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**Selective Reactions and Molecular Recognition
using Aluminum Reagents**

Shigeru Nagahara

Department of Applied Chemistry

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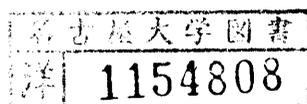
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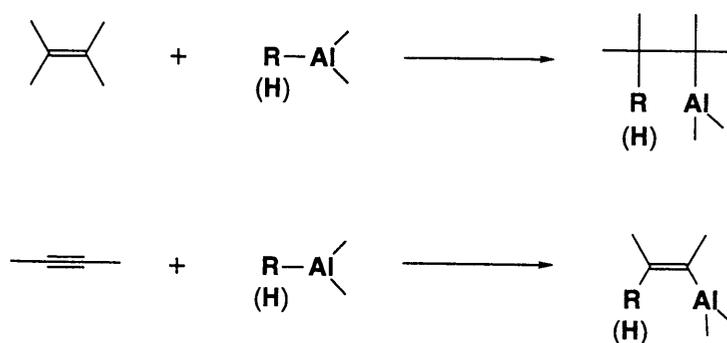
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Chapter 1

Introduction and General Summary

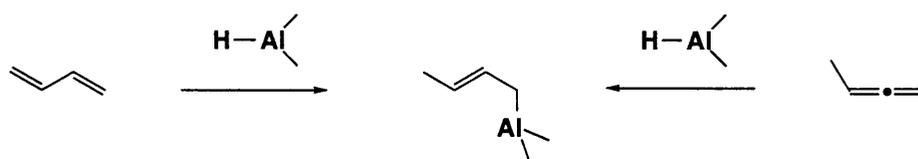
During the past several decades, organoaluminum compounds have been increasingly recognized as a versatile class of reagents and intermediates for organic synthesis and other fields because of the effectiveness of their inherent multipurpose action.¹ First, Ziegler and co-workers demonstrated the typical ability of organoaluminum compounds by combining them with transition metal compounds, in particular $\text{TiCl}_4/\text{Et}_3\text{Al}$, as catalyst for the low pressure polymerization of ethylene.² The active catalyst is prepared *in situ* from a transition metal compound and an organoaluminum compound. Based on mechanistic studies, it was concluded that the transition metal is the active center, and that the organoaluminum compound can carry out one or more of several tasks:³ (i) alkylation of the transition metal center to form an active transition metal-carbon bond; (ii) reduction of the transition metal ion to bring it eventually into a valency state required for catalysis; (iii) formation of a complex with the transition metal center to operate as an activating ligand. Organoaluminum compounds are now accepted as exerting such possible actions as alkylating, reducing, complexing, and other useful agents for various catalytic or stoichiometric transformations, both when used alone and in combination with transition metal (or other metallic) compounds, as proven in numerous examples.¹

Among the more remarkable instances of synthetic application utilizing organoaluminum compounds, carboalumination^{4,5} and hydroalumination^{6,7} reactions are fundamental transformations, because of their convenience for *in situ* preparation of a variety of organoaluminum compounds from simple unsaturated hydrocarbons and commercially available organoaluminums. Since the resulting organoaluminum compounds, organic groups of which possess a strong carbanion character, can act as powerful alkylating agents, these undergo facile intermolecular alkyl transfer reactions with various organic and inorganic electrophiles under mild conditions. This process is probably one of the most important applications of organoaluminum compounds for carbon-carbon and carbon-heteroatom bond formation. At the same time, by the combined use of an inorganic complex aluminum hydride-type reagent such as LiAlH_4 and a catalytic amount of transition metal compound as a hydroalumination agent, catalytic hydroalumination reactions of olefins have been realized with high efficiency and selectivity under mild conditions.⁸ This catalytic transformation is of great importance because noncatalytic hydroalumination reactions occur towards olefins reluctantly even at elevated temperature, and hence have so far been largely restricted to reactions of alkynes with organoaluminum hydrides (R_2AlH).^{1b, 1c, 6}



Many types of organometallics (e.g., aryl, methyl, most allyl and benzyl metal compounds) are not easily available by hydrometalation reactions, so that various alternative methods such as transmetallation and disproportionation have been used in the laboratory.⁹ Nevertheless, considerable interest has been directed towards the potential application of hydroalumination reactions for the generation of allylaluminum compounds that are more reactive and unique

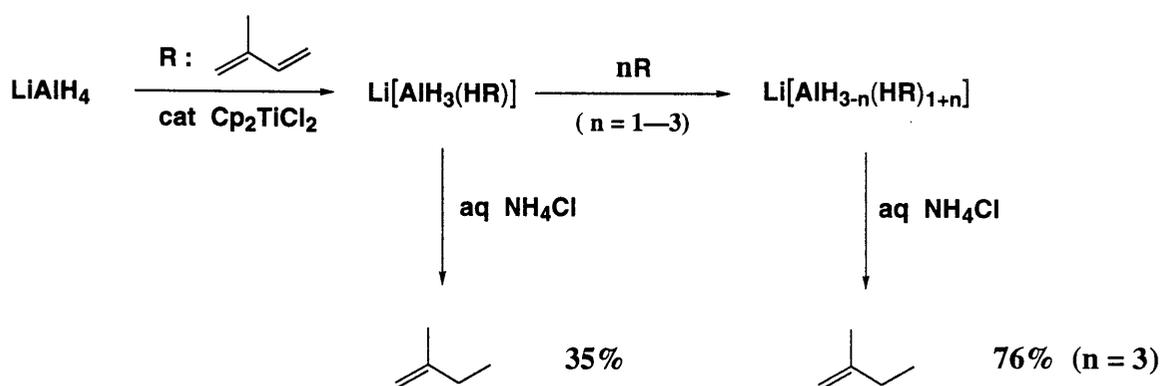
characteristic synthetic intermediates and reagents than their saturated counterparts.¹⁰ Indeed, the transition metal-catalyzed hydroalumination of conjugated dienes with complex aluminum hydrides^{8d, 8i} and the noncatalytic hydroalumination of allene compounds with *i*-Bu₂AlH^{6f, 6g} has been reported to provide allylaluminum compounds. However, both systems showed serious shortcomings on the regioselectivity or low reactivity for subsequent functionalization, and further investigations have not been reported. On the other hand, the organoborane-catalyzed hydroalumination of olefins has recently been developed by Yamamoto and his colleagues.¹¹ Internal olefins as well as terminal ones were readily hydrometalated with AlHCl₂ in the presence of catalytic organoboranes such as PhB(OH)₂ and Et₃B,¹² although much less information has been available about attempted hydroalumination of conjugated dienes and allenic compounds for the generation of allylaluminum compounds. Accordingly, the author should like to explore the further possibility of applying hydroalumination reactions for selective generation of allylaluminum compounds, as disclosed in the following two chapters.



