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Catalysis Today 66 (2001) 33–45

CATALYSIS TODAY

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Bidentate Lewis acids for organic synthesis

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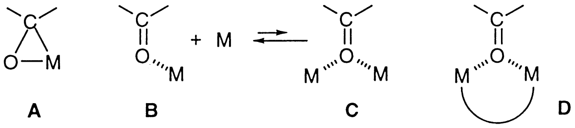
Abstract

The chemistry of bidentate Lewis acids belongs to an unexplored field of science and has been only poorly studied so far. This review illustrates the design of several bidentate aluminum Lewis acids and their successful application to selective organic synthesis. The chemistry disclosed herein implies the vast potential of bidentate Lewis acids in other fields of chemistry including molecular recognition and asymmetric synthesis. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Bidentate Lewis acids; Asymmetric synthesis; Organic synthesis

1. Introduction

Electrophilic activation of carbonyl groups with certain Lewis acids is a well-established method for enhancing their reactivity and selectivity toward nucleophilic addition. The two principal modes of coordination of carbonyls to metals are the π-bonding (**A**) and σ-bonding (**B**) [1,2]. The latter mode is generally preferred with main-group and early-transition metal Lewis acids. In addition simultaneous coordination to carbonyl groups with two metals of type (**C**) would alter the reactivity and selectivity of the carbonyl substrates. Examples of such double coordination with two metals are rare despite its potential importance simply because of the high preference for the single coordination mode (**B**) even in the presence of excess Lewis acids and hence the nature of such di-σ-bonding (**C**) remains elusive [3]. In this context, we have been interested in the possibility of designing bidentate Lewis acids that are capable of preferring di-σ-bonding (**D**) with two metals [4–6]. Among various main-groups and early-transition metal elements, aluminum and titanium seem to be the metals of choice in view of their high affinity toward oxygen atom (see bidentate transition-metal/carbonyl complexes [7–11]). In this review, I wish to introduce my recent progress on this subject by using modified bis(organoaluminum) reagents for the efficient simultaneous coordination toward carbonyls, thereby elucidating the characteristics of the double electrophilic activation of carbonyl substrates.



2. Bidentate aluminum Lewis acids with biphenylenediol spacer

The requisite bidentate ligand, 2,7-dimethyl-1,8-biphenylenediol (**2**) for the design of a bidentate aluminum Lewis acid was synthesized according to the literature procedure [12] and the bidentate organoaluminum reagent, (2,7-dimethyl-1,8-biphenylenedioxy) bis(dimethylaluminum) (**1**) was prepared by treatment of the biphenylenediol **2** with Me_3Al (2 equiv.) in CH_2Cl_2 at room temperature [12]. Initial complexation of 5-nonanone with the in situ generated **1** (1.1

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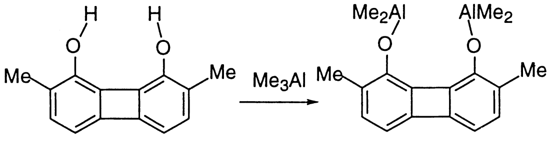
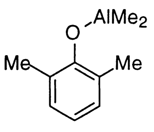
PII: S0920-5861(00)00602-7

equiv.) in CH_2Cl_2 and subsequent reaction of Bu_3SnH (1.2 equiv.) at −78°C for 20 min gave rise to the corresponding 5-nonanol in 86% yield. In marked contrast, however, reduction of 5-nonanone with Bu_3SnH in the presence of monodentate organoaluminum reagent **3** (prepared from 2,6-xylenol and Me_3Al (1:1 molar ratio)) under similar reaction conditions afforded 5-nonanol in low yield. These results clearly demonstrate that the bidentate Lewis acid **1** strongly enhances the reactivity of ketone carbonyl toward hydride transfer via the double electrophilic activation of carbonyl moiety. It should be noted that reduction of excess 5-nonanone (2 equiv.) with bidentate **1** (1.1 equiv.)/Bu_3SnH (2.2 equiv.) in CH_2Cl_2 at −78°C for 20 min lowered the yield of 5-nonanol (47%), suggesting the intervention of the 1:1 ketone/Lewis acid complex even in the presence of excess ketone. Furthermore, the use of excess **3** (2 equiv.) for 1 equiv. of 5-nonanone resulted in formation of 5-nonanol in 10% yield, implying the favorable monocoordination complex (**B**) with excess Lewis acids.



2 **1**



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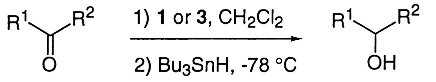
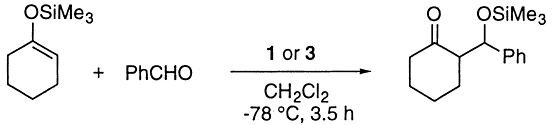


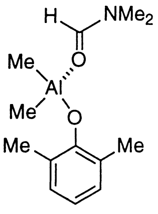
$R^1 = R^2 = Bu$: 86% with **1** (6% with **3**)
$R^1 = Ph, R^2 = Me$: 91% with **1** (9% with **3**)

A similar tendency is observed in the acetophenone carbonyl reduction. Further, the Mukaiyama aldol reaction of 1-(trimethylsiloxy)-1-cyclohexene and benzaldehyde was affected with the bidentate **1**, giving the aldol products (erythro/threo = 1 : 3) in high yield, though its monodentate counterpart **3** showed no evidence of reaction under similar conditions.

