

(2,7-Disubstituted-1,8-biphenylenedioxy)bis(dimethylaluminum) as Bidentate Organoaluminum Lewis Acids: Elucidation and Synthetic Utility of the Double Electrophilic Activation Phenomenon

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Abstract: A series of (2,7-disubstituted-1,8-biphenylenedioxy)bis(dimethylaluminum) (**2**) has been readily prepared in situ by treatment of the requisite 2,7-disubstituted-1,8-biphenylenediol (**1**) with Me₂Al (2 equiv) in CH₂Cl₂ at room temperature; this primarily relies on the successful establishment of a new synthetic procedure of **1** starting from inexpensive *m*-anisidine. Evaluation of **2** as a bidentate organoaluminum Lewis acid has been performed by the reduction of ketonic substrates using Bu₃SnH as a hydride source in comparison to the conventional monodentate Lewis acid dimethylaluminum 2,6-xylenoxide (**11**), uncovering the significantly high activation ability of **2** toward carbonyl. Particularly, (2,7-dimethyl-1,8-biphenylenedioxy)-bis(dimethylaluminum) (**2a**) exerted the highest reactivity, which has also been emphasized in the Mukaiyama aldol reaction. The structure of the bidentate Lewis acid **2** was unambiguously determined by single-crystal X-ray diffraction analysis of **2g** possessing a bulky 3,5-di-*tert*-butylphenyl substituent, revealing the rigid dimeric assembly in the solid state. The double electrophilic activation of carbonyl substrate by **2a** has been supported by low-temperature ¹³C NMR analysis as well as theoretical study using the Gaussian 98 program. Moreover, unique stereoselectivity has been observed in the **2a**-promoted Mukaiyama Michael addition, and highly chemoselective functionalization of carbonyl compounds in the presence of their acetal counterparts has been realized using **2a**. Finally, the effectiveness of **2a** for the activation of ether functionality has been demonstrated in the Claisen rearrangement of allyl vinyl ethers.

Introduction

Lewis acids are becoming an extremely powerful tool in many different modern organic reactions as is clearly demonstrated in the Lewis acid-promoted carbon-carbon bond formation reactions as well as the recent explosive development of chiral Lewis acids for catalytic asymmetric synthesis.^{1,2} In the Lewis acid-promoted reactions, the carbonyl group has certainly appeared as an extremely useful and important functionality to be manipulated.³ The electrophilic activation of the carbonyl group by Lewis acids through coordination with a central metal allowed the addition of various nucleophiles under mild conditions with high chemo-, regio-, and stereoselectivity, and, consequently, the scope of the carbonyl addition reaction has

been extensively expanded. Having been deeply involved in this bold stream, we have been interested in the fundamental aspects of the carbonyl activation by metal centered Lewis acids, that is, the mode of coordination and its chemical consequences.

The two principal modes of coordination of carbonyls to Lewis acids are the π -bonding (**A**) and σ -bonding (**C**).^{1a,4} Generally, the transition metal favors the former mode,⁵ and the latter is preferred by the main group Lewis acid.^{3,4,6} Two additional coordination modes **B** and **D** are also conceivable, where two metals coordinate simultaneously to the carbonyl moiety, and these types of coordination are expected to alter

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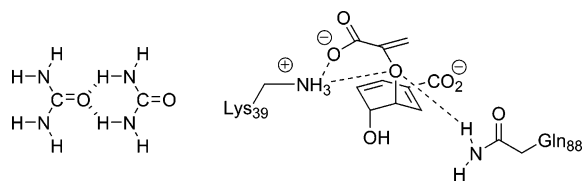
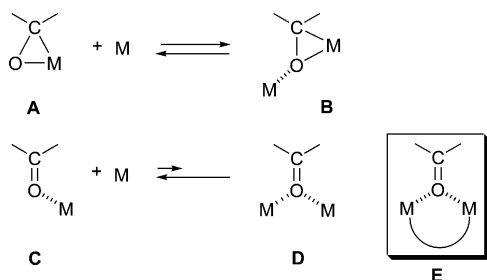


Figure 1.

the reactivity and selectivity of the carbonyl–Lewis acid complexes to a great extent. However, this characteristic of the bidentate complexes has been poorly studied, and its potential utility in selective organic synthesis has rather been neglected by the entire chemistry community.



In casting an eye to the behavior of Brønsted acids, double activation of oxygen-containing functionalities seems to be a frequently encountered phenomenon. For example, simultaneous coordination of two amide protons of urea to another urea carbonyl oxygen has previously been observed in the crystal structure.⁷ Ganem demonstrated that two terminal N–H protons in mutase accelerate Claisen rearrangement of chorismate through double activation of its ethereal oxygen (Figure 1).⁸

Further, Hine observed that 1,8-biphenylenediol derivatives form 1:1 complexes with carbonyls through double hydrogen bonding,⁹ which were found to be effective for the acceleration of Diels–Alder reactions¹⁰ and the ring-opening reaction of oxiranes.¹¹ Recently, Fujimoto calculated the activation energy of the epoxide ring-opening reaction as a model case, providing good agreement with the experimental result.¹² Wuest also reported the bidentate Brønsted acid–base complex with simple ketone as carbonyl substrate,¹³ and Crabtree disclosed that the disulfonamide receptor catalyzed imine formation of aldehyde with amine by hydrogen bonding (Figure 2).¹⁴

Little is known, however, about such double coordination with certain Lewis acids. After the first systematic study of the synthesis and coordination chemistry of bidentate Lewis acid by Shriver and Biallas in 1966,¹⁵ most of the research effort in

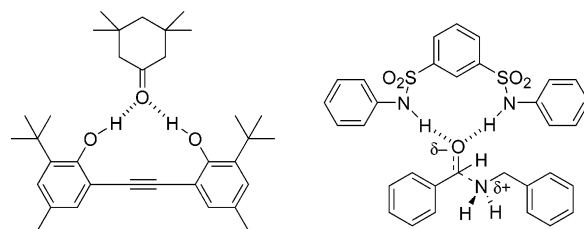


Figure 2.

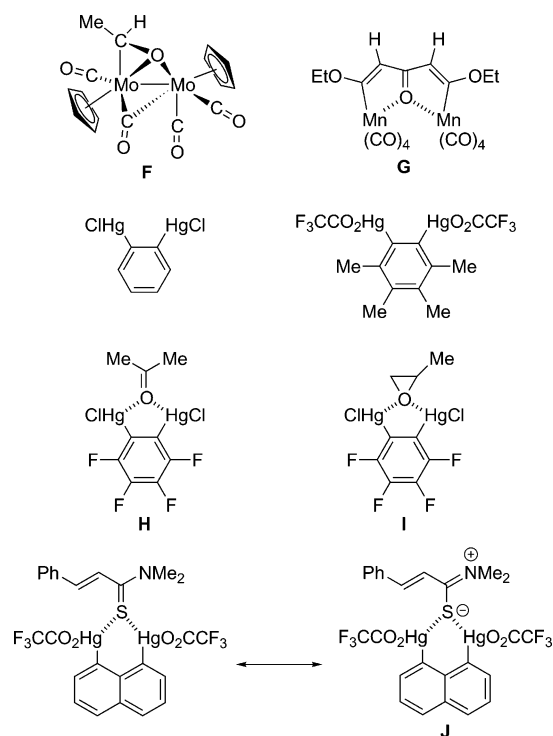


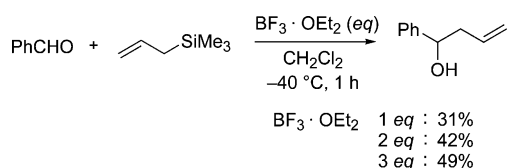
Figure 3.