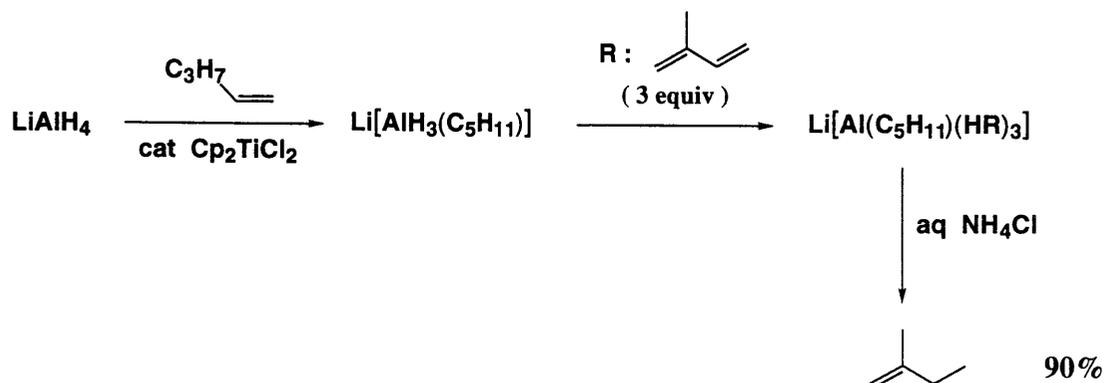
In chapter 2, the transition metal-catalyzed hydroalumination of isoprene with modified complex aluminum hydrides is described in terms of applicability to *in situ* generation of allylaluminum intermediate and the mechanistic proposal of this reaction. Although noncatalytic isoprene hydroalumination has proceeded sluggishly and yielded a mixture of various products,^{1a} the hydroalumination of isoprene with LiAlH₄ catalyzed by Ti and Ni compounds has been effected under mild conditions and it has become evident that 2-methyl-1-butene-3-*d* was produced predominantly by deuterolysis; it was contaminated, however, by mixtures of regioisomers and of mono- and dihydroalumination products.^{8d}

When Cp₂TiCl₂-catalyzed hydroalumination of isoprene with LiAlH₄ was examined to

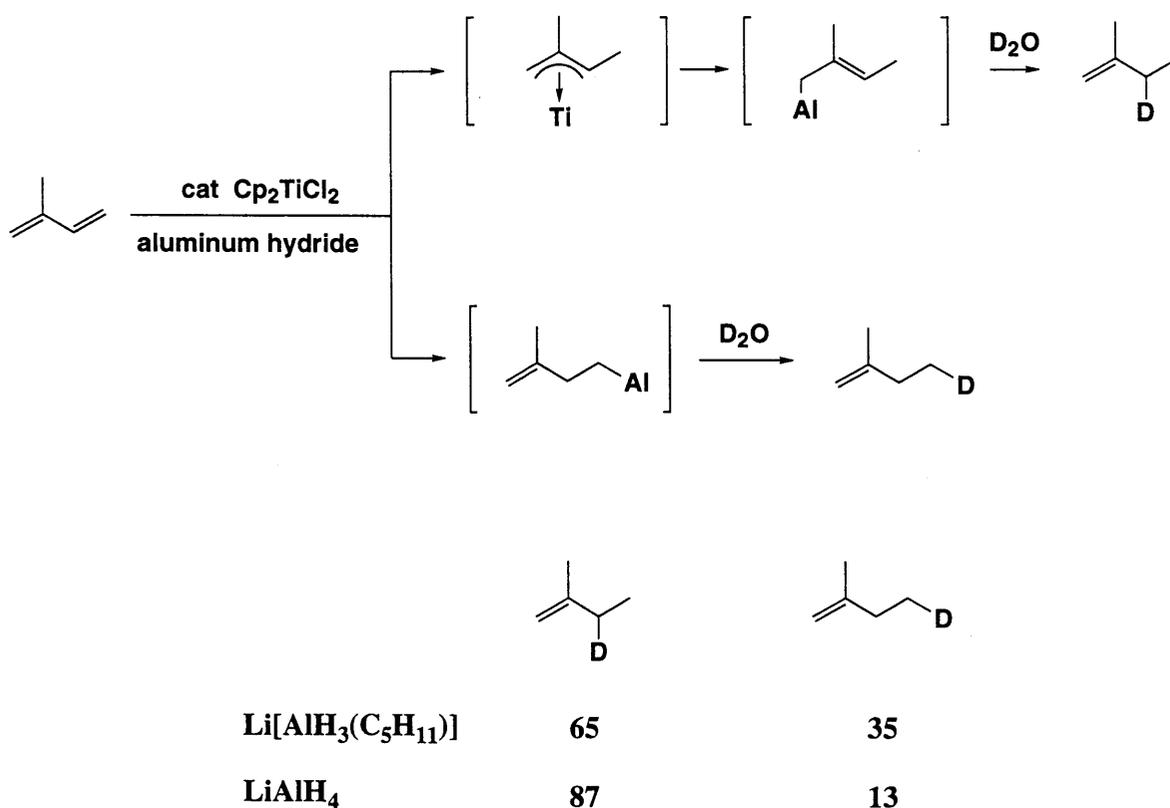
determine the factors affecting product-selectivity, it was found that the hydroalumination with LiAlH_4 proceeded by a sequence of four successive addition steps, each step slower than the preceding one. The hydrolysis product-selectivity of the desired 2-methyl-1-butene was very low in the first addition step (35%) but in the subsequent steps it was the exclusive, its selectivity increasing to 76%. This fact has been interpreted to mean that the steric bulkiness of an organic group of lithium trihydridoaluminates ($\text{Li}[\text{AlH}_3(\text{HR})]$), which might be produced from the reaction of isoprene with LiAlH_4 in the first step, was responsible for the selective formation of 2-methyl-1-butene as hydrolysis product.



