

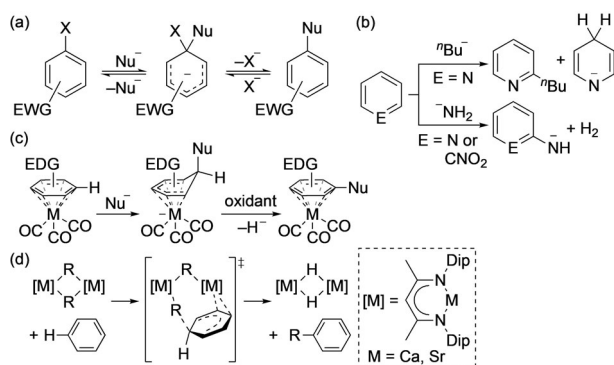
## Reaction Mechanisms

A *meta*-Selective C–H Almination of Mono-Substituted Benzene by Using An Alkyl-Substituted Al Anion through Hydride-Eliminating S<sub>N</sub>Ar Reaction

Satoshi Kurumada, Kengo Sugita, Ryo Nakano, and Makoto Yamashita\*

**Abstract:** Reaction of an Al-centered anion with toluene proceeded to form C–H cleaved product with a perfect *meta*-selectivity and a relatively small kinetic isotope effect (KIE,  $k_i/k_D = 1.51$ ). DFT calculations suggested a two-step reaction mechanism and electronically controlled *meta*-selectivity arising from the electron-donating methyl group. The reaction with other mono-substituted arenes was also investigated.

**N**ucleophilic aromatic substitution (S<sub>N</sub>Ar) reactions proceed through a formation of Meisenheimer intermediate and a subsequent elimination of a leaving group (Scheme 1 a).<sup>[1]</sup> Although an elimination of hydride is thermodynamically disadvantageous, hydride-eliminating S<sub>N</sub>Ar (H-S<sub>N</sub>Ar) reactions would have a huge potential to functionalize aromatic compounds.<sup>[2]</sup> In the presence of hydride-abstracting reagents, electron-poor pyridine<sup>[3]</sup> and nitrobenzene<sup>[4]</sup> derivatives have been known as a substrate for the H-S<sub>N</sub>Ar reaction (Scheme 1 b). In contrast, H-S<sub>N</sub>Ar reaction of electron-neutral and -rich benzenes require a formation of η<sup>6</sup>-arene-transition metal complex followed by a treatment with an external oxidant (Scheme 1 c).<sup>[5]</sup> Recently, a direct alkylation of electronically neutral benzene by using alkyl-calcium or -strontium hydride reagents has been reported as an example of H-S<sub>N</sub>Ar reactions (Scheme 1 d).<sup>[6]</sup>



**Scheme 1.** a) Classical S<sub>N</sub>Ar, b) H-S<sub>N</sub>Ar on electron-poor arenes, c) H-S<sub>N</sub>Ar on electron-rich arenes via π-arene complex, d) H-S<sub>N</sub>Ar alkylation of electronically neutral arenes.