bimetallic Lewis acids has been focused on anionic sequestration^{16–19} or the utilization of the transition metals such as molybdenum, manganese, and especially mercury (Figure 3). In 1984, H. Adams prepared an acetaldehyde complex of dimolybdenum **F** which adopted a coordination mode **B**,²⁰ and the complex **G** reported by R. D. Adams represents the first example of the di- σ -bonding coordination with a ketonic group having a substantial double-bond character.²¹ Since 1985, Wuest has reported impressive and detailed studies on the unique coordination chemistry of 1,2-diphenylenedimercury derivatives.²² These compounds hold two Lewis acidic atoms of mercury in an orientation that favors the double coordination

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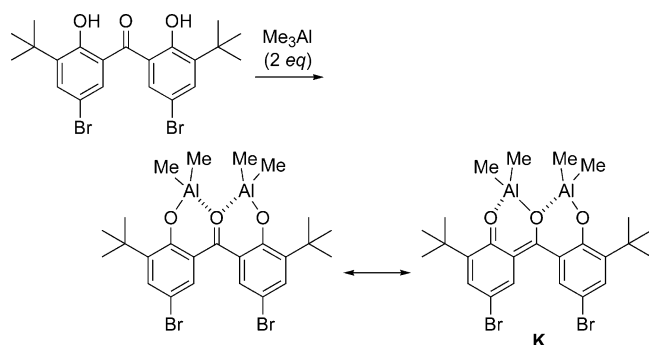
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Scheme 1



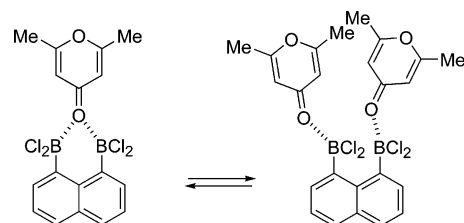
of Lewis bases such as dialkylformamides. On the basis of this research, Gabbaï synthesized the fluorinated analogue to increase the acceptor properties of the mercury centers and succeeded in the first isolation of chelate complexes with the weakly basic oxygens acetone and propylene oxide (**H** and **I**).²³ Oh also investigated the bidentate mercury complexes with thioamide, in which substantial participation of the iminium ion structure **J** was observed.²⁴

On the other hand, studies on the bidentate Lewis acids of main group metals featuring the di- σ -bonding complexation and its synthetic utility have remained even more elusive primarily because of considerably high preference for a single coordination mode **C**. For instance, attempted Hosomi–Sakurai allylation of benzaldehyde with allyltrimethylsilane in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ revealed that even the use of an excess amount of Lewis acid did not necessarily bring a drastic increase of the chemical yield of the desired homoallylic alcohol as shown in Scheme 1.²⁵ This experimental result is consistent with the theoretical study by Wiberg and LePage that shows the second coordination of Lewis acidic metal to the free lone pair of the carbonyl–Lewis acid 1:1 complex is energetically unfavorable.²⁶ Therefore, to achieve the usually unfavorable double coordination, it seems indispensable to precisely design bidentate Lewis acids possessing two metal centers aligned neatly in the same direction with an ideal distance for capturing both of the carbonyl lone pairs through the simultaneous coordination mode **E**. In this regard, Wuest examined intramolecular simultaneous coordination of bis(phenoxyaluminum) possessing the central ketonic group, where the major contribution of the corresponding resonance hybrid **K** was revealed by low-temperature ¹³C NMR analysis.²⁷

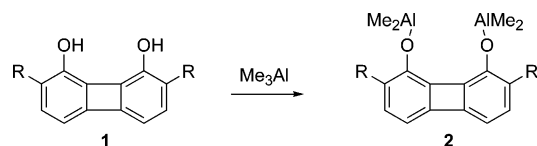


Oh recently studied the complexation of 3,5-dimethyldihydropyranone with 1,8-bis(dichlorobora)naphthalene by NMR analysis and found that the equilibrium between 1:1 and 1:2 complexes was established.²⁸

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Despite the present fundamental difficulties, we have pursued the design of a new bidentate Lewis acid capable of forming double coordination mode **E** using 1,8-biphenylenediols **1** as a requisite spacer to fulfill the structural requirements and organoaluminums as an ideal main group element in view of their high affinity toward an oxygen atom. Here, we wish to describe the development of bis(organoaluminum) reagents **2** for the efficient simultaneous coordination toward carbonyls, thereby elucidating the characteristic features of the double electrophilic activation of carbonyl substrates particularly from the synthetic and mechanistic viewpoints.²⁹



Results and Discussion

Preparation of 2,7-Disubstituted-1,8-biphenylenediols: Development of a New Synthetic Route. First, we had to synthesize 2,7-disubstituted-1,8-biphenylenediols (**1**) as a spacer for the preparation of bidentate Lewis acids **2**. Although Hine reported the synthesis of 2,7-dimethyl-1,8-biphenylenediol, it unfortunately required the use of a large amount of the heavy metal reagents $\text{Hg}(\text{OAc})_2$, Cu, and Cu_2O , and the starting 5-nitro-*o*-cresol is a very expensive compound.^{9b,c} Therefore, we decided to develop an entirely new route to biphenylenediol derivatives starting from an inexpensive and commercially available material. With the eventual feasibility of introducing different aliphatic as well as aromatic substituents on the 2,7-position (R) in mind, we have successfully established a new synthetic procedure starting from *m*-anisidine as illustrated in Scheme 2. After protection of the amino functionality, the consecutive *o*-lithiation³⁰ and bromination sequence provided **4** in 90% yield. The amino moiety, after deprotection under acidic conditions, was then transformed into the corresponding iodide **6** by means of diazonium salt. Upon constructing the