Thus, attempted Cp_2TiCl_2 -catalyzed isoprene hydroalumination with modified complex aluminum hydrides, lithium trihydridopentylaluminum ($\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$), which can be readily prepared *in situ* by Cp_2TiCl_2 -catalyzed hydroalumination of 1-pentene with LiAlH_4 , afforded 2-methyl-1-butene with good selectivity (90%).

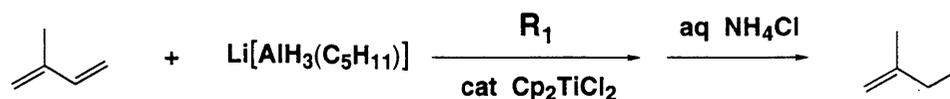


Unfortunately, the deuterolysis of this hydroalumination products appeared that the deuterium incorporated 2-methyl-1-butene consisted of a mixture of 2-methyl-1-butene-3-*d* and 2-methyl-1-butene-4-*d* (65:35), as well as the result in the use of LiAlH₄ (87 : 13). The homoallyl-deuterated alkene would arise from the deuterolysis of the corresponding homoallylaluminum compounds, while the allyl-deuterated alkene can be considered to derive from the deuterolysis involving the allylic rearrangement¹⁰ of 2-methyl-2-butenylaluminum intermediate via the transmetallation of *syn*-1,2-dimethylallyltitanium complex.¹³



A kinetic study of Cp₂TiCl₂-catalyzed isoprene hydroalumination with Li[AlH₃(C₅H₁₁)] was also carried out to elucidate the mechanism of the isoprene hydroalumination. Initial rate, R₁, for the formation of 2-methyl-1-butene (90—95% selectivity) could be expressed by R₁ = K [Li[AlH₃(C₅H₁₁)]] [Cp₂TiCl₂], where [Li[AlH₃(C₅H₁₁)]] and [Cp₂TiCl₂] denote the initial

concentration of complex aluminum hydride and Ti-catalyst, respectively. This experimental

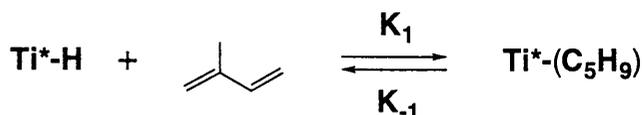


formula can be anticipated in terms of the mechanism in which the isoprene hydroalumination proceeded by a sequence of two successive reactions: (1) the coordination and subsequent insertion of an isoprene to an active Ti-H bond as the fast step; and (2) the transmetalation of the intermediary alkenyltitanium compound ($\text{Ti}^*(\text{C}_5\text{H}_9)$), thus generated, with $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$ involving regeneration of the active titanium hydride species ($\text{Ti}^*\text{-H}$) as the rate-determining step.

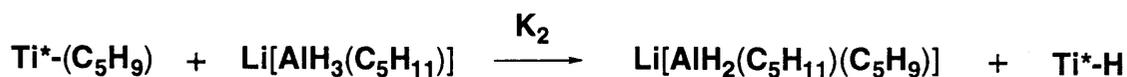
Generation of Active Titanium Hydride



Coordination and Insertion

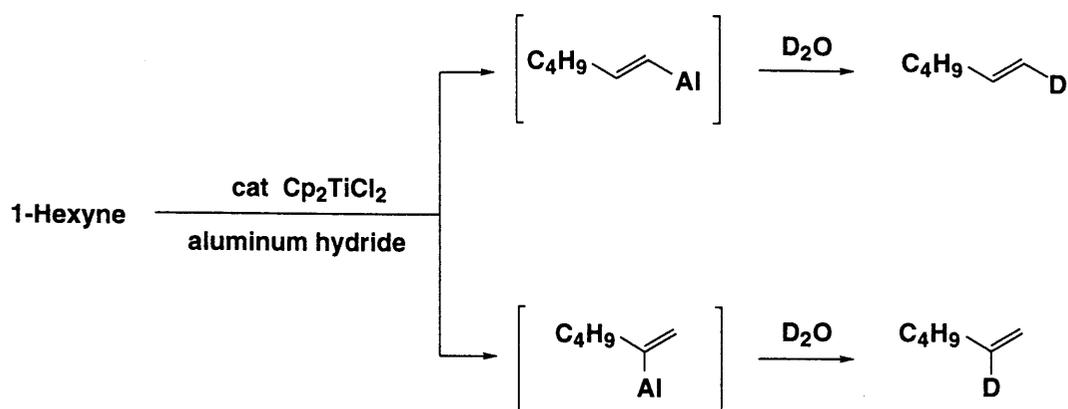


Transmetalation



In the Cp_2TiCl_2 -catalyzed hydroalumination of 1-alkynes with $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$ for selective generation of vinylaluminum compounds, the similar tendency of the product-selectivity was

observed.¹⁴ The hydroalumination of 1-hexyne with $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$ followed by deuterolysis gave rise exclusively to the deuterium incorporated 1-hexene (97%), which was a mixture of 1-hexene-1-*d* and 1-hexene-2-*d* in a ratio of 68:32.