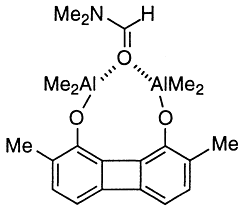


87% with **1**
~0% with **3**

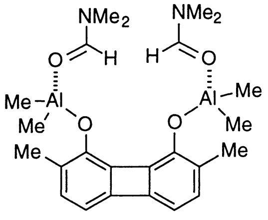
Although double coordination behavior of the bidentate **1**-carbonyl complex is consistent with the above experimental findings, more direct evidence was obtained by low-temperature ^{13}C NMR spectroscopy using DMF as a carbonyl substrate [12]. Thus, the 75 MHz ^{13}C NMR measurement of the 1:1 monodentate **3**-DMF complex (**E**) in $CDCl_3$ at −50°C showed that the original signals of DMF carbonyl at δ 162.66 shifted downfield to δ 164.05. In contrast, 1:1 bidentate **1**-DMF chelation complex under similar conditions undergoes a further downfield shift for the DMF carbonyl (δ 165.62), implying the strong electrophilic activation of the DMF carbonyl by the intervention of double coordination complex (**F**). Addition of one more equiv. of DMF to the 1:1 bidentate **1**-DMF complex gives two signals at δ 163.71 and δ 165.63 in a ratio of about 1:1, suggesting the equilibrium between the coordination complex (**G**) and the double coordination complex (**F**).



E

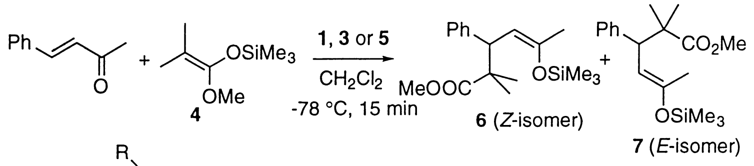


F



G

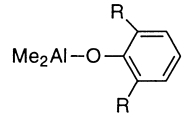
In addition to these reactivity profiles, our bidentate Lewis acid chemistry is also highly effective for obtaining the unique selectivity. The following regio- and stereocontrolled Michael addition of silyl ketene acetals to α,β-unsaturated ketones as acceptors is another interesting feature of the bidentate Lewis acid **1** in organic synthesis [12]. Thus, reaction of benzalacetone and silyl ketene acetal **4** with dimethylaluminum aryloxides of type **5** gave rise to a mixture of Michael adducts **6** and **7** almost exclusively, where the *Z* selectivity decreased with increase in the steric size of a phenoxy ligand in **5**. Indeed, switching the phenoxy group to 2,6-xylenoxy, 2,6-diisopropylphenoxy and 2,6-di-*tert*-butylphenoxy groups, the *Z* selectivity decreased from 80:20 to 70:30, 67:33, and 33:67, respectively. Based on the experimental findings, the stereochemical outcome of the *Z*-isomeric Michael adduct **6** is interpreted for by the preferrable complex (**H**) formation of benzalacetone with sterically less hindered **5a** or **3**. With more hindered **5b** or **5c**, the coordination complex (**J**) is then favored rather than the sterically congested complex (**I**), thereby increasing the formation of *E*-isomeric Michael adduct **7**. In the ultimate case, bidentate **1** can be utilized to obtain *E*-isomeric **7** as a major product via the complex (**K**) formation with *s*-*trans* conformation.



4

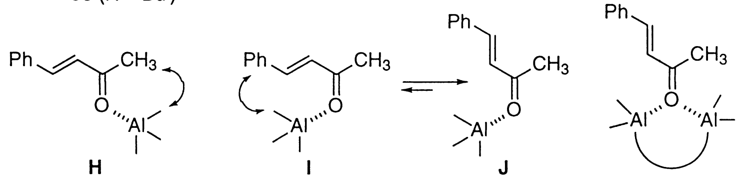
6 (*Z*-isomer)

7 (*E*-isomer)



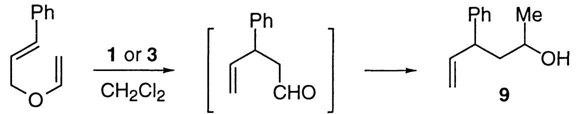
5a (R = H)
5b (R = Pr^i)
5c (R = Bu^t)

Lewis acid	5a	3	5b	5c	1
Z/*E* ratio	80:20	70:30	67:33	33:67	28:72
% yield	74	80	75	53	73



H **I** **J** **K**

The high double coordination ability of bidentate Lewis acid **1** is also applicable to the activation of the ethereal substrates as exemplified by the Lewis acid-promoted Claisen rearrangement of allyl vinyl ethers [12]. Indeed, treatment of *trans*-cinnamyl vinyl ether (**8**) with bidentate **1** in CH_2Cl_2 at 0°C produced the rearrangement-methylation product **9** in 96% yield. With monodentate Lewis acid **3**, however, the reaction is very sluggish, resulting in almost total recovery of the starting material under the comparable reaction conditions.