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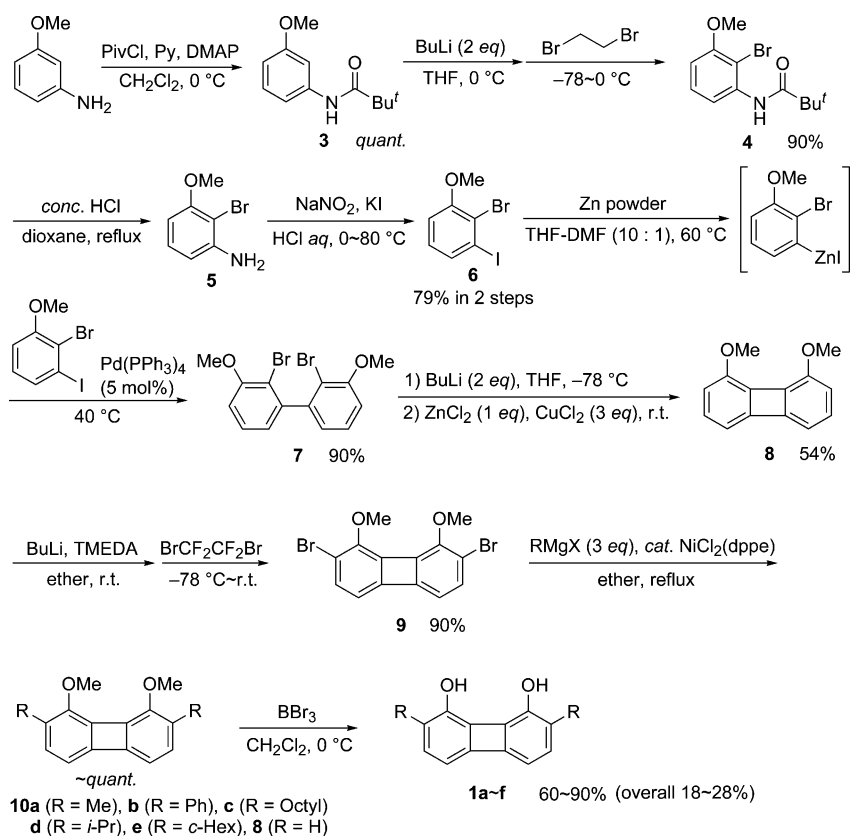
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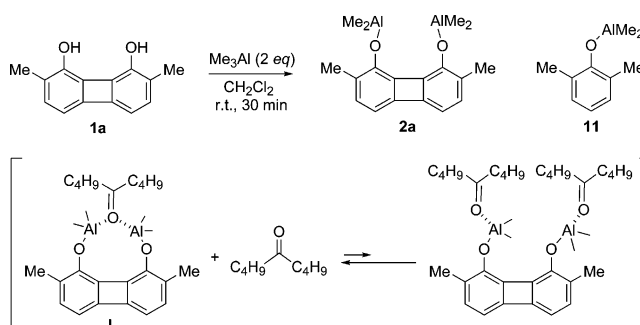
Scheme 2



biaryl structure, we employed the Pd⁰-catalyzed coupling reaction of the in situ generated arylzinc reagent with the parent iodide,³¹ which afforded the desired **7** (90%). This process represents one of the characteristic features of our effort to avoid using excess heavy metals. Subsequently, the requisite four-membered ring formation was accomplished by the method recently introduced by Iyoda,³² giving **8** in 54% yield. *o*-Lithiation with the aid of the methyl ether oxygens and trapping of the resulting anions with BrCF₂CF₂Br produced the bromide **9** in 90% yield, from which a variety of biphenylenediol derivatives with different substituents (**10a-f**) can be synthesized by the subsequent coupling reaction with alkyl or aryl Grignard reagents in the presence of Ni catalyst.³³ Finally, demethylation with BBr₃ furnished the biphenylenediols **1a-f** in 18-28% overall yields.

Evaluation of the Reactivity of Bidentate Organoaluminum Lewis Acids: Carbonyl Reductions. With this new synthetic scheme at hand, we are now in the position of obtaining desired 2,7-disubstituted-1,8-biphenylenediol in a reasonable quantity, and preliminary investigation was carried out with 2,7-dimethyl-1,8-biphenylenediol (**1a**, R = Me) as a spacer. Although **1a** was not as soluble in CH₂Cl₂, introduction of 2 equiv of a 2 M hexane solution of Me₃Al to the suspension of **1a** in CH₂Cl₂ at room temperature under argon atmosphere and subsequent stirring for 30 min gave a deep wine-red

solution, which was used as a bidentate Lewis acid **2a** (R = Me) without purification. To gain information on the reactivity of **2a**, we chose reduction of ketones as a model reaction and compared the reactivity to the conventional monodentate Lewis acid **11** prepared from 2,6-xyleneol and Me₃Al in a similar manner. Initial complexation of 5-nonanone with the in situ



prepared **2a** (1.1 equiv) in CH₂Cl₂ and subsequent reaction with Bu₃SnH (1.1 equiv) at -78 °C for 20 min gave rise to the corresponding 5-nonanol in 86% yield (entry 1 in Table 1). In marked contrast, however, reduction of 5-nonanone with Bu₃SnH in the presence of monodentate organoaluminum reagent **11** under similar reaction conditions afforded 5-nonanol in only 6% yield (entry 2). These results clearly demonstrate that the bidentate Lewis acid **2a** strongly enhances the reactivity of ketone carbonyl toward hydride transfer via the double electrophilic activation of the carbonyl moiety. It should be noted that reduction of excess 5-nonanone (2 equiv) with bidentate **2a** (1 equiv)/Bu₃SnH (2.2 equiv) in CH₂Cl₂ at -78 °C for 20 min lowered the yield of 5-nonanol (47%) (entry 3), suggesting

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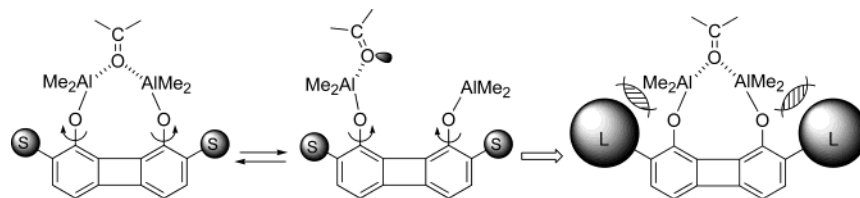


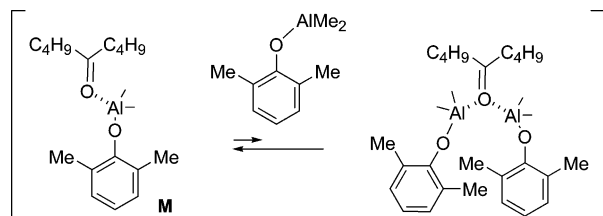
Figure 4.

Table 1. Comparison of the Reactivity between **2a** (R = Me) and **11** in the Reduction of Ketones^a

entry	ketone (R ¹ R ² C=O)	equiv	Lewis acid	equiv	react. time (h)	% yield ^b
1	R ¹ = R ² = C ₄ H ₉	1.0	2a (R = Me)	1.1	0.33	86
2		1.0	11	1.1	0.33	6
3 ^c		2.0	2a (R = Me)	1.0	0.33	47
4		1.0	11	2.0	0.33	10
5	R ¹ = Ph, R ² = Me	1.0	2a (R = Me)	1.1	5	91
6		1.0	11	1.1	5	9