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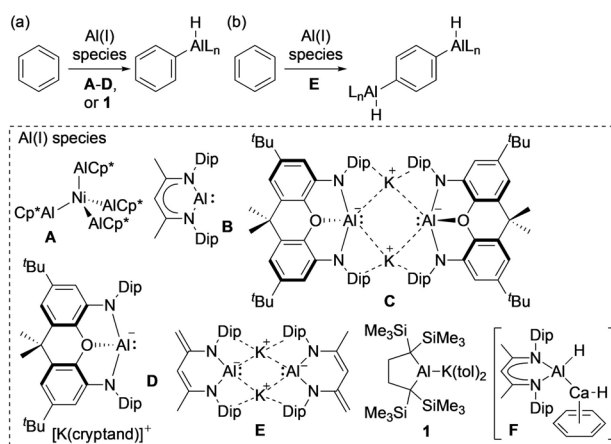
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Aluminum-substituted arenes have been widely used as a reagent in organic synthesis.<sup>[7]</sup> There are two types of the reactions on C–H almination of benzene: 1) *ortho*-deprotonation/alumination reaction of an arene possessing a directing group by using bulky and basic ate complex of Al<sup>III</sup>,<sup>[8]</sup> and 2) oxidative addition of C–H bond to Al<sup>I</sup> species (Scheme 2). In a combination with transition metals, Cp\*Al/Ni<sup>0</sup> **A**<sup>[9]</sup> and (nacnac)Al species **B**/Pd catalyst reacted with benzene,<sup>[10]</sup> in which C–H cleavage was proposed to occur on the transition-metal center. In contrast to these neutral Al<sup>I</sup> species,<sup>[11]</sup> some of recently developed Al-centered anions<sup>[12]</sup> underwent C–H cleavage of benzene without transition metals. A base-stabilized Al anion **C** reacted with benzene at 57 °C to afford (hydrido)(phenyl)aluminate.<sup>[12a]</sup> Reaction of a separated ion pair **D** derived from **C** with naphthalene furnished an isomeric mixture of 1- and 2-aluminated naphthalenes.<sup>[12c]</sup> Diaminoaluminum anion **E** generated from **B** is also capable for C–H cleavage of benzene to give dialuminated benzene.<sup>[12d]</sup> A dialkylaluminumpotassium **1** also underwent C–H cleavage of benzene at RT.<sup>[12e]</sup> It should be noted that **B** reacted with benzene in the presence of [(nacnac)CaH]<sub>2</sub> catalyst to give (nacnac)Al(H)(Ph) through an intermediate **F** having a character of base-stabilized Al-centered anion,<sup>[13]</sup> although **B** itself does not react with benzene.<sup>[14]</sup>

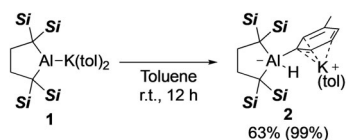
Herein, we report H-S<sub>N</sub>Ar reaction of toluene with a perfect selectivity for *meta*-C–H bond by using dialkylaluminum anion **1**. Mechanistic study with DFT calculations and kinetic analysis proposed the reaction proceeded through a H-S<sub>N</sub>Ar reaction and the perfect selectivity for *meta*-C–H bond cleavage was controlled by electronics of the methyl



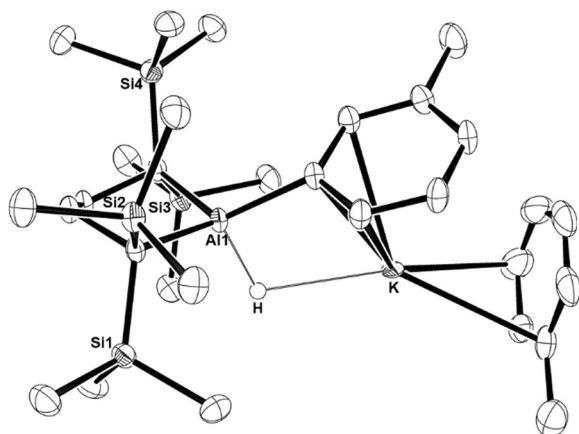
**Scheme 2.** Almination of benzene using Al<sup>I</sup> species (L: neutral or anionic ligand,  $n = 2-3$ , Dip = 2,6-<sup>i</sup>Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>).

group. The present aluminatation was also applied to the reaction with other monosubstituted arenes.