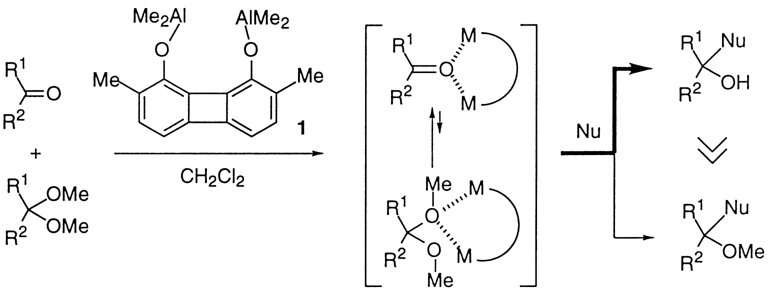


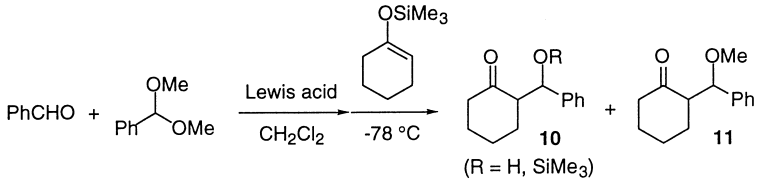
8

9

96% with **1**
~0% with **3**

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 [13]. The discrimination of acetals over carbonyls is commonly achievable by using $TiCl_4$ and Me_3SiOTf, which induce selective activation of acetal functionality in the presence of carbonyl groups [14–16]. However, the opposite selectivity, i.e., chemoselective functionalization of carbonyls in electrophilic substitution reactions seems quite difficult to attain in view of the high reactivity of acetal counterparts for Lewis acids. Quite recently, Otera et. al. reported unprecedented preference for activation of aldehyde carbonyls over acetals in organotin Lewis acid-promoted Mukaiyama-aldol reaction of ketene silyl acetals, which is unfortunately not applicable for selective activation of ketone carbonyls [17]. In this context, we are interested in the possibility of the chemoselective activation of carbonyls by using our recently developed bidentate organoaluminum Lewis acid [18].

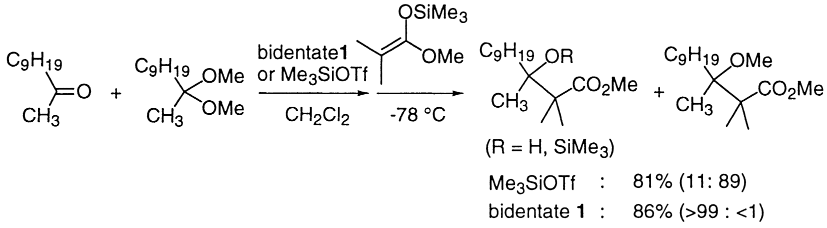


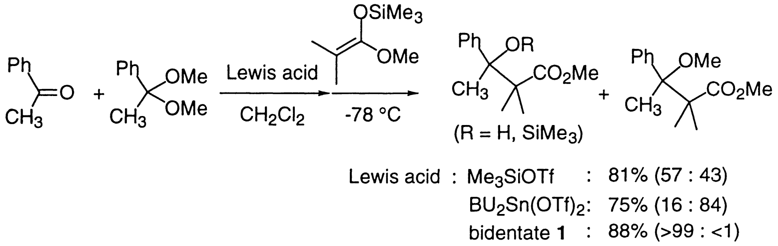


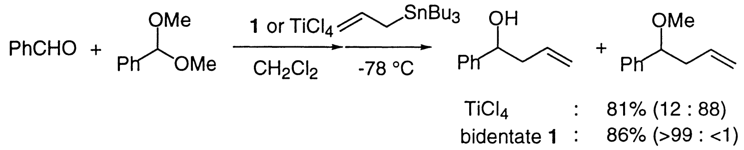
Lewis acid		
Me_3SiOTf	:	86% (9 : 91)
$TiCl_4$	:	77% (59 : 41)
$SnCl_4$	:	92% (73 : 27)
$BF_3 \cdot OEt_2$	:	66% (74 : 26)
bidentate **1**	:	84% (97 : 3)

First, we examined Mukaiyama-aldol reaction of benzaldehyde and its dimethyl acetal with a silyl enol ether. Reaction of a mixture of 1 equiv. each of benzaldehyde and its dimethyl acetal with 1-(trimethylsiloxy)-1-cyclohexene under the influence of catalytic Me_3SiOTf (10 mol%) in CH_2Cl_2 at −78°C for 2 h afforded aldol products **10** (R = $SiMe_3$) and **11** (86% combined yield) in a ratio of 9:91, which indicates the higher reactivity of acetal functionality for Me_3SiOTf-catalyzed aldol reaction as reported by Noyori et al. [17]. Switching a Lewis acid from Me_3SiOTf to $TiCl_4$ resulted in the loss of selectivity and both $SnCl_4$ and $BF_3 \cdot OEt_2$ exhibited moderate and opposite chemoselectivity. In contrast, however, (2,7-dimethyl-1,8-biphenylenedioxy)bis(dimethylaluminum) (**1**) as a bidentate Lewis acid [12], on treatment of an equimolar mixture of benzaldehyde and its dimethyl acetal, is capable of activating aldehyde carbonyl selectively as evident by the subsequent reaction with 1-(trimethylsiloxy)-1-cyclohexene, giving **10** (R = $SiMe_3$: 71%; erythro/threo = 26 : 74 and R = H : 10% yield) almost exclusively.

The following selected examples clearly demonstrate the effectiveness of bidentate organoaluminum Lewis acid **1** for the recognition and activation of carbonyl functionality based on the double electrophilic activation, thereby allowing chemoselective funtionalization of carbonyl compounds. Excellent chemoselective Mukaiyama-aldol condensation of ketone carbonyl with ketene silyl acetals appears feasible by the use of **1**, while Me_3SiOTf caused the lack of selectivity depending upon the reactivity of the substrates. Notably, discriminative aldol reaction of acetophenone and its dimethyl acetal with ketene silyl acetal in the presence of catalytic dibutyltin bis(triflate) (DBTT) (10 mol%) [17], which is quite useful for activation of aldehyde carbonyls over acetals, gave unsatisfactory results, producing β-methoxy ester preferentially. In the Lewis acid-promoted allylation of aldehydes with allyltributyltin, virtually complete chemoselective functionalization of aldehyde carbonyls is also observable and the opposite chemoselectivity is easily accessible using $TiCl_4$ as promoter.