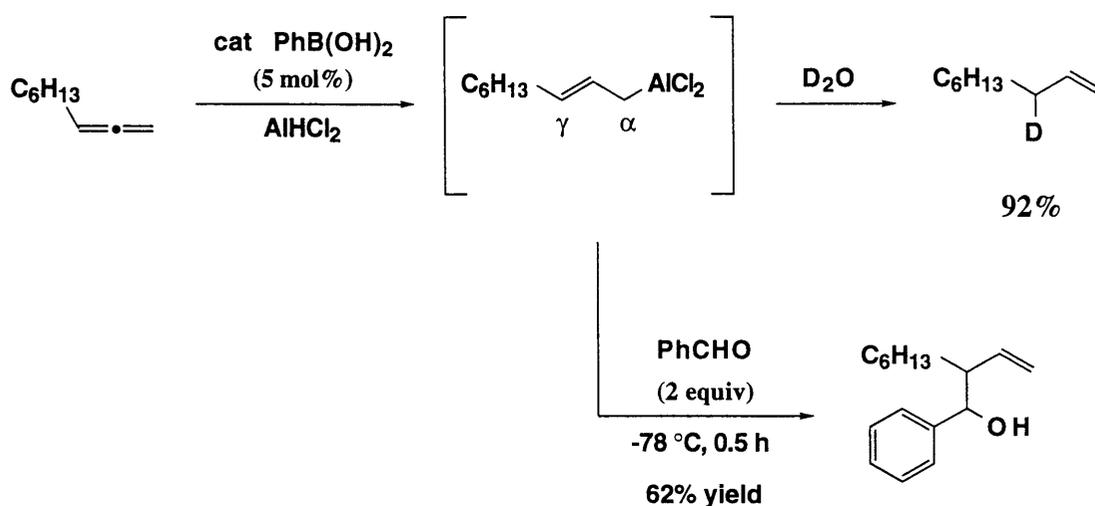


	$\text{C}_4\text{H}_9\text{-CH=CH-D}$	$\text{C}_4\text{H}_9\text{-C(=CH}_2\text{)-D}$
$\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$	68	32
LiAlH_4	72	28

Thus, the use of modified complex aluminum hydrides has efficiently controlled to give monohydroalumination products in Cp_2TiCl_2 -catalyzed hydroalumination of isoprene, but this method ultimately revealed disappointing regioselectivity similar to that in the sole use of LiAlH_4 .

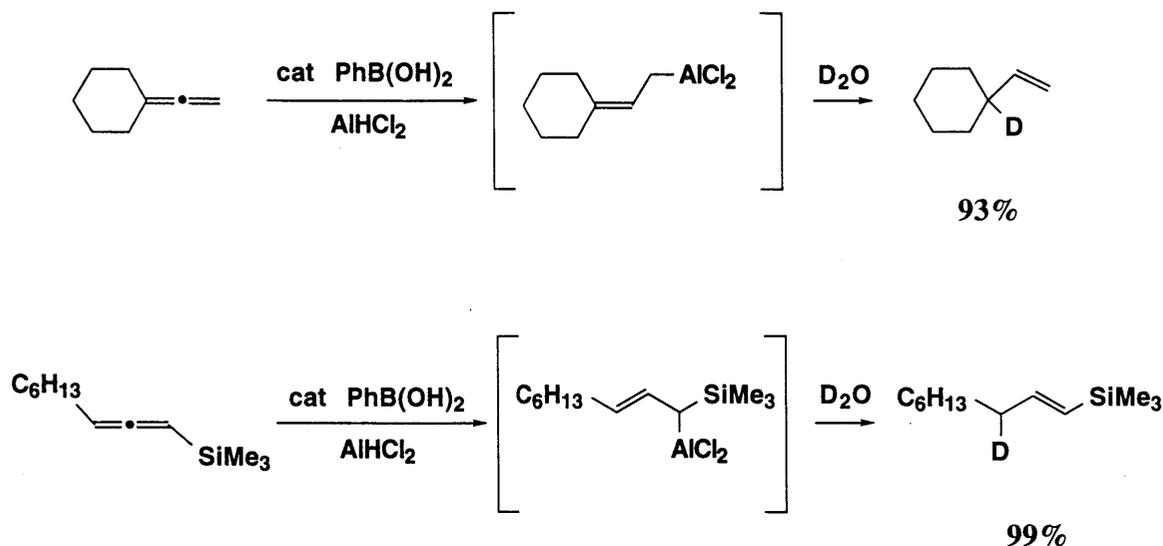
Chapter 3 deals with an organoborane-catalyzed hydroalumination of allenes for the same purpose, i.e., selective generation of allyl aluminum compounds. Although hydroalumination of allenes is a reasonably convenient method for the generation of allyl aluminum compounds, only few studies have been attempted on this subject.^{6f,6g} One recent study includes the hydroalumination of allenes with *i*- Bu_2AlH that gave excellent yields of allyl aluminum compounds regioselectively, but this system was not employable for subsequent functionalization due to its inertness towards

carbonyl compounds.^{6f} In this context, the allene hydroalumination with the inorganic aluminum hydride-type reagents LiAlH_4 and AlHCl_2 ¹⁵ in combination with transition metal and organoborane catalysts was examined. The hydroalumination of a terminal allene, 1,2-nonadiene, with LiAlH_4 or AlHCl_2 using various transition metal catalysts in THF at 30 °C afforded a wide variety of deuterated species by quenching with D_2O . In sharp contrast, PhB(OH)_2 -catalyzed hydroalumination¹¹ of 1,2-nonadiene with AlHCl_2 in Et_2O at room temperature gave >95% pure 1-nonene-3-*d* with excellent selectivity (92%) and in high yield.



The allylation of benzaldehyde in Et_2O at $-78\text{ }^\circ\text{C}$ using the PhB(OH)_2 -catalyzed hydroalumination product of 1,2-nonadiene gave rise to the homoallylic alcohol in 62% yield, suggesting that the intermediary allyl aluminum compound might be 2-nonenylaluminum dichloride.¹⁰ Allylation of *trans*-cinnamaldehyde with this allyl aluminum compound also proceeded successfully, whereas allylative ring-opening reaction of epoxides was less regioselective. It is noteworthy that this allyl aluminum compound exhibited a high chemoselectivity, leaving the ketone functionality intact. This result is in sharp contrast to the inertness of allyldiisobutylaluminum intermediates generated by the noncatalytic allene hydroalumination using *i*- Bu_2AlH .^{6f}

Similarly, this hydroalumination system consisting of catalytic PhB(OH)_2 and AlHCl_2 was effective for the regioselective hydroalumination of disubstituted allenes (93—99% selectivity), although a trisubstituted allene showed nonregioselective orientation results.