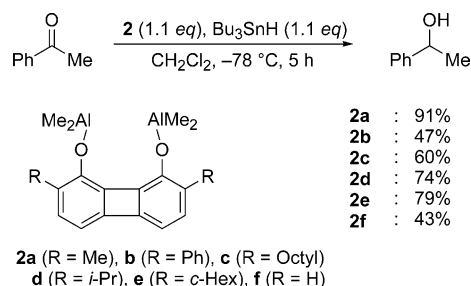
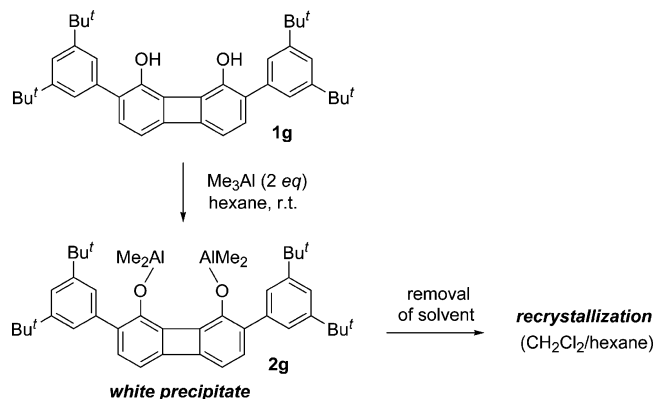
^a The reaction was carried out in CH₂Cl₂ with **2a** (R = Me) or **11** and Bu₃SnH (1.1 equiv) under the indicated reaction conditions. ^b Isolated yield. ^c Use of 2.2 equiv of Bu₃SnH [based on **2a** (R = Me)].

the intervention of the 1:1 ketone–Lewis acid complex (**L**) even in the presence of excess ketone. Furthermore, use of excess **11** (2 equiv) resulted in the formation of 5-nonanol in 10% yield (entry 4), implying the favorable monocoordination complex (**M**) even with excess Lewis acids. A similar tendency is observed in the acetophenone carbonyl reduction as is also included in Table 1.



On the basis of these results, we next investigated the effect of 2,7-substituents of the biphenylene unit on the reactivity of bidentate organoaluminum Lewis acids **2**. Because the O–Al bonds have ample flexibility due to the rotation of Ar–O bonds, the possible bidentate complex with carbonyl substrate could unravel to the monodentate complex in solution in a reversible manner, especially when the 2,7-substituents are small. Here, we envisioned that the introduction of sterically more hindered substituents would play a role to regulate the position of each aluminum atom, thereby stabilizing the bidentate complex as illustrated in Figure 4.

To confirm this hypothesis, we examined the reduction of acetophenone with a series of bis(organoaluminum) Lewis acid **2** under identical reaction conditions (–78 °C, 5 h) (Scheme 3). A substantially diminished yield (43%) of the corresponding reduction product, 2-phenethyl alcohol, in the reaction with **2f** seemed understandable, and the similar yield obtained with **2b** was mainly because of its insolubility even in chlorinated solvents. Although the chemical yields were found to be increased as the steric bulkiness of the 2,7-substituents increased, such an effect was not as dramatic as we expected, and,

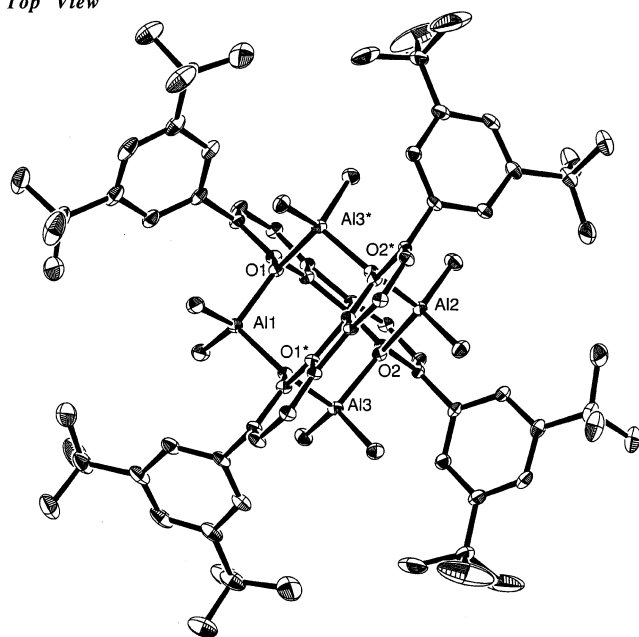
Scheme 3**Scheme 4**

interestingly, the reaction using bis(organoaluminum) **2a** with a methyl group on the 2,7-positions gave the highest yield rather than the one with the sterically more demanding cyclohexyl group.

X-ray Crystallographic Study. Having been puzzled by the results, we sought to gain a clear picture of the exact structure of this type of organoaluminum Lewis acids, which should be unequivocally determined by X-ray crystallography. For this purpose, we synthesized new biphenylenediol **1g** possessing a 3,5-di-*tert*-butylphenyl substituent with the expectation of easily developing a suitable crystal of the corresponding bis(organoaluminum) for X-ray analysis.

As shown in Scheme 4, preparation of bis(organoaluminum) **2g** was carried out by treatment of **1g** with 2 equiv of Me₃Al in hexane at room temperature for 30 min, and the resulting white precipitate, after removal of solvents, was recrystallized from the CH₂Cl₂/hexane solvent system. Surprisingly, single-crystal X-ray diffraction analysis of the colorless crystal thus obtained revealed that **2g** exists as a dimer, where each aluminum coordinates to the lone pair of phenoxy oxygens, forming a rigid, eight-membered cyclic structure as shown in Figure 5. This dimeric organoaluminum was found to be exceptionally stable against moisture and oxygen and can be stored in a screw-cap bottle for months without any indication of decomposition. This unexpected observation suggested that the dimeric **2g** would not dissociate in solution even in the presence of carbonyl

Top View



Side View

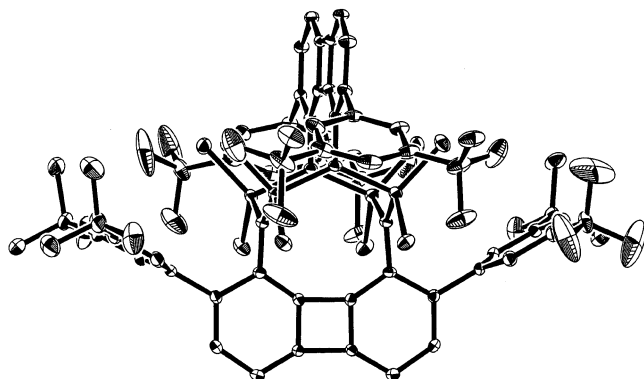


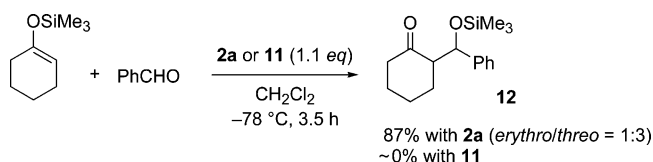
Figure 5. ORTEP diagram of the dimeric **2g**. The solvent molecules and all hydrogen atoms are omitted for clarity.

compound as a Lewis base. Indeed, initial treatment of acetophenone with **2g** (1.1 equiv) in CH_2Cl_2 and subsequent reaction with Bu_3SnH (1.1 equiv) at -78°C for 5 h resulted in total recovery of starting acetophenone. These results strongly implied that the bidentate organoaluminum Lewis acids of type **2** were in equilibrium with their dimers in solution, which could be greatly stabilized by the large 2,7-substituents and thus prevent **2** from exerting the inherent Lewis acidity through double coordination to carbonyl oxygen. Consequently, we decided to undertake further investigation of the reactivity and selectivity of bidentate organoaluminum Lewis acids with bis(organoaluminum) **2a**.