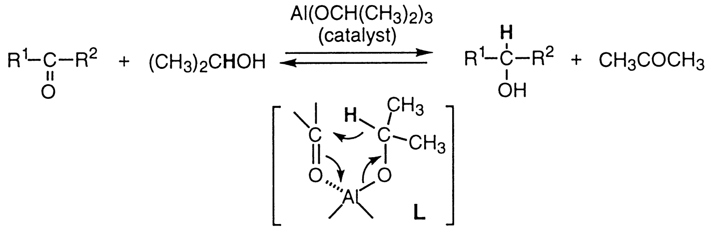




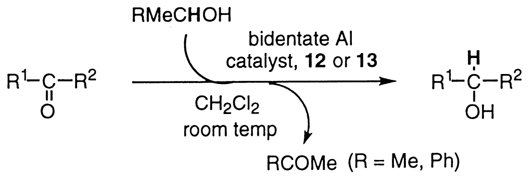


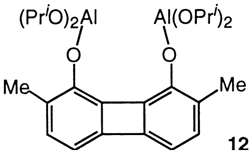
3. Synthetic utility of bidentate Lewis acids for MPV reduction

The Meerwein–Ponndorf–Verley (MPV) reaction is the chemoselective reduction of various carbonyl substrates by using aluminum alkoxides, generally Al(OPr^i)$_3$ as catalyst and *i*-PrOH as hydride source [19–22]. In the MPV reduction, a hydride transfer from the membered to a carbonyl acceptor reversibly via a six-membered transition state [**L**] is initiated by the activation of the carbonyl upon coordination to Lewis acidic aluminum. The advantage of the MPV reduction includes its chemoselectivity, mild reaction conditions, operational simplicity, safe handling, and ready adaptation both in the laboratory and on a large-scale. Nonetheless, there are several practical problems in the reduction such as need for excess of alcohol as hydride source, low reaction rate, formation of condensation products, and use of higher reaction temperature with concurrent removal of acetone to shift the equilibrated reaction towards the formation of alcohol. Accordingly, various modifications of the MPV reduction have been developed in order to overcome these disadvantages. The more recent improvements of the MPV reduction are the use of catalytic lanthanide alkoxides [23,24], microwave irradiation [25], and the addition of CF_3CO_2H to Al(OPr^i)$_3$ to accelerate the reduction [26,27]. In addition to these modifications, we have successfully developed the highly accelerated MPV reduction of carbonyl substrates with bidentate aluminum catalyst [28,29].



The typical MPV reduction of carbonyl substrates normally proceeds quite reluctantly. For example, reduction of benzaldehyde in CH_2Cl_2 with *i*-PrOH (1.3 equiv.) in the presence of commercially available $Al(OPr^i)_3$ (1 equiv.) at room temperature for 2 h gave rise to benzyl alcohol in only 10% yield. Under the similar reduction conditions, ketone substrates (e.g., 4-phenylcyclehexanone and 2-undecanone) were totally unreactive with most recovery of the starting ketones. In marked contrast, however, the initial formation of bidentate aluminum catalyst **12** derived from 2,7-dimethyl-1,8-biphenylenediol, Me_3Al (2 equiv.), and *i*-PrOH (4 equiv.), followed by treatment of benzaldehyde with in situ generated (2,7-dimethyl-1,8-biphenylenedioxy)-bis(diisopropoxyaluminum) (**12**) at room temperature instantaneously produced the reduced benzyl alcohol almost quantitatively. Moreover, even with 5 mol% of catalyst **12** the reduction proceeds smoothly at room temperature to furnish benzyl alcohol in 81% yield after 1 h.





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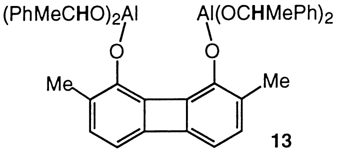
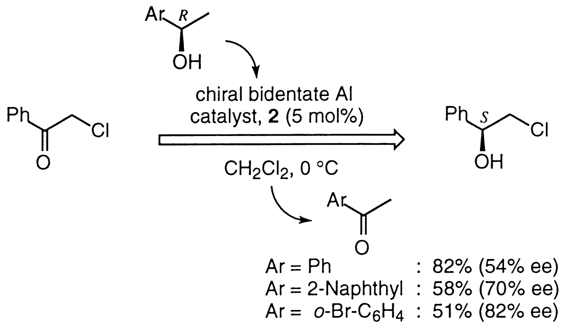


13

Other selected examples are listed in Table 1. In addition to aldehydes, both cyclic and acyclic ketones can be reduced equally well. *sec*-Phenethyl alcohol as hydride source works more effectively than *i*-PrOH. This finding prompted us to examine the asymmetric MPV reduction of unsymmetrical ketones with optically active catalysts of type **13**. Indeed, treatment of 2-chloroacetophenone with optically pure (*R*)-(+)-*sec*-phenethyl alcohol under the influence of catalytic **13** at 0°C for 10 h afforded (*S*)-2-chloro-1-phenylethanol with moderate asymmetric induction. Switching chiral alcohols from (*R*)-(+)-*sec*-phenethyl alcohol to (*R*)-(+)-α-methyl-2-naphthalenemethanol and (*R*)-(+)-*sec-o*-bromophenethyl alcohol further enhanced the optical yields of (*S*)-2-chloro-1-phenylethanol in 70 and 82% ee, respectively.