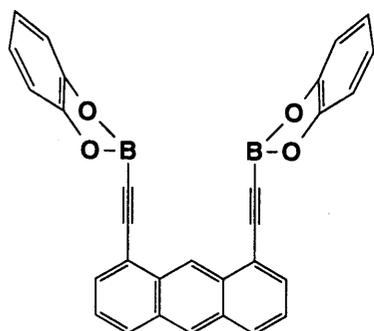


Organoaluminum compounds, which are well known to show strong Lewis acidity and possess a strong affinity with various heteroatoms in organic molecules, can act as effective complexing agents. Particularly, these form long-lived Lewis acid-base coordination complexes with oxygen- and carbonyl-containing substrates, even with neutral bases such as ethers. Utilization of this property in organic synthesis has allowed facile selective reactions with heteroatom-containing compounds.¹ On the other hand, the author has been intrigued by the possibility of a conceptually new treatment of this well-known complexation phenomenon, which may contribute greatly to the design of selective reactions using organoaluminums.

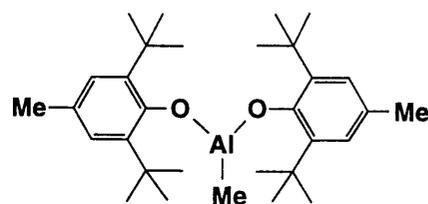
Chapter 4 is concerned with molecular recognition of oxygen-containing substrates with modified organoaluminum reagents. One area of recent interest in modern organic and bioorganic chemistry has been concerned with the synthetic molecules that mimic various aspects of enzyme chemistry.¹⁶ Progress has been made in the chemistry of molecular recognition in particular, and a number of artificial receptors capable of reversible binding interactions with ionic or neutral substrates in solution have been synthesized.¹⁷ The successful design, synthesis, and use of

receptors is of great interest not only because these can provide insight into the nature of enzyme functions, but also because of potential application in catalysis, separation technology, and other areas involving molecular recognition. Most of these artificial receptors primarily utilize the complementary noncovalent interactions such as hydrogen-bonding interactions between substrate and receptor, as also seen in natural enzymes. With organic substrates of weak hydrogen-bonding capability such as ethers, however, such tight binding behavior cannot be expected unless a cavity or cleft of the receptors contains a large number of effective hydrogen-bonding groups and a rigid supporting framework to hold these a fixed distance apart. An alternative approach redressing this difficult problem has been speculated as being to design and synthesize a new receptor possessing highly selective complexation ability based on certain stronger interactions than noncovalent interactions.

Recently, the complexation of ionic and neutral species by organometallic compounds containing Lewis acidic functionalities has been achieved for mercury-,¹⁸ tin-,¹⁹ and boron-containing²⁰ receptors. For example, Katz has developed a bidentate diboronate receptor capable of interacting with 1,3-dibasic pyrimidine derivatives, and demonstrated that this receptor can form a bridged complex with 5-methylpyrimidine, in contrast to the sterically hindered 4-methyl derivative.^{20c} Interestingly, the exceptionally bulky organoaluminum reagent, methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)²¹ (hereafter, abbreviated to MAD), which is a very useful synthetic reagent,²² has been introduced as a temporary protecting group for the normally more reactive functionality of two different carbonyl compounds by Yamamoto and co-workers, enabling



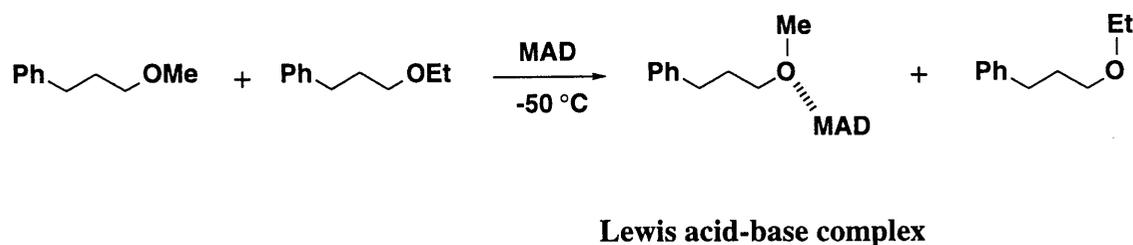
diboronate receptor



MAD

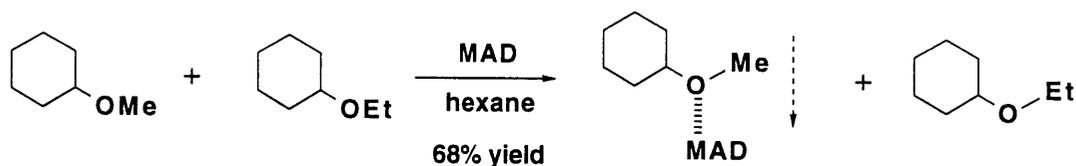
the successful selective reduction of sterically more hindered or electronically less polarizable carbonyl substrate of two different carbonyl substrates with *i*-Bu₂AlH.²³ Accordingly, the author anticipated that a modified organoaluminum compound such as MAD may be utilized as a new class of Lewis acidic receptors for recognition of various ether substrates based on the selective Lewis acid-base complex formation.

The recognition ability of MAD with two different ether substrates was examined by low-temperature ¹³C NMR spectroscopy. For example, ¹³C NMR measurement of a mixture of 1 equiv each of MAD, methyl 3-phenylpropyl ether, and ethyl 3-phenylpropyl ether in CDCl₃ at -50 °C has shown that MAD exhibited the virtually complete recognition between methyl and ethyl ethers, forming the Lewis acid-base complex with the sterically less hindered methyl ether exclusively (100 : 0). MAD preferentially formed a coordination complex with an ether substrate possessing sterically less hindered alkyl substituent or more basic ethereal oxygen of two structurally or electronically very similar ether substrates. This remarkable selectivity can only be achieved with the exceptionally bulky organoaluminum reagent, MAD as ascertained by comparison with other Lewis acids.