Leaving a toluene solution of **1** at room temperature led to a formation of (hydrido)(*m*-tolyl)aluminat **2** as a crystalline solid in 63% yield (Scheme 3). The <sup>1</sup>H NMR spectrum of the crude product exhibited no signal that corresponds to other isomers (NMR yield: 99%). The perfect *meta*-selectivity is slightly better than that in the recently reported aluminatation reaction of toluene by using **B** in the presence of [(nacnac)-CaH]<sub>2</sub> catalyst (*meta:para* = 9:1).<sup>[13]</sup> The existence of *m*-tolyl group in **2** was unambiguously confirmed by a single crystals X-ray diffraction analysis (Figure 1). The solid-state structure of **2** is similar to the previously reported (hydrido)-(phenyl)aluminat<sup>[12]</sup> generated by a reaction of **1** with benzene. Considering the low electronegativity of Al (1.61)<sup>[15]</sup> and the similar reactivity of diaminoboryl anion toward benzene,<sup>[16]</sup> we originally assumed alumanyl anion **1** has a high Brønsted basicity to deprotonate benzene.<sup>[12]</sup> However, the present *meta*-selective C–H cleavage by **1** is completely different from the reactivity of diaminoboryl anion that deprotonates benzylic C–H bond of toluene.<sup>[17]</sup> Therefore, the kinetic isotope effect (KIE) was investigated to reveal further details of the reaction mechanism. Consumption of **1** or **1**-*d*<sub>16</sub><sup>[18]</sup> in either toluene or [D<sub>8</sub>]toluene were monitored at 35 °C by UV/Vis spectroscopy. The decay of the absorption at 468 nm obeyed pseudo-first order kinetics with rate constants of  $k_H = 5.42 \pm 0.03 \times 10^{-4} \text{ s}^{-1}$  and  $k_D = 3.58 \pm 0.02 \times 10^{-4} \text{ s}^{-1}$  (Supporting Information, Figure S11). The obtained KIE ( $k_H/k_D = 1.51$ ) is smaller than the reported values for the deprotonation of benzene with either ethylpotassium ( $k_H/k_D = 2.0$ ),<sup>[19]</sup> *n*BuLi/*t*BuOK ( $k_H/k_D = 2.7$ ),<sup>[20]</sup> or



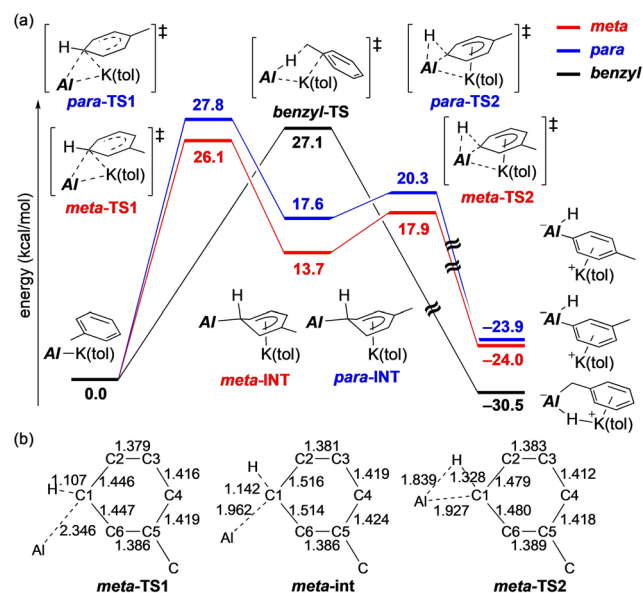
**Scheme 3.** Reaction of **1** with toluene to afford **2** (Si = SiMe<sub>3</sub>, <sup>1</sup>H NMR yield in parentheses).