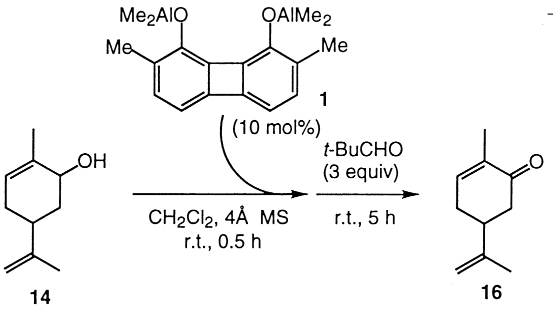


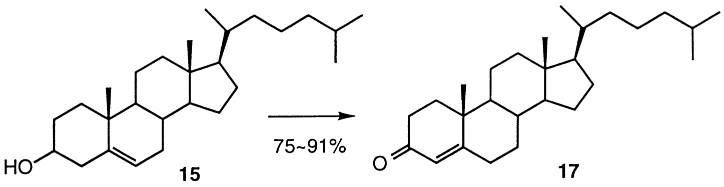
Ar = Ph : 82% (54% ee)
Ar = 2-Naphthyl : 58% (70% ee)
Ar = *o*-Br-C_6H_4 : 51% (82% ee)

The present approach is also applicable to the reverse reaction of the MPV reduction, i.e., the Oppenauer oxidation [30,31]. In addition to its high chemoselectivity and mild reaction conditions, this type of oxidation is of particular interest because the over-oxidation of aldehydes and ketones towards carboxylic acids should be minimized. Indeed, a highly accelerated Oppenauer oxidation system has been realized using a bidentate aluminum catalyst **1** [28]. This modified catalytic system effectively oxidizes a variety of secondary alcohols to the corresponding ketones. For example, carveol (**14**) and cholestanol (**15**) are smoothly transformed to carvone (**16**) and 4-cholesten-3-one (**17**), respectively, in high yields.

Table 1
Catalytic MPV reduction of carbonyl substrates with bidentate Al catalyst **12** or **13**

Entry	Substrate	Al reagent	Hydride source	Conditions	Yield (%)
1	PhCHO	$Al(OPr^i)_3$ (1 *eq*)	*i*-PrOH (1 *eq*)	RT, 2 h	10
2		**12** (1 eq)	*i*-PrOH (1 *eq*)	RT, 1 min	>99
3		**12** (5 mol%)	*i*-PrOH (1 *eq*)	RT, 1 h	81
4	$PhCH(CH_2)_2C{=}O$	$Al(OPr^i)_3$ (1 *eq*)	*i*-PrOH (1 *eq*)	RT, 2 h	$\sim$0
5		**12** (5 mol%)	*i*-PrOH (1 *eq*)	RT, 2 h	99
6	$PhC(=O)CH_2Cl$	$Al(OPr^i)_3$ (1 *eq*)	*i*-PrOH (1 *eq*)	RT, 2 h	$\sim$0
7		**12** (5 mol%)	*i*-PrOH (1 *eq*)	RT, 10 h	89
8		**13** (5 mol%)	PhMeCHOH (1 *eq*)	RT, 2 h	>99
9	$CH_3(CH_2)_8COCH_3$	**12** (5 mol%)	*i*-PrOH (1 *eq*)	RT, 5 h	52
10		**13** (5 mol%)	PhMeCHOH (1 *eq*)	RT, 5 h	73
11		**13** (5 mol%)	PhMeCHOH (3 *eq*)	RT, 5 h	89



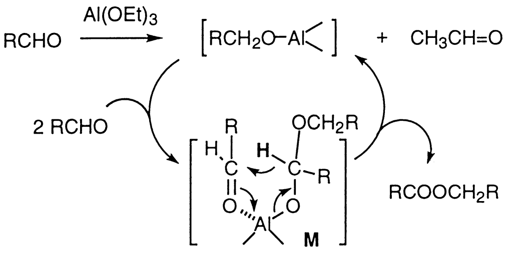


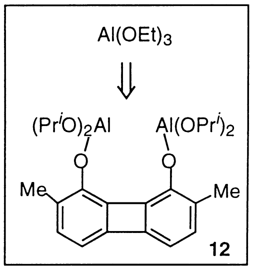
4. Synthetic utility of bidentate Lewis acids for tishchenko reaction

The Tishchenko reaction involves the dimerization of aldehydes giving the corresponding esters by an oxidation–reduction sequence [**M**] under the catalytic influence of aluminum alkoxides [32–36]. In view of the low reactivity, however, several transition metal complexes have been elaborated,

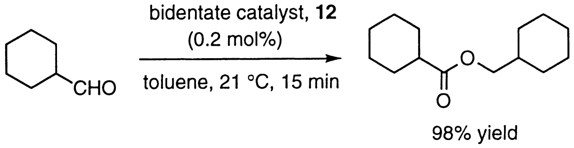
$$2RCHO \xrightarrow{Al(OR')_3\text{catalyst}} RCOOCH_2R$$

with limited success [37–41]. Quite recently, lanthanide amides have been found to be highly effective for this purpose [42]. Despite the industrial importance of the Tishchenko reaction (e.g., a precursor of epoxy resins) one might hesitate to use certain toxic, costly transition metal catalysts in place of the traditional, non-toxic aluminum alkoxides. Accordingly, we apply our bidentate Lewis acid chemistry to the Tishchenko reaction, and have successfully developed a catalytic, high-speed Tishchenko reaction using (2,7-dimethyl-1,8-biphenylenedioxy)bis(diisopropoxyaluminum) (**12**) as a desirable catalyst [43].