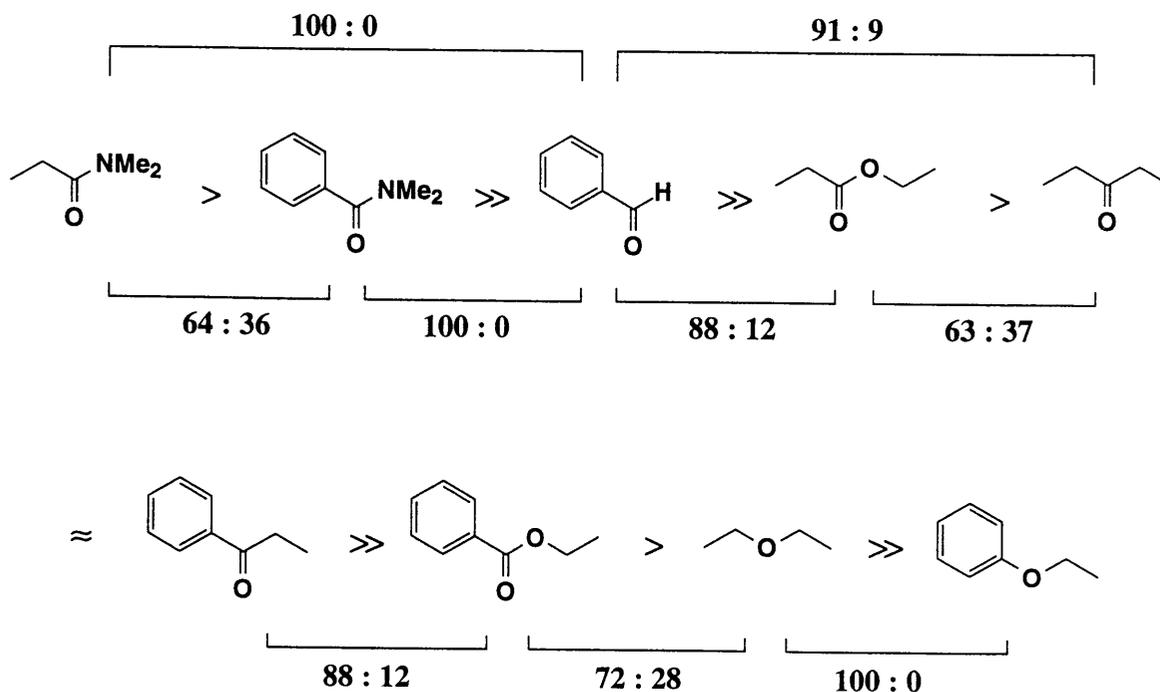
Furthermore, selective separation of the less hindered or electronically more labile of two different ethers has been accomplished with MAD by yielding precipitates as Lewis acid-base complexes. Treatment of a mixture of cyclohexyl methyl ether and cyclohexyl ethyl ether with MAD (1 equiv each) in hexane at room temperature followed by the recrystallization from hexane furnished only MAD-methyl ether complex as a white precipitate in 68% yield. This method demonstrates an effective way to purify not only simple ethers but also various structurally or

electronically very similar ether substrates in the segment synthesis of polyether natural products.²⁴

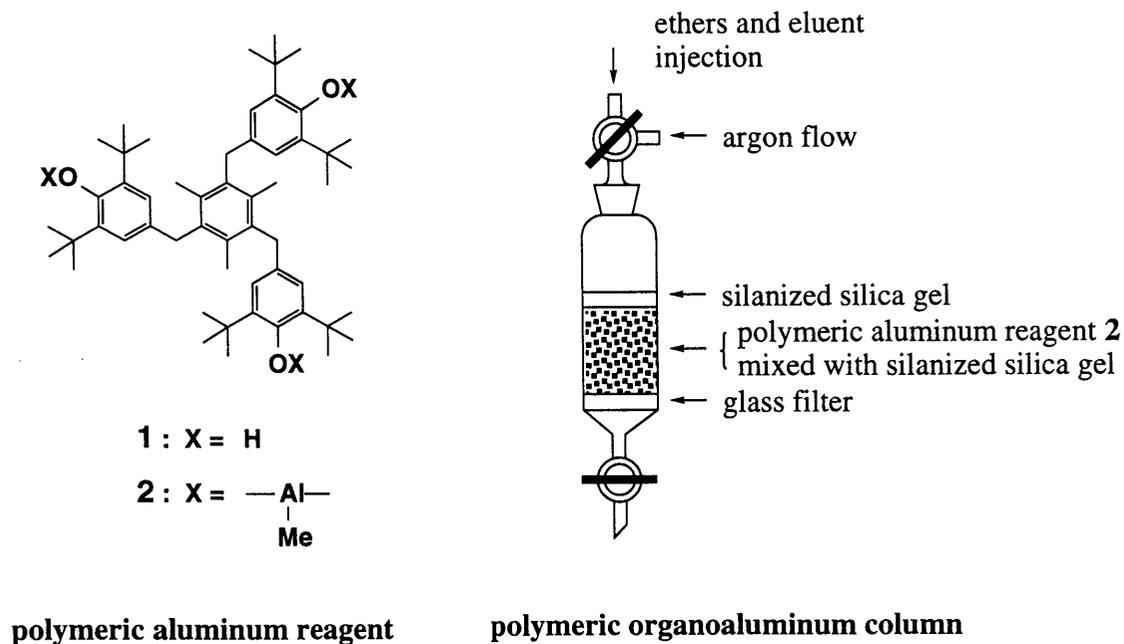


**MAD-ether complex
as a white precipitate**

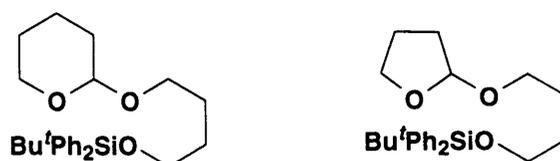
The binding behaviors of the Lewis acidic receptor, MAD for various oxygen-containing substrates have been studied by low-temperature ¹³C NMR analysis. As oxygen-containing substrates, both aliphatic and aromatic aldehydes, amides, esters, ethers, and ketones with similar structural substituents were utilized. Amides were found to coordinate more strongly to MAD than aldehydes, esters, or ketones, while coordination of ethereal oxygens was rather weak. The order has implied that even the same functional groups show different binding behaviors to Lewis acidic MAD depending on the types of substituents (aliphatic and aromatic) and their steric requirements.