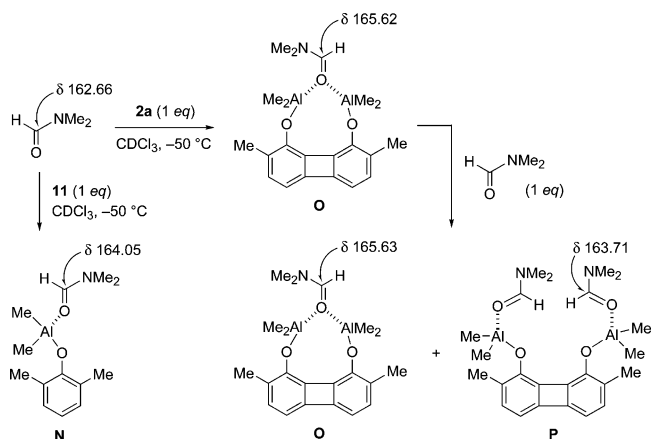
Aldol Reactions. The double electrophilic activation ability of **2a** was further demonstrated in the Mukaiyama aldol reactions as is depicted in Scheme 5. Reaction of 1-(trimethylsilyloxy)-1-cyclohexene and benzaldehyde under the influence of the bidentate **2a** proceeded smoothly at -78°C , giving the aldol product **12** (*erythro/threo* = 1:3) in 87% yield, while its monodentate counterpart **11** showed no evidence of reaction under similar conditions.

Low-Temperature ^{13}C NMR Measurements. Although the double coordination behavior of the bidentate **2a**–carbonyl complex is consistent with the above experimental findings,

Scheme 5



more direct evidence was obtained by low-temperature ^{13}C NMR spectroscopy using DMF as a carbonyl substrate. The original signal of DMF carbonyl carbon occurred at δ 162.66 in the 75 MHz ^{13}C NMR measurement, which shifted downfield to δ 164.05 upon complexation with monodentate aluminum Lewis acid **11** in a 1:1 molar ratio (**N**) in CDCl_3 at -50°C . In contrast, when DMF was treated with 1 equiv of bidentate **2a** under similar conditions, the original DMF peak experienced a more downfield shift to appear at δ 165.62, implying the strong electrophilic activation of the DMF carbonyl by the intervention of double coordination complex (**O**). Addition of one more equivalent of DMF to the 1:1 bidentate **2a**–DMF complex gave two signals at δ 163.71 and δ 165.63 in a ratio of about 1:1, suggesting the equilibrium between the coordination complex (**P**) and the double coordination complex (**O**).



Theoretical Analyses. We further studied the structure and the properties of the bidentate Lewis acid **2a**–carbonyl complex by theoretical method with the aid of the Gaussian 98 programs.³⁴ We chose formaldehyde as a model substrate, and the structural optimization of the complex with **2a** was carried out at the B3LYP/6-31G* level. The orbital analysis was conducted utilizing the wave function obtained at the RHF/6-31G* level for the B3LYP optimized structures to figure out the possible mechanism for activation of the substrate. We also performed similar analyses on the complex of monodentate Lewis acid **11** with formaldehyde.

Figure 6 shows the optimized structures of the 1:1 **2a**–formaldehyde complex (**Q**) and the 1:1 **11**–formaldehyde

(34) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

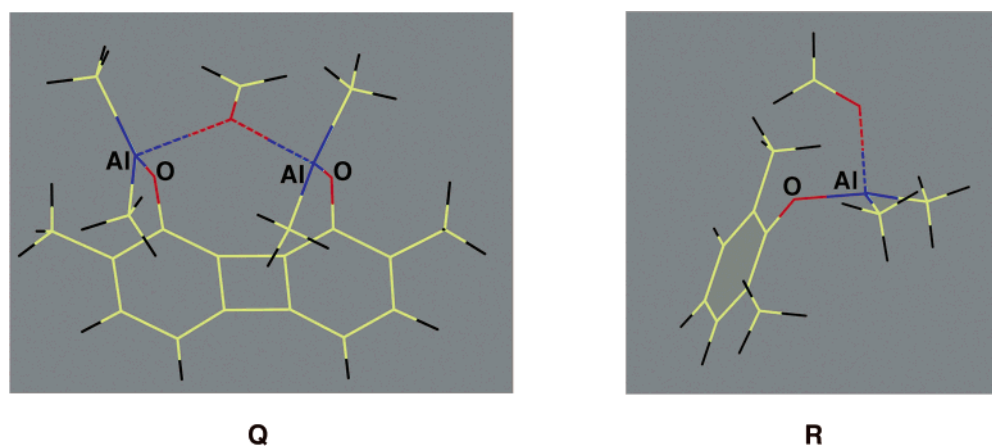


Figure 6.

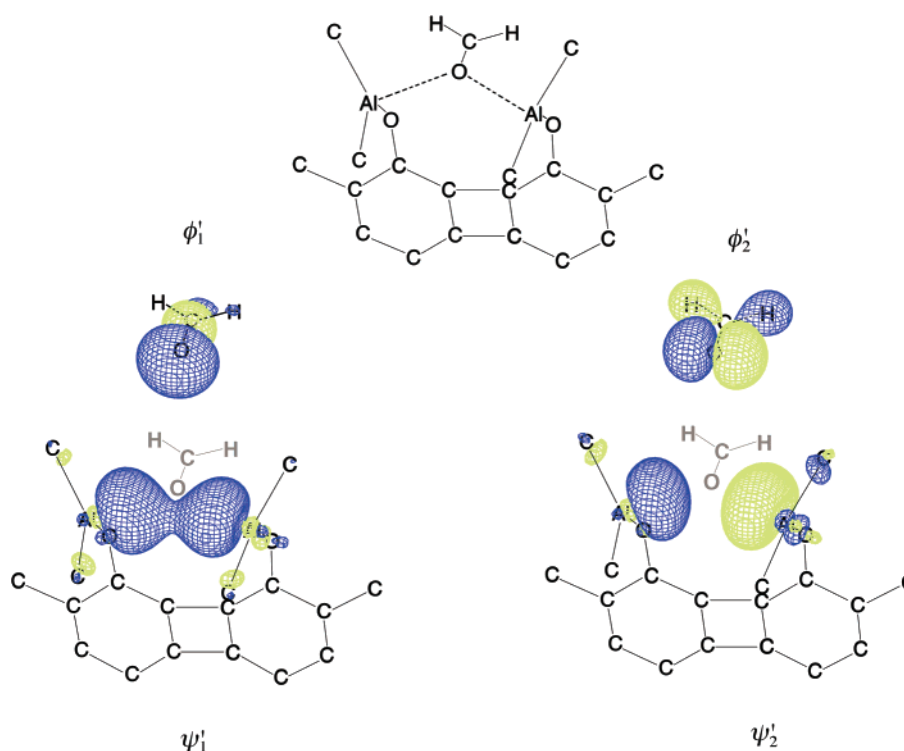


Figure 7.