We examined the catalytic activity of bidentate **12** in the Tishchenko reaction of cyclohexanecarbaldehyde. Treatment of cyclohexanecarbaldehyde with 1 mol% of in situ generated bidentate aluminum alkoxide **12** in toluene at 21°C resulted in the rapid formation of the corresponding carboxylic ester almost quantitatively. It should be emphasized that the amount of the catalyst **12** can be reduced to 0.2 mol% without loss of catalytic efficiency and the dimerization product was uniformly obtained in almost quantitative yield. Notably, the dimerization of cyclohexanecarbaldehyde with the standard aluminum catalyst (Al(OPr^i)$_3$; 0.2 mol%) under otherwise similar reaction conditions gave only a trace amount of the ester.

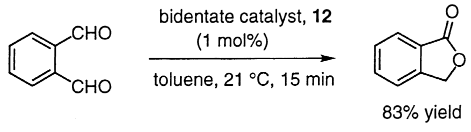


98% yield

A variety of aldehydes can be smoothly dimerized to carboxylic esters usually within 15 min, revealing the practicability of the present method. *o*-Phthalaldehyde was found to be rapidly converted to the 5-membered lactone.

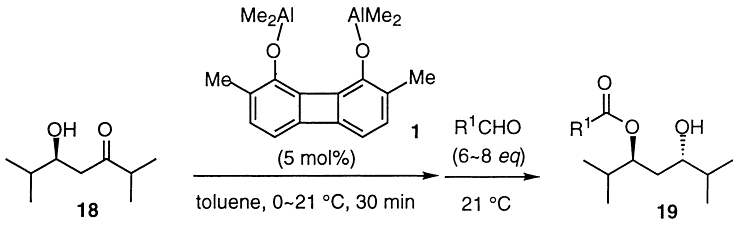
$$CH_3(CH_2)_4CHO \xrightarrow[\text{toluene, 21 °C, 15 min}]{\text{bidentate catalyst, } \mathbf{12}\text{ (0.3–0.5 mol\%)}} CH_3(CH_2)_4CCO_2(CH_2)_5CH$$

86–92% yields



83% yield

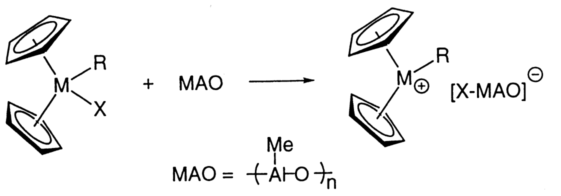
Our approach has been successfully applied to the stereoselective intramolecular Tishchenko reduction of β-hydroxy ketones [43]. This transformation affords the corresponding *anti* diol monoesters in high yield with an excellent level of stereochemical control, as exemplified by the transformation of β-hydroxy ketone **18** with several aldehydes to the corresponding *anti* diol monoester **19** (R^1 = Ph) exclusively.



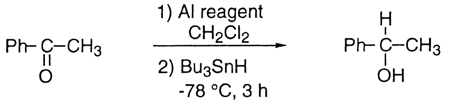
R^1 = Ph : 99% (*anti*/*syn* = >99:<1)
R^1 = C_5H_{11} : 92% (*anti*/*syn* = 96:4)

5. Bidentate aluminum Lewis acids with Al–O–Al unit

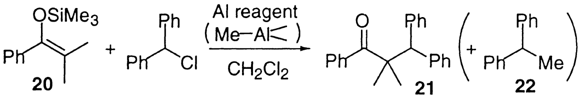
Since the pioneering work of olefin polymerizations with homogeneous metallocene catalysts (i.e., Kaminsky catalysts) in selective polymer synthesis by Kaminsky et al. [44,45], a variety of metallocene complexes have been elaborated for this purpose [46–51]. In all of these, methylalumoxane (MAO) has been extensively utilized as co-catalyst to generate highly active cationic olefin polymerization catalysts [52–55]. This co-catalyst is now indispensable and recognized to play a pivotal role as a highly efficient ligand abstractor from metallocene complexes. Why is MAO so effective as co-catalyst for various olefin polymerizations compared to other organoaluminum compounds? This question was under cover of darkness for a long time and we recently provided new insight into this long-standing problem utilizing our recently developed bidentate Lewis acid chemistry [56].



The reactivity of MAO was first examined for typical carbonyl reduction and electrophilic alkylation by comparison with $MeAl(OPr^i)_2$ as monomeric MAO analog and the selected results are shown as follows. Complexation of acetophenone with MAO (1–2 equiv. in Al-unit) in toluene/CH_2Cl_2 and subsequent treatment of Bu_3SnH (1.1 equiv.) at low temperature afforded α-phenethyl alcohol in 35–70% yields. In marked contrast, however, treatment of this ketone with $MeAl(OPr^i)_2$ (1–2 equiv.) under otherwise similar reduction conditions gave none of the reduction product. These results imply the importance of the Al–O–Al unit for the activation of ketone carbonyl. More interesting results were obtained in the reduction of acetophenone with a series of other methylaluminum reagents. Thus, $(Me_2Al)_2O$ exhibited higher reactivity than MAO. Notably, the activation mode of $(Me_2Al)_2O$ is superior to that of the parent Me_3Al. We also carried out the electrophilic alkylation of isobutyrophenone trimethylsilyl enol ether (**20**) with benzhydryl chloride producing α-alkylated ketone **21**. In the case of dialkylaluminum derivatives, simple alkylation of benzhydryl chloride giving Ph_2CHMe (**22**) was found to be a serious side-reaction. Hence, MAO seems to be an appropriate catalyst for such electrophilic alkylation in terms of both its electrophilic and nucleophilic character.