This molecular recognition chemistry has been applied to a new type of complexation chromatography²⁵, i.e., separation of heteroatom-containing solutes by complexation with stationary, insolubilized organoaluminum reagents.²⁶ Thus, treatment of sterically hindered triphenol **1** in CH_2Cl_2 with Me_3Al at room temperature gave rise to the polymeric aluminum reagent **2** and this was packed in a short-path glass column as a stationary phase. Then, a solution of two different ethers in degassed hexane was introduced and eluted with more degassed hexane. After collection of hexane fractions (e.g., 40×5 mL), eluent was changed to Et_2O in hexane ($\text{Et}_2\text{O}/\text{hexane} = 1:10$). This technique allowed the surprisingly clean separation of structurally or electronically similar ether substrates that cannot be readily accomplished by ordinary silica gel or alumina chromatography.²⁷

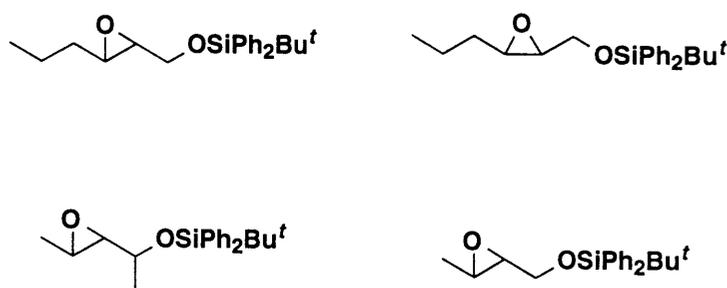


For example, the THF and THP ethers of 4-(*tert*-butyldiphenylsiloxy)-1-butanol could be separated successfully with this short-path column chromatography: the THP ether was eluted



quantitatively with hexane, while the THF ether strongly coordinated to the stationary, polymeric aluminum reagent **2**, being eluted only with Et₂O in hexane (Et₂O/hexane = 1:10). This case would demonstrate an effective way to purify structurally or electronically similar ethers in the segment synthesis of polyether antibiotics.

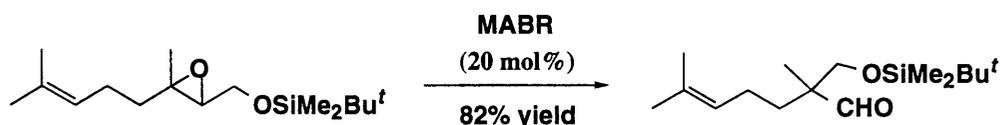
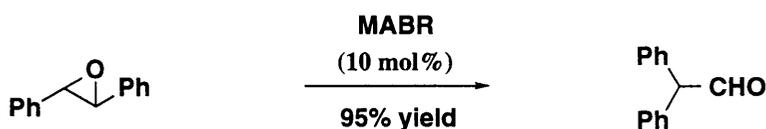
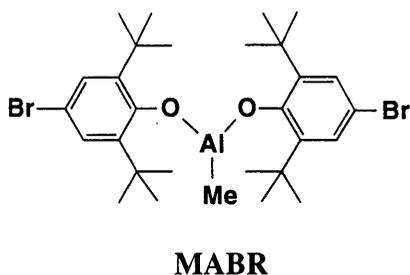
The present technique also allowed the effective separation of various structurally similar α,β -disubstituted epoxy silyl ethers by discrimination of their structural environment such as the configuration of epoxides and the size of epoxide substituents. For instance, the chromatographic separation of geometrical isomers of epoxy silyl ethers such as *cis*- and *trans*-3-propyloxiranemethanol *tert*-butyldiphenylsilyl ethers at -15 °C could be accomplished easily, only the *trans*-isomer being eluted with hexane.



In chapter 5, the author describes synthetic application of complexation chromatography on polymeric organoaluminum column. Apart from its obvious utility in separation mixtures of structurally or electronically very similar ethers, complexation chromatography on polymeric organoaluminum column can be expected to become a very useful synthetic procedure for various organoaluminum-mediated reactions.

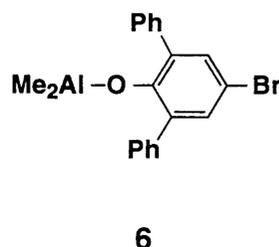
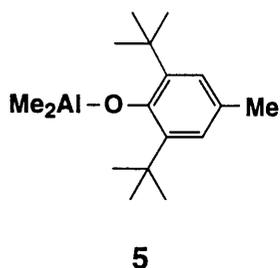
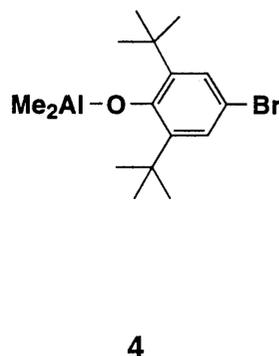
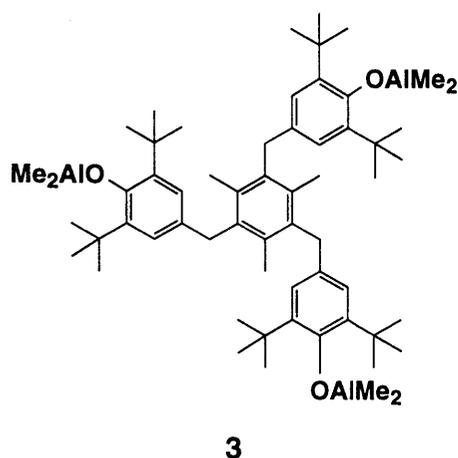
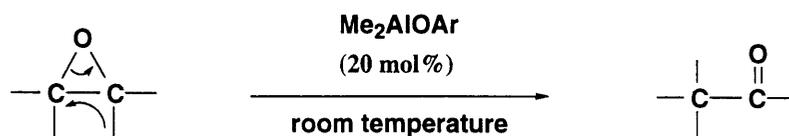
Recently, Yamamoto *et al.* reported that the more Lewis acidic, exceptionally bulky methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (abbreviated to MABR) can be utilized as a stoichiometric reagent and a catalyst for the stereocontrolled rearrangement of optically active epoxy silyl ethers to optically active β -siloxy aldehydes under mild conditions.²⁸ Therefore, the author examined catalytic rearrangement of simple epoxides using MABR and various

dimethylaluminum reagents to produce carbonyl compounds selectively. For example, treatment of the *trans*-stilbene oxide with the catalytic amount of MABR (10 mol%) in CH₂Cl₂ at -20 °C led to rearranged diphenylacetaldehyde in 95% yield. Also, the reaction of *tert*-butyldimethylsilyl ether of epoxy geraniol gave rise to the desired β -siloxy aldehyde in 82% yield under the same conditions.