complex (**R**). In the bidentate complex **Q**, the two Al–O coordination bonds have almost the same bond length and are longer by about 0.21 Å as compared to that in the monodentate complex **R**. Here, it is of significance to clarify how the carbonyl substrate is activated by the Lewis acids. This can be well achieved by examining the orbital interactions between formaldehyde and the Lewis acids, through which electron delocalization from the carbonyl oxygen to the aluminum sites takes place. For this purpose, we first expanded the MOs of the system composed of formaldehyde molecule and the Lewis acid molecules in a linear combination of the MOs of the two fragments (LCMO) and evaluated the strength of the interaction between MOs by the density matrix (D) obtained from their LCMO coefficient. The unitary transformations of the fragment orbitals were then conducted simultaneously within the occupied MO space of one fragment and within the unoccupied MO space of the other fragment to diagonalize the density matrix.³⁵ Consequently, the electron delocalization was reduced to a few

pairs of fragment interaction orbitals (ϕ_f' and ψ_f') that included not only the HOMO of the donor part and the LUMO of the acceptor part, but also all of the occupied MOs of the former and all of the unoccupied MOs of the latter. The diagonal elements of the diagonalized matrix (D') showed the strength of the interaction of these paired transformed orbitals.

Figure 7 illustrates two pairs of the interaction orbitals that represent electron delocalization from the formaldehyde fragment to the **2a** fragment in complex **Q**. The two unoccupied interaction orbitals ψ_1' and ψ_2' are given, respectively, by the bonding and antibonding combinations of the vacant p-type orbitals on the two aluminum sites. The interaction orbital ψ_1' is bonding and overlaps in-phase with the sp-hybrid-type lone pair ϕ_1' of the oxygen atom of the formaldehyde, while ψ_2' is antibonding and also overlaps in-phase with the p-type lone pair ϕ_2' . In contrast, the electron delocalization occurs through only

(35) Fujimoto, H.; Yamasaki, T.; Mizutani, H.; Koga, N. *J. Am. Chem. Soc.* **1985**, *107*, 6157.

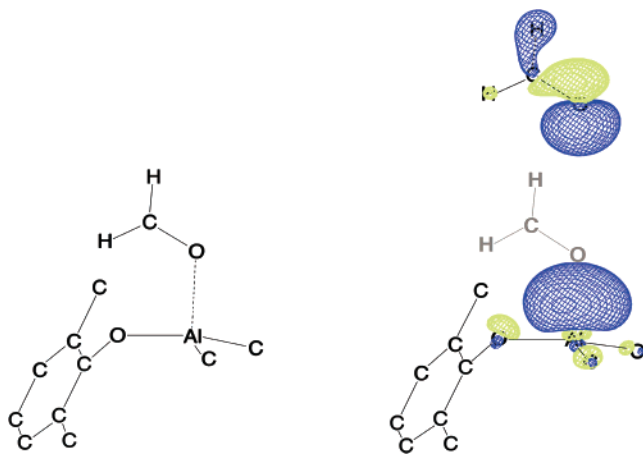


Figure 8.

one pair of interaction orbitals in the monodentate complex **R** (Figure 8). Actually, the electronic charge shifted from the formaldehyde to Lewis acid was calculated to be 0.171 for the complex **Q** and 0.134 for the complex **R**, respectively,³⁶ suggesting that the carbonyl group is more strongly activated in **Q** toward an attack of a nucleophile.

Next, we evaluated numerically the extent of the activation of the formaldehyde moiety by the Lewis acids. Because the SCF calculations for each complex system show that the carbonyl π^* orbital is obtained as one of the canonical unoccupied orbitals and is almost 100% localized on the carbonyl group as in the formaldehyde molecule in an isolated state, the energy level of this π^* MO (LUMO) orbital can be a good index for the reactivity of the carbonyl moiety. It has been calculated to be 0.052 au in **Q** and 0.068 au in **R**, 0.086 and 0.070 au lower than the value of formaldehyde itself, respectively. This, together with the result obtained above, directly support the double electrophilic activation of the carbonyl group by the bidentate Lewis acid **2a**.^{13a,22f,23b,c}

Evaluation of the Selectivity of Bidentate Organoaluminum Lewis Acids: Stereoselectivity. We then focused our attention on examining the selectivity of bidentate Lewis acids in organic synthesis and first applied bis(organoaluminum) **2a** to the regio- and stereocontrolled Michael addition of silyl ketene acetals to α,β -unsaturated ketones as acceptors.³⁷ Reaction of benzalacetone and silyl ketene acetal **13** with dimethylaluminum aryloxides of type **14** gave rise to a mixture of Michael adducts **15** and **16** almost exclusively, where the stereoselectivity was found to be profoundly influenced by the steric size of a phenoxy ligand. Initial treatment of benzalacetone with dimethylaluminum phenoxide **14a** and subsequent reaction with **13** in CH_2Cl_2 at -78°C instantaneously produced **15** and **16** in 74% combined yield, and the **15/16** (*Z/E*) ratio was determined to be 80:20 by ^1H NMR analysis. Switching the

phenoxy group to 2,6-xyleneoxy (**11**), 2,6-diisopropylphenoxy (**14b**), and 2,6-di-*tert*-butylphenoxy (**14c**) groups, the *Z*-selectivity decreased from 80:20 to 70:30, 67:33, and 33:67, respectively. Based on the results, the stereochemical outcome of the present organoaluminum-promoted Michael addition should be discussed. The *Z*-selectivity observed with sterically less hindered **14a** or **11** is interpreted by the preferable formation of complex **S**. The aluminum phenoxide **14b** or **14c** possessing more hindered 2,6-substituents would tend to coordinate to the carbonyl lone pair anti to the methyl group (complex **T**), which would be in equilibrium shifted to the conformationally more stable complex **U** due to the steric repulsion between the phenoxy ligand and ketone substituent, thereby increasing the formation of *E*-isomeric Michael adduct **16**. In the ultimate case, bidentate **2a** can be utilized to obtain *E*-isomeric **16** as a major product via the formation of complex **V** with *s-trans* conformation (Scheme 6).³⁸

Chemoselectivity. In addition to the stereoselectivity, the chemoselectivity of the bidentate Lewis acids was investigated in conjunction with our interest in the molecular recognition ability of bis(organoaluminum) **2a**. The chemoselective functionalization between carbonyls and their masked acetals is a synthetically useful operation. Most of the ordinary Lewis acid promoters activate both carbonyl and acetal functions.³⁹ The discrimination of acetals over carbonyls is commonly achievable using TiCl_4 and Me_3SiOTf ; these, for instance, induce selective aldolization of acetal functionality with enol silyl ethers in the presence of carbonyl groups by taking advantage of the inherent inertness of ketones and aldehydes toward enol silyl ethers under the influence of them.⁴⁰ However, the opposite selectivity, that is, chemoselective functionalization of carbonyls, seems quite difficult to attain in view of the high reactivity of acetal counterparts for Lewis acids, and hence it has not yet been fully realized in electrophilic reactions despite long-standing concern. In this situation, chemoselective preference for carbonyl compounds in the aldol reactions with ketene silyl acetals has been achieved by use of organotin Lewis acids,⁴¹ utilizing the fact that ketene silyl acetals intrinsically react with aldehydes more readily than with acetals, whereas enol silyl ethers are compatible with acetals. Actually, reaction of a mixture of 1 equiv each of benzaldehyde and its dimethyl acetal with 1-(trimethylsilyloxy)-1-cyclohexene under the influence of catalytic Me_3SiOTf (5 mol %) in CH_2Cl_2 at -78°C for 3 h afforded aldol products **12** (*R* = H) and **18** (86% combined yield) in a ratio of 9:91 (Scheme 7).^{40a,b,42} Switching a Lewis acid from Me_3SiOTf to TiCl_4 resulted in the loss of selectivity (ratio of **12:18** = 59:41), and both SnCl_4 and $\text{BF}_3\cdot\text{OEt}_2$ exhibited moderate and opposite chemoselectivity (73:27 and 74:26, respectively). In contrast, however, bis(organoaluminum) **2a** as a bidentate Lewis acid, on treatment with an equimolar mixture of benzaldehyde and

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(38) The *E*-isomer **16** is a thermodynamically less stable product, and standing of **16** resulted in gradual conversion to a thermodynamically more stable *Z*-isomer **15**.