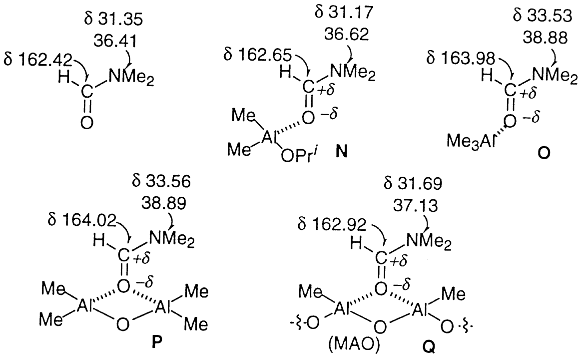


MAO (1 equiv in Al-unit) : 35%
MAO (2 equiv in Al-unit) : 70%
$MeAl(OPr^i)_2$ (1~2 equiv) : ~0%
Me_3Al (1 equiv) : 42%
$(Me_2Al)_2O$ (1 equiv) : 82%
Me_2AlOPr^i (2 equiv) : ~0%

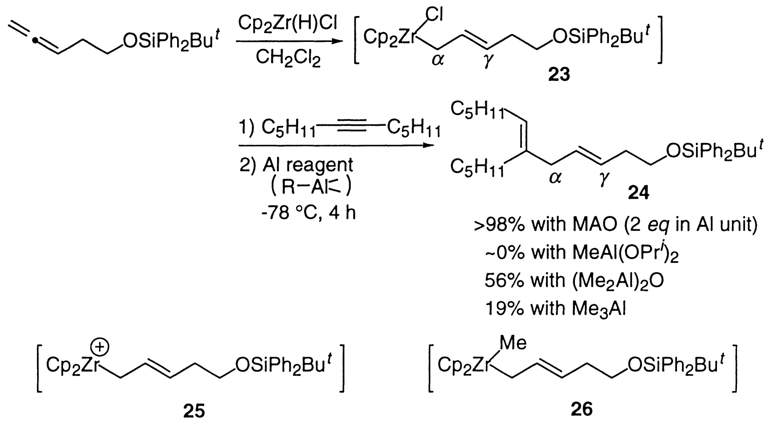


MAO (1 equiv in Al-unit) : 43% (11%)
MAO (2 equiv in Al-unit) : 73% (18%)
$MeAl(OPr^i)_2$ (1~2 equiv) : ~0%
Me_3Al (1 equiv) : 40% (33%)
$(Me_2Al)_2O$ (1 equiv) : 59% (30%)
Me_2AlOPr^i (2 equiv) : ~0%

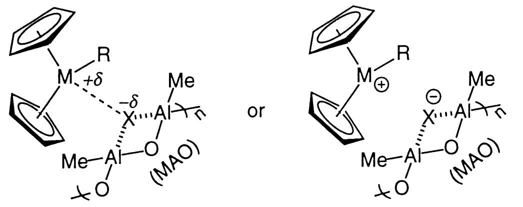
Based on these experimental data, the high reactivity of the Al–O–Al moiety is ascribed to the eminent simultaneous coordination to a carbonyl oxygen and alkyl chloride, thereby allowing the double activation of such hetero functionality with the Al–O–Al unit. Convincing evidence was obtained by low-temperature ^{13}C NMR spectroscopy using DMF as a carbonyl substrate. Thus, the ^{13}C NMR measurement of the 1:1 Me_2AlOPr^i–DMF complex (**N**) in $CDCl_3$ at $-50°C$ showed that the original signal of DMF carbonyl shifted only slightly, suggesting the feeble Lewis acidity of Me_2AlOPr^i. In contrast, Me_3Al showed higher Lewis acidity as observed by the downfield shift for the DMF carbonyl in the 1:1 Me_3Al–DMF complex (**O**). The 1:1 $(Me_2Al)_2O$–DMF chelation complex (**P**) under similar conditions undergoes a downfield shift for the DMF carbonyl, implying the strong electrophilic activation of the DMF carbonyl by intervention of the double coordination complex (**C**). MAO, $(MeAlO)_n$, showed moderate coordination ability in (**Q**) compared to $(Me_2Al)_2O$ and Me_3Al. A similar tendency is observed in the signals of DMF *N*,*N*-dimethyl groups among these methylaluminum reagents.



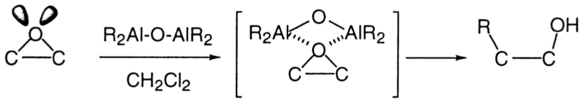
Recently, Suzuki and co-workers reported the regioselective allylzirconation of terminal alkynes in the presence of MAO in high yields [57–59]. We have examined the ligand-abstraction ability of MAO and its analogues for zirconocene complex **23** by the following allylzirconation of internal alkyne, giving the allylation product **24**. Here again, MAO was found to be most satisfactory as co-catalyst in terms of reactivity [56]. $(Me_2Al)_2O$ showed lower reactivity than MAO. With Me_3Al, the key zirconocene cation complex **25** is readily susceptible to the facile nucleophilic alkylation producing **26**, which, compared to **23**, is not a good precursor for regenerating this complex.