**Figure 1.** Crystal structure of **2** with ellipsoids set at 50% probability; hydrogen atoms except Al–H and intermolecular interaction between potassium cation and SiMe<sub>3</sub> group have been omitted for clarity.<sup>[24]</sup>

diaminoboryl anion ( $k_H/k_D = 2.8$ ).<sup>[16]</sup> This relatively small value of  $k_H/k_D$  in the present study would reflect non-deprotonating character with triangular or non-linear transition state (see below), where the change in C–H bending is more important than the change in C–H stretching.<sup>[21]</sup>

To shed light on the origin of the present *meta*-selective C–H cleavage of toluene with **1** to furnish **2**, the reaction mechanism and property of the transition state were examined by using DFT calculations (Figure 2). Energy profiles for C–H cleavage at *meta*-, *para*-, and benzylic positions were summarized in Figure 2a. The *ortho*-cleavage was not taken account because of the steric hindrance. The obtained pathway for *meta*-C–H cleavage is two-step reaction involving a formation of Meisenheimer intermediate *meta*-INT. The first transition state, *meta*-TS1, for the nucleophilic attack of Al anion, has an almost coplanar configuration of the bending hydrogen atom and benzene ring with incoming out-of-plane aluminum atom with an activation energy of 26.1 kcal mol<sup>-1</sup> (Figure 2b for structural parameters). It should be noted that the π\*-orbital of toluene in **1** was lower than that of free toluene (Supporting Information, Figure S13), indicating the decrease of electron density of toluene upon coordination. The second transition state, *meta*-TS2, for the hydride migration to the Al center has a lower activation energy (4.2 kcal mol<sup>-1</sup>) where the aluminum atom is almost coplanar with the benzene ring. The sum of two TSs having non-linear arrangement of Al, C, and H atoms would contribute to the experimentally obtained small KIE value.<sup>[21]</sup> Similar two-step pathway for *para*-C–H cleavage through *para*-TS1 was found to have a slightly higher activation energy (27.8 kcal mol<sup>-1</sup>). In the case of benzylic C–H cleavage, reaction proceeds through a concerted pathway without an intermediate. The difference between two transition states, *para*-TS1 and *meta*-TS1, would



**Figure 2.** a) Energy profiles of the DFT-based mechanism for C–H cleavage of toluene by **1**, including schematic structures of transition states, calculated at the M06-HF/def2-TZVP//PBE0/def2-SVP/PCM(SMD, Toluene) level of theory. Relative Gibbs free energies are given in kcal mol<sup>-1</sup>. b) Selected bond lengths (Å) of *meta*-TS1.

arise from the electron-donating character of the methyl group. In fact, HOMO of both transition states has large coefficients at *ortho*- and *para*-positions of the carbon atom being attacked by Al anion (Figure 3), therefore, the methyl group on the *para*-position in *para*-TS1 contributes to destabilize HOMO of the transition state. The calculated NPA charges of the *ipso*-carbon of the methyl group ( $-0.06$  in *meta*-TS1 and  $-0.17$  in *para*-TS1) also support destabilization of *para*-TS1. Thus, absence of destabilizing effect by methyl group in *meta*-TS1 would be the reason why the *meta*-selective C–H cleavage was obtained. It should be noted that the second transition states *para*-TS2 and *meta*-TS2 having a coplanarity between the aluminum atom and the benzene ring seem to be similar to that found in the reaction of **B** with toluene with an assistance of calcium catalyst.<sup>[13]</sup>

Subsequently, we examined the reactivity of alumanyl anion **1** toward mono-substituted benzenes (Scheme 4). The reaction of **1** with fluorobenzene followed by an addition of I<sub>2</sub> gave a crude reaction mixture, which involves 3-fluoroiodobenzene **3** (25%) and iodobenzene **4** (28%) as judged by the <sup>1</sup>H NMR spectrum. The former would be generated from a *m*-fluorophenyl-substituted aluminate, which has a similar structure of **2**. The latter would form via S<sub>N</sub>Ar reaction at the *ipso* carbon of the fluorine substituent, as found for the reaction of **1** with C<sub>6</sub>F<sub>6</sub>.<sup>[12]</sup> Treatment of **1** with anisole gave (methyl)-(phenoxy)aluminate **5** in 90% yield through S<sub>N</sub>2 reaction at methyl group with phenoxide anion as a leaving group. The structure of **5** was determined by NMR spectroscopy and X-ray crystallographic analysis (see the Supporting Information). On the other hand, the reaction of **1** with diphenyl ether gave (hydrido)(*m*-phenoxyphenyl)aluminate **6** through C–H