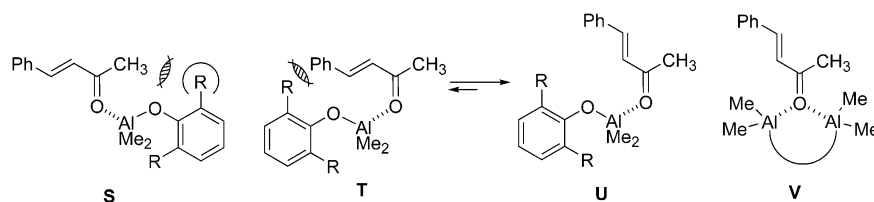
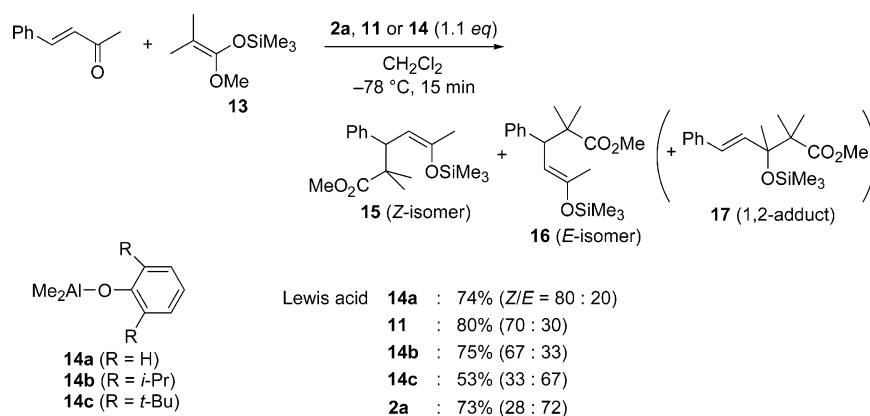
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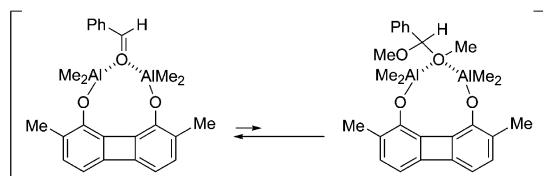
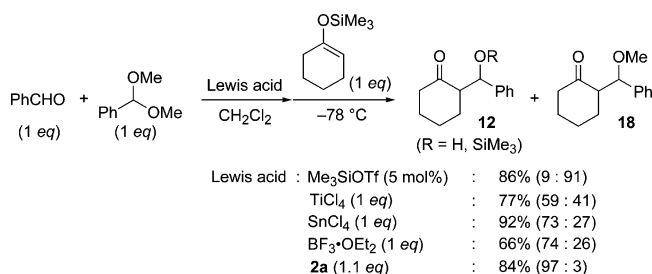
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(42) For reviews of the Mukaiyama aldol reaction, see: (a) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817. (b) Mukaiyama, T. *Org. React.* **1982**, 1043. See also: Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043.

Scheme 6



Scheme 7



its dimethyl acetal, is capable of activating aldehyde carbonyl selectively as is evident by the subsequent reaction with 1-(trimethylsiloxy)-1-cyclohexene, giving **12** (R = SiMe₃: 71%; *erythro/threo* = 26:74 and R = H: 10% yields) almost exclusively (97:3). It should be added that the aldol reaction with the monodentate counterpart **11** resulted in the very reluctant formation of **12** and **18** under similar reaction conditions (4.5% combined yield).

Our examination has advanced to the Mukaiyama aldol condensation of various aldehydes and ketones with ketene silyl acetals in the presence of their acetals. As revealed in Table 2, excellent chemoselectivity was uniformly observed with bis-(organoaluminum) **2a**, particularly in the functionalization of ketone carbonyls, whereas the employment of Me₃SiOTf or dibutyltin bis(triflate) (DBTT) as a catalyst brought a lack of selectivity depending upon the reactivity of the substrates (entries 1–11).⁴³ These results clearly demonstrate the effectiveness of **2a** for recognition and activation of carbonyl functionality based on the double electrophilic activation. Furthermore, virtually complete chemoselective functionalization of aldehyde carbonyls was also found to be feasible in the Lewis acid-

promoted allylation of aldehydes with allyltributyltin, and the opposite chemoselectivity is easily accessible using TiCl₄ as promoter (entries 12–15).^{44,45}

Activation of Ethers. The high activation and recognition ability of bidentate Lewis acid **2a** through double coordination is, in principle, applicable to activation of the ethereal substrates, and hence the Lewis acid-promoted Claisen rearrangement of allyl vinyl ethers,⁴⁶ one of the most powerful tools for carbon–carbon bond-forming reactions in organic synthesis, was investigated as a representative example. Treatment of *trans*-cinnamyl vinyl ether (**21**) with **2a** in CH₂Cl₂ at 0 °C for 1 h cleanly produced the secondary alcohol **22** in 96% yield, indicating the rapid methyl transfer from **2a** to the aldehyde carbonyl derived in situ by the initial **2a**-promoted rearrangement. With monodentate Lewis acid **11**, however, the reaction proceeded very sluggishly and resulted in almost total recovery of the starting **21** under comparable reaction conditions, which unambiguously demonstrated the potential of bidentate Lewis acids for the activation of ethers (Scheme 8).

Conclusion

We have successfully developed a new and reliable synthetic procedure of 2,7-disubstituted-1,8-biphenylenediols starting from commercially available *m*-anisidine, which enables the preparation of a variety of (2,7-disubstituted-1,8-biphenylenedioxy)-bis(dimethylaluminum) (**2**). Their reactivity as a bidentate

(43) The aldol reaction of cyclohexanecarboxaldehyde dimethyl acetal with ketene silyl acetal **13** by **2a** was attempted at –78 °C to evaluate the intrinsic reactivity of the acetal itself, which resulted in the formation of aldol product in 37% yield (cf. entries 1 and 2 in Table 2). Therefore, the high chemoselectivity observed herein is ascribed to the rate difference between the aldol reaction of carbonyl compounds and that of their corresponding acetals based on the double electrophilic activation of carbonyls.

