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GALLIUM DICHLORIDE-MEDIATED REDUCTIVE FRIEDEL-CRAFTS REACTION

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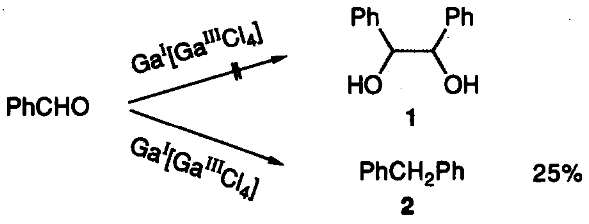
Summary : In the presence of gallium dichloride, carbonyl compounds reacted with anisole to give alkylated anisoles in good yields. It was suggested that the adducts were obtained by way of the reduction of the carbonyl compounds followed by the Friedel-Crafts reaction in a one-pot. This is the first organic synthetic method with gallium dichloride, low valent gallium.

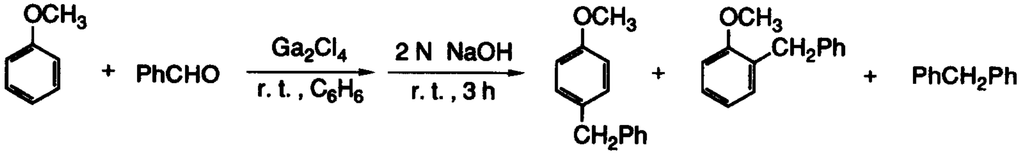
Boron and aluminum are very useful elements in organic synthesis, and many synthetic methods with them are widespread at present. However, there have been only a few examples of synthetic reactions using gallium which belongs to the same group.[3,4)] Recently, we paid attention to the softness of gallium compared with boron and aluminum, and reported gallium(III) chloride-mediated hydrolysis and allylation reaction of dithioacetals.[3)] In the course of our synthetic study utilizing gallium compounds, we tried to use gallium dichloride, a low valent compound of IIIA group, which is characteristic of gallium and has never been identified among the compounds of boron and aluminum. It is known that gallium dichloride, a formally divalent compound, is a double salt which consists of univalent and trivalent galliums.[5)] Owing to its unique character, gallium dichloride would make it possible to realize a novel type of reaction which is difficult to proceed by activation with conventional reagents, if we can take advantage of the reducing ability of univalent gallium and the Lewis acidity of trivalent one. We herein report gallium dichloride-mediated reductive Friedel-Crafts reaction by using carbonyl compounds as electrophilic reagents.

Gallium dichloride was prepared according to the known method with a slight modification and used as a benzene solution without purification.[6)] At first, the reductive dimerization of benzaldehyde was examined. However, desired diol **1** was not obtained at all but diphenylmethane (**2**) in 25% yield (Scheme 1). This unexpected compound was considered to be formed through the reductive Friedel-Crafts reaction between benzaldehyde and benzene which was the solvent for gallium dichloride. We took notice of this phenomenon and thoroughly investigated the reaction by using anisole, which is more nucleophilic than benzene, as a nucleophile.



Scheme 1.

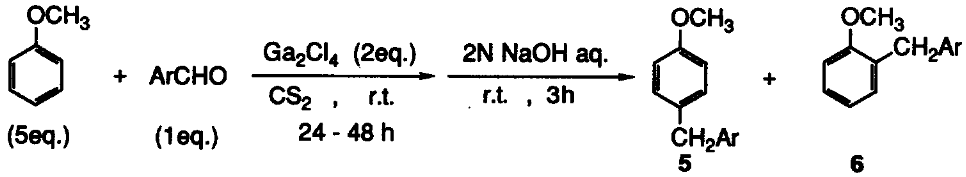
When benzaldehyde was treated with two equimolar amounts of gallium dichloride and five equimolar amounts of anisole in benzene at room temperature, followed by quenching with aqueous sodium hydroxide, the desired products, *p*- and *o*-benzylanisoles (**3**, **4**) were obtained in 19 and 25% yields, respectively. In addition, undesired diphenylmethane (**2**) was also obtained in 30% yield (Scheme 2). The formation of diphenylmethane was considered to be attributable to benzene in the reaction system. On the basis of this consideration, the reaction was carried out by removing benzene out of the system and by using various solvents other than benzene. Among the solvents examined, carbon disulfide was found to be most suitable; the desired products, **3** and **4**, were obtained in the highest yields (31 and 42%, respectively), and diphenylmethane was not detected at all.



3 19% **4** 25% **2** 30%

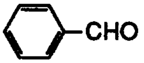
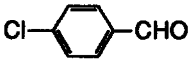
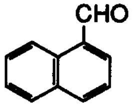
Scheme 2.

Under these optimized conditions, the reductive Friedel-Crafts reaction of various aromatic aldehydes with anisole was carried out. The results are shown in Table 1. Each aromatic aldehyde reacted smoothly with anisole to afford the corresponding diphenylmethane derivatives in relatively good yields. It is noteworthy that



5 **6**

Table 1. Reductive Friedel-Crafts Reaction of Aromatic Aldehydes with Anisole

run	ArCHO	yield(%)	5 : 6
1		73	42 : 58
2		64	78 : 22
3		47	89 : 11
4		69	59 : 41
5		71	86 : 14

the *ortho*-substituted compounds, which are able to be obtained only in quite low yields by the usual Friedel-Crafts reaction, are produced with a comparatively high ratio in this reaction. The ratio of the *para* products tends to increase with increasing electron-donating character of the substituent at the *para* position of benzaldehydes.