bond cleavage at *meta*-position. The dimeric structure of isolated **6** was confirmed by X-ray analysis, in which the hydride was found as a peak in the Fourier difference map (see the Supporting Information). In the reaction of **1** with trifluoromethylbenzene, detectable product is limited to tetraalkyldialumane (65% NMR yield), which would be generated via single-electron-transfer from **1** to trifluoromethylbenzene (Supporting Information, Scheme S1).<sup>[22]</sup> Thus, *meta*-selective C–H aluminations could be applied to fluorobenzene and diphenyl ether.

In summary, we revealed the reactivity of alumanyl potassium **1** toward toluene to form C–H cleaved product **2** with a perfect *meta*-selectivity.<sup>[23]</sup> A relatively small kinetic isotope effect ( $k_{\text{H}}/k_{\text{D}} = 1.51$ ) suggested a non-linear transition state. DFT calculations suggested a two-step reaction mechanism and electronically controlled *meta*-selectivity arising from the electron-donating methyl group. The reactivity of **1** toward other mono-substituted arenes was also investigated.

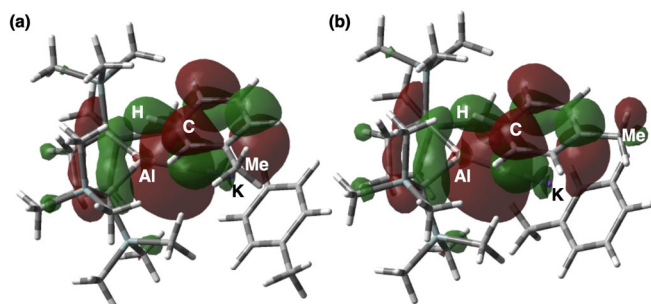
### Acknowledgements

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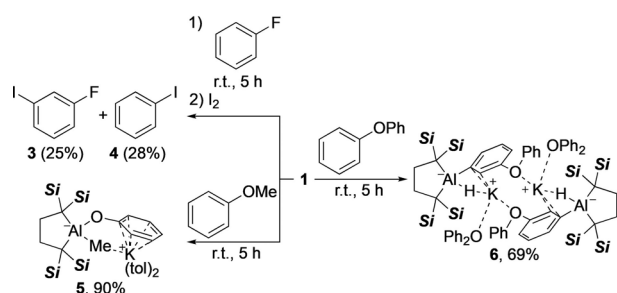
### Conflict of interest

The authors declare no conflict of interest.

**Keywords:** aluminum anions · density functional calculations · kinetic isotope effect · nucleophilic aromatic substitution · substituent effect



**Figure 3.** HOMO of a) *meta*-TS1 and b) *para*-TS1 (isovalue = 0.02). Al, C, and H atoms around the reaction center are labeled.



**Scheme 4.** Reaction of **1** with mono-substituted arenes. (Si = SiMe<sub>3</sub>, <sup>1</sup>H NMR yield in parentheses).

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- [24] Deposition Numbers 2012416, 2012417, and 2012418 (for **2**, **5**, and **6**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service [www.ccdc.cam.ac.uk/structures](http://www.ccdc.cam.ac.uk/structures).

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

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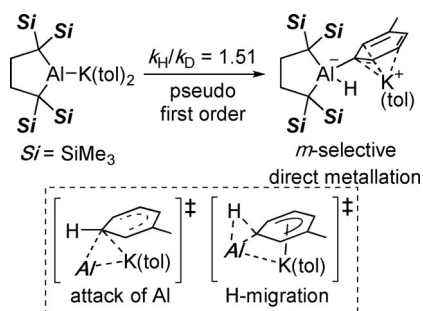
## Zuschriften



## Reaction Mechanisms

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A *meta*-Selective C–H Almination of  
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