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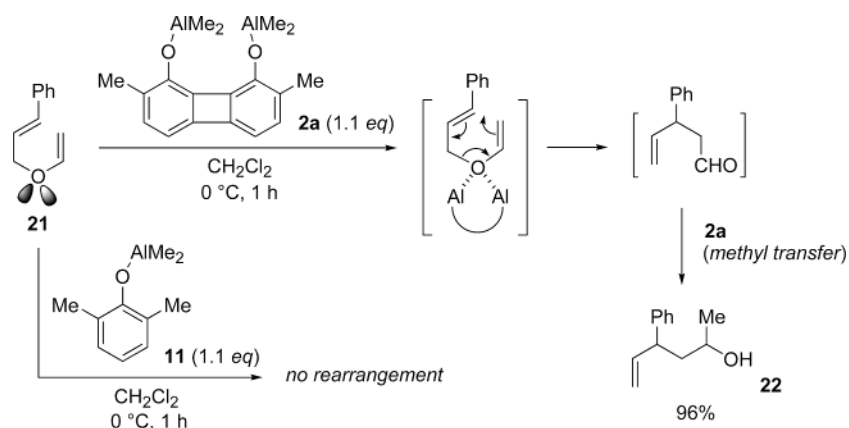
(45) Preliminary report: Ooi, T.; Tayama, E.; Takahashi, M.; Maruoka, K. *Tetrahedron Lett.* **1997**, *38*, 7403.

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Table 2. Discrimination Reaction between Carbonyl Compounds and Their Acetals^a

entry	nucleophile (Nu)	R ³	R ⁴	Lewis acid	yield (%) ^b (19 + 20)	ratio ^c
1	 13	C ₆ H ₁₁	H	Me ₃ SiOTf	89 (19a + 20a)	26 : 74
2				2a	89	90 : 10
3		C ₇ H ₁₅	H	Me ₃ SiOTf	76 (19b + 20b)	58 : 42
4				2a	82	87 : 13
5		Ph	H	Me ₃ SiOTf	92 (19c + 20c)	79 : 21
6				2a	97	90 : 10
7		C ₉ H ₁₉	CH ₃	Me ₃ SiOTf	81 (19d + 20d)	11 : 89
8				2a	86	>99 : <1
9		Ph	CH ₃	Me ₃ SiOTf	81 (19e + 20e)	57 : 43
10				Bu ₂ Sn(OTf) ₂ ^d	75	16 : 84
11				2a	88	>99 : <1
12	 SnBu ₃	C ₆ H ₁₁	H	TiCl ₄ ^e	87 (19f + 20f)	14 : 86
13				2a	80	>99 : <1
14	Ph	H	TiCl ₄ ^e	81 (19g + 20g)	12 : 88	
15			2a	86	>99 : <1	

^a The electrophilic reaction of carbonyl compounds and acetals (1 equiv each) was carried out in CH₂Cl₂ at -78 °C for 2–3 h with nucleophiles (1 equiv) in the presence of either a catalytic amount of Me₃SiOTf (0.05 equiv) or 1.1 equiv of **2a**. ^b Isolated yield. ^c The ratio of carbonyl and acetal adducts was determined by 300 MHz ¹H NMR analysis. ^d Dibutyltin bis(triflate) (DBTT) (0.1 equiv) was used as catalyst. ^e Use of 1 equiv of TiCl₄.

Scheme 8

organoaluminum Lewis acid has been evaluated in the reduction of acetophenone, and (2,7-dimethyl-1,8-biphenylenedioxy)bis(dimethylaluminum) (**2a**) gave the highest chemical yield. Single-crystal X-ray diffraction analysis of the colorless crystalline of bis(organoaluminum) **2g** revealed its assembly into a rigid dimer; this suggests that the bidentate organoaluminum Lewis acids of type **2** are in equilibrium with their dimers in solution, which could be greatly stabilized by the large 2,7-substituents and thus prevent **2** from exerting the Lewis acidity through double coordination to carbonyl oxygen. This understanding seems consistent with the highest reactivity of **2a**,

which has also been characterized by comparing it to that of the corresponding monodentate dimethylaluminum 2,6-xyleneoxide (**11**) in the reduction of 5-nonanal and the Mukaiyama aldol reaction. The strong activation of carbonyls by **2a** was supported by low-temperature ¹³C NMR analysis and theoretical study using the Gaussian 98 programs. The bidentate Lewis acid **2a** was found to exhibit unusual stereoselectivity in the Mukaiyama Michael addition and allowed highly chemoselective functionalization of carbonyl compounds in the presence of their acetals, representing salient features of bidentate Lewis acid in organic synthesis. In addition, application of **2a** to the

Claisen rearrangement of allyl vinyl ethers demonstrates the effectiveness of **2a** for the activation of ether functionality. This type of bidentate system seems to be general^{47–49} and applicable to other metals including transition metals. Indeed, examples utilizing Li,⁵⁰ Si,⁵¹ Sn,⁵² Ti,^{48c,53} Zr,^{53c} and Hf^{53c} have been reported to date, and their potential utility in selective organic synthesis including asymmetric catalysis has also been demonstrated,⁵⁴ contributing to the expansion of this field of

- (47) For other synthetic applications of the bidentate organoaluminum Lewis acid, see: (a) Ooi, T.; Takahashi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 835. (b) Ooi, T.; Miura, T.; Itagaki, Y.; Ichikawa, H.; Maruoka, K. *Synthesis* **2002**, 279 and references therein.
- (48) For other examples of bidentate aluminum Lewis acids, see: (a) Saied, O.; Simard, M.; Wuest, J. D. *Organometallics* **1996**, *15*, 2345. (b) Saied, O.; Simard, M.; Wuest, J. D. *Organometallics* **1998**, *17*, 1128. (c) Saied, O.; Simard, M.; Wuest, J. D. *Inorg. Chem.* **1998**, *37*, 2620. (d) Hanawa, H.; Abe, N.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 5365. (e) Abe, N.; Hanawa, H.; Maruoka, K.; Sasaki, M.; Miyashita, M. *Tetrahedron Lett.* **1999**, *40*, 5369. (f) Hanawa, H.; Maekawara, N.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 8379.
- (49) For a recent impressive study by Scott on the discrete bimetallic aluminum assembly with chlorine, see: Cottone, A., III; Scott, M. J. *Organometallics* **2002**, *21*, 3610.
- (50) Ooi, T.; Saito, A.; Maruoka, K. *Tetrahedron Lett.* **1998**, *39*, 3745.
- (51) (a) Asao, N.; Shibato, A.; Itagaki, Y.; Jourdan, F.; Maruoka, K. *Tetrahedron Lett.* **1998**, *39*, 3177. (b) Shibato, A.; Itagaki, Y.; Tayama, E.; Hokke, Y.; Asao, N.; Maruoka, K. *Tetrahedron* **2000**, *56*, 5373.
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research. We believe the concept of bidentate Lewis acids may continue to have considerable impact on organic and inorganic chemistries as well as on molecular recognition chemistry.

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Supporting Information Available: Experimental procedures and spectroscopic characterization of new compounds (PDF); crystallographic data for **2g** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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