A typical experimental procedure is as follows: Benzene was removed from a solution containing gallium dichloride (1.34 mmol) upon heating at 80 °C for 1 h under reduced pressure. Then, to gallium dichloride was successively added a solution of anisole (362.3 mg, 3.35 mmol) in CS_2 (2 ml), and a solution of benzaldehyde (70.6 mg, 0.67 mmol) in CS_2 (2 ml) at room temperature under an argon atmosphere. Stirring was continued for 24 h at the same temperature. The reaction mixture was quenched by adding 2 N aqueous sodium hydroxide (20 ml), and stirring was continued for 3 h at room temperature. Then, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 ml). The combined organic layers were dried over Na_2SO_4, and the solvents were removed under reduced pressure. The residue was purified by preparative TLC to afford *p*-benzylanisole (40.5 mg, 0.205 mmol, 31%) and *o*-benzylanisole (56.1 mg, 0.283 mmol, 42%).

Similarly, the reaction of several ketones and aliphatic aldehydes with anisole was carried out in the presence of gallium dichloride. The results are shown in Table 2. Although the yield was rather low in the case of acetophenone due to the formation of a complex mixture arising from its high reactivity, the corresponding adducts were obtained from cyclohexanone, cyclohexanecarbaldehyde, and octanal. It is especially interesting that unexpected products having a rearranged carbon framework arose from the reaction with aliphatic aldehydes.

Taking into account the above results, the reaction mechanism is considered as shown in Scheme 3. The reduction of cyclohexanecarbaldehyde, for instance, occurs at first on the action of univalent gallium and a

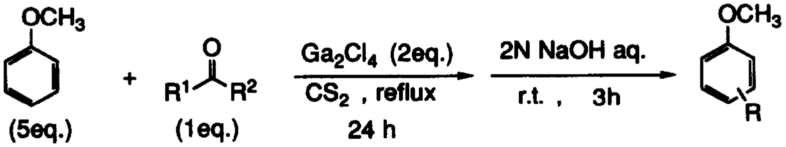
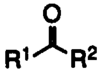
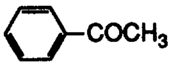
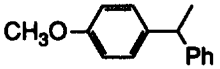
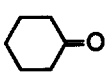
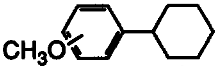
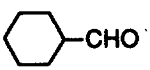
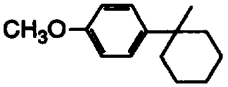
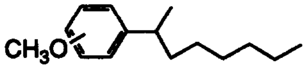
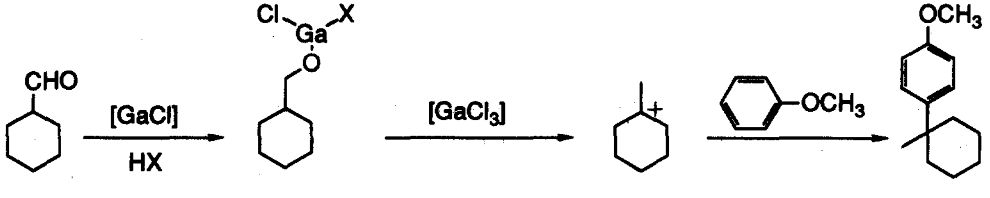


Table 2. Reductive Friedel-Crafts Reaction of Carbonyl Compounds with Anisole

run		yield(%)	main product
1		15	
2		72	 *para* : *ortho* = 29 : 71
3		66	
4		41	 *para* : *ortho* = 39 : 61

proton donor, which originates from atmospheric moisture and slightly contaminates in the reaction system, to give the corresponding gallium(III) alkoxide, **7**. Then, the alkoxide is converted into tertiary carbocation **8** via a primary carbocation generated through the trivalent gallium-mediated elimination of the metaloxy group. Finally, **8** attacks anisole to give an alkylated anisole, **9**. If there are no protons at the carbonyl α position, such as benzaldehyde and its derivatives, a benzylic cation is generated without a rearrangement.



7 8 9

Scheme 3.

In conclusion, reductive Friedel-Crafts alkylation of anisole with carbonyl compounds was developed by using gallium dichloride, a novel Lewis acidic reducing agent. This is the first organic synthetic method with low valent gallium. Further synthetic applications including reductive Friedel-Crafts reaction of aromatic compounds other than anisole are now under investigation in this laboratory.

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References and Notes

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2) Present address: Department of Materials Science and Technology, Toin University of Yokohama, Kurogane-cho, Midori-ku, Yokohama 225, Japan.
3) K. Saigo, Y. Hashimoto, N. Kihara, H. Umehara, and M. Hasegawa, *Chem. Lett.*, **1990**, 831; K. Saigo, Y. Hashimoto, N. Kihara, K. Hara, and M. Hasegawa, *Chem. Lett.*, **1990**, 1097.
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5) L. A. Woodward, G. Garton, and H. L. Roberts, *J. Chem. Soc.*, **1956**, 3723; G. Garton and H. M. Powell, *J. Inorg. Nucl. Chem.*, **4**, 84 (1957).
6) L. S. Foster, *Inorg. Synth.*, **IV**, 111 (1953). The following procedure is representative: A mixture of gallium metal and gallium(III) chloride was heated at 200 °C under an argon atmosphere for several days. The excess gallium(III) chloride was distilled off and resulting gallium dichloride was dissolved in benzene. The concentration of gallium dichloride solution was determined by iodometry.

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