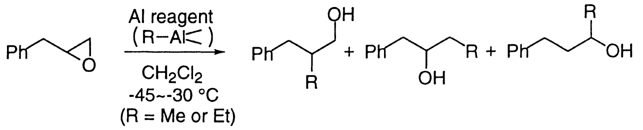
A plausible structure of homogeneous metallocene catalysts would therefore be described as shown below where the bidentate Al–O–Al unit of MAO is crucially important for activating a metallocene ligand X effectively.



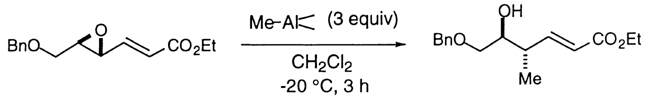
The new finding disclosed above prompted us to examine the alkylation ability of bis(dialkyl)aluminoxanes toward epoxy substrates as a new type of efficient alkylation agents [60].



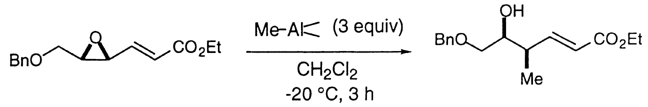
Treatment of 3-phenylpropene oxide with the in situ generated $(Me_2Al)_2O$ in CH_2Cl_2 at −45°C for 3 h afforded a mixture of 2-methyl-3-phenyl-1-propanol, 1-phenyl-2-butanol and 4-phenyl-2-butanol in 65% yield in a ratio of 76:15:9. In contrast, alkylation of this epoxide with simple Me_3Al (1–2 equiv.) under similar conditions produced only trace amounts of methylation products. Furthermore, use of Me_2AlOPr^i (1–2 equiv.) as a monodentate counterpart of $(Me_2Al)_2O$ resulted in almost total recovery of the starting epoxide. A similar tendency was observed with ethyl analogues. These results clearly demonstrate that the bidentate Al catalyst, $(R_2Al)_2O$ strongly enhances the reactivity of epoxy oxygen toward alkyl transfer via the double electrophilic activation of epoxy moiety.



Me_3Al (1~2 equiv) : *trace*
$(Me_2Al)_2O$ (1 equiv) : 65% (76:15:9)
Me_2AlOPr^i (1~2 equiv) : *trace*
Et_3Al (1 equiv) : 2%
$(Et_2Al)_2O$ (1 equiv) : 59% (18:9:73)

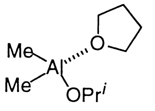


Me_3Al : 23%
$(Me_2Al)_2O$: 92%
Me_2AlOPr^i : *trace*

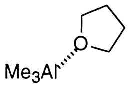


Me_3Al : 15%
$(Me_2Al)_2O$: 87%
Me_2AlOPr^i : *trace*

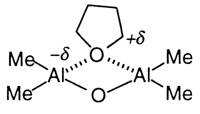
The double coordination behavior of the bidentate bis-Al/epoxide complex is observed by ^{13}C and ^{1}H NMR spectroscopy using tetrahydrofuran (THF) as an ethereal substrate. Thus, the 75 MHz ^{13}C NMR measurement of the 1:1 Me_2AlOPr^i/THF complex [**R**] in $CDCl_3$ at −50°C showed that the original signal of THF α-carbons at δ 67.87 shifted slightly to δ 68.45. The 1:1 Me_3Al-THF complex [**S**] showed further downfield shift for the THF α-carbons (δ 69.18). In contrast, 1:1 bidentate $(Me_2Al)_2O$/THF chelation complex under similar conditions undergoes a further downfield shift for the THF α-carbons (δ 70.39), indicating the strong electrophilic activation of the THF α-carbons by intervention of the double coordination complex [**T**]. A similar tendency is also observed in the low-temperature ^{1}H NMR spectroscopy: δ 3.79 (free THF α-protons); δ 3.87 (THF α-protons of the complex [**R**]); δ 3.94 (THF α-protons of the complex [**S**]); δ 4.05 (THF α-protons of the complex [**T**]); δ 4.01 (THF α-protons of the complex with Me_3Al/H_2O system).



R

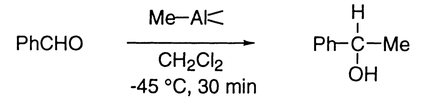


S

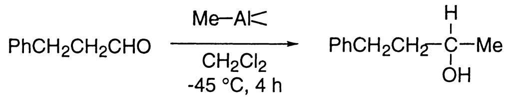


T

Our system is also applicable to the carbonyl alkylation experiments as illustrated by the methylation of benzaldehyde and 3-phenylpropanal with a series of methylaluminum reagents.



65% with $(Me_2Al)_2O$
~0% with Me_2AlOPr^i
5% with Me_3Al



78% with $(Me_2Al)_2O$
~0% with Me_2AlOPr^i
6% with Me_3Al

6. Conclusion

In this review, we only illustrate the synthetic utility of highly oxygenophilic aluminum reagents for bidentate Lewis acid chemistry. A similar, interesting phenomena is also observed in the Ti-based bidentate Lewis acid chemistry [61], including the application to catalytic asymmetric synthesis with chiral bidentate Ti Lewis acid catalysts [62]. Hence, the vast potential for bidentate Lewis acids in organic synthesis is now becoming increasingly apparent. Bidentate Lewis acids serve as equally important tools for the chemistry of molecular recognition. Thus, it should not be surprising if research on bidentate Lewis acid chemistry develops increasingly, thereby providing various exciting results over the next few years.

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