Functionalized Benzyne
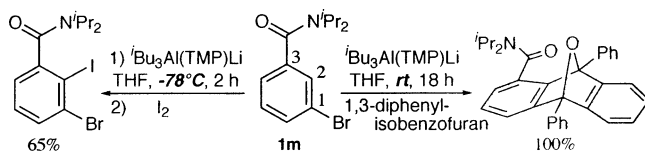
the initial electrostatic complex of **1c** and ^{i}Bu$_3$Al(TMP)Li gradually decreased, and the newly generated blue-shifted absorption (1600 cm^{-1}) increased during the course of the metalation.[13] The mechanism of this ortho-alumination is considered to be more complex than that of the conventional ortho-lithiation,[14] complex-induced proximity effects should play an important role,[15] and the (hetero)bimetallic system of ^{i}Bu$_3$Al(TMP)Li is considered to form an effectively complexed transition state for efficient agostic hydrogen activation.

In summary, highly chemo- and regioselective deprotonative alumination of functionalized aromatic and heteroaromatic compounds was realized using ^{i}Bu$_3$Al(TMP)Li as a base. Further studies to establish the scope and limitations of this alumination reaction are under way, together with a structural study of ^{i}Bu$_3$Al(TMP)Li and a mechanistic investigation of this novel metalation.

Note Added after ASAP Posting. Due to a production error, Scheme 2 was incorrect as published on the Web July 29, 2004. The corrected version was posted on August 3, 2004.

Supporting Information Available: Experimental procedures and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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