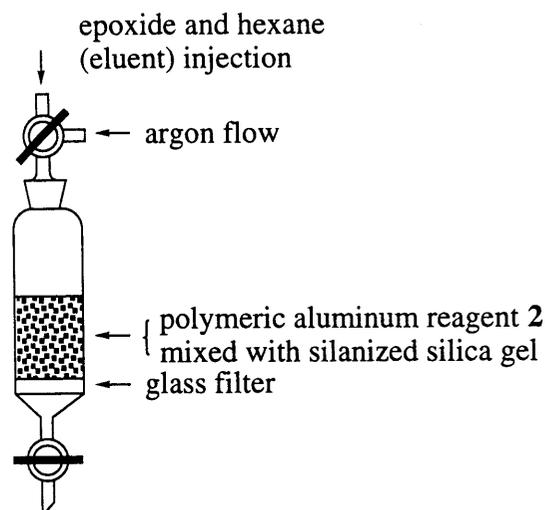
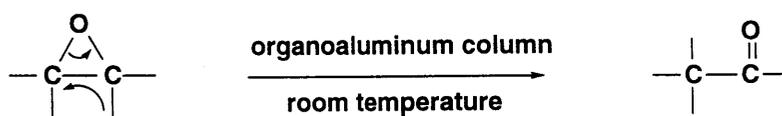
Similarly, the rearrangement of epoxides using 20 mol% of various dimethylaluminum aryloxy reagents (Me₂AlOAr) was examined, and thus the modified dimethylaluminum reagents such as tris(dimethylaluminum)aryloxy (3), dimethylaluminum 4-bromo-2,6-di-*tert*-butylphenoxide (4), dimethylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide (5), and dimethylaluminum 4-bromo-2,6-diphenylphenoxide (6) could be utilized as mild Lewis acidic catalysts for the selective rearrangement of epoxides to carbonyl compounds at room temperature. Among these, tris(dimethylaluminum)aryloxy (3) was highly effective for epoxy silyl ether

substrates such as *tert*-butyldimethylsilyl ether of epoxy geraniol, while dimethylaluminum 4-bromo-2,6-diphenylphenoxide (**6**) was useful for simple epoxides such as *trans*-stilbene oxide.



In studying the separation mixtures of α,β -disubstituted epoxy silyl ethers using the polymeric aluminum column as described in chapter 4, *gem*-disubstituted and trisubstituted epoxy silyl ethers were prone to be partially susceptible to the rearrangement on the stationary, polymeric aluminum reagent **2**. This finding and the study of epoxy rearrangement using the organoaluminum reagents mentioned above have prompted us to develop the synthetic application of polymeric

organoaluminum column as a workup-free reactor to catalytic rearrangement of epoxides. The polymeric organoaluminum column for catalytic rearrangement was prepared as described previously with some modification for *in situ* preparation. Thus, a solution of *tert*-butyldimethylsilyl ether of epoxy geraniol in degassed hexane was passed through the column (20 mol% aluminum reagent) for 10 min at room temperature, the desired β -siloxy aldehyde being obtained in 67% yield.



**polymeric organoaluminum column as
a workup-free reactor**

Interestingly, the eluate by this flow method contained only a trace of by-products in contrast to the result of a conventional batch method using 20 mol% polymeric aluminum reagent **2** in CH_2Cl_2 at room temperature. The polar by-products coordinated selectively to the stationary, polymeric aluminum reagent **2** possessing high recognition ability in complexation with Lewis-basic compounds, since the by-products could be eluted with 5% THF in hexane.

In conclusion, the present studies are divided into two sectors distinguished by notable features of the action of organoaluminum compounds: one relies on the action as the alkylating agents and the other on the action as the Lewis acidic complexing agents, namely, the Lewis acidic receptors. The author has contributed to the following points:

- (1) The synthetic potential of the hydroalumination of isoprene, 1-alkynes, and allene compounds using transition metal and/or organoborane catalysts is studied in detail. Among these, PhB(OH)₂-catalyzed hydroalumination of allenes with AlHCl₂ provides a convenient and highly regioselective way to generate allylaluminum compounds that can then be satisfactorily utilized for regioselective allylation of aldehydes.
- (2) The virtually complete recognition of structurally or electronically very similar ether substrates is realized with the exceptionally bulky organoaluminum reagent, MAD as a Lewis acidic receptor based on the selective Lewis acid-base complex formation. Recognition chemistry is successfully applied to complexation chromatography using polymeric monomethylaluminum reagent **2** as a stationary phase, thereby allowing a surprisingly clean separation of structurally or electronically similar ethers that cannot be accomplished by ordinary silica gel or alumina chromatography.
- (3) The complexation chromatography on polymeric organoaluminum column can be readily utilized for the facile workup-free catalytic rearrangement of epoxides to carbonyl compounds. The polymeric aluminum reagent **2** on the column exhibits its high efficiency not only as a catalyst for the epoxy rearrangement, but also as a filter for the selective removal of the resulting polar by-products based on the Lewis acid-base complex formation.

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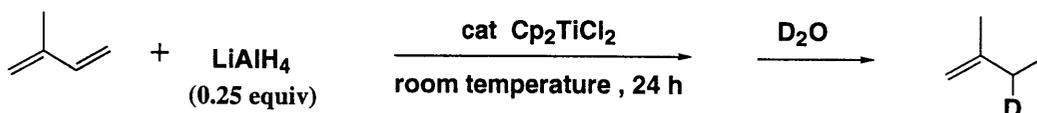
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Chapter 2

Transition Metal-Catalyzed Hydroalumination with Modified Complex Aluminum Hydrides

Abstract: Cp_2TiCl_2 -catalyzed hydroalumination of isoprene with LiAlH_4 and modified complex aluminum hydrides such as $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$ has been investigated. The catalytic hydroalumination with LiAlH_4 followed by hydrolysis gave 2-methyl-1-butene (1), 2-methyl-2-butene (2), 2-methylbutane (3), and 3-methyl-1-butene (4), while the reaction with $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$ afforded 1 with good selectivity. NMR analysis of the main product 1 obtained by the deuterolysis of the reactions with LiAlH_4 and $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$ indicated that the deuterium incorporated 1 consisted of a mixture of 2-methyl-1-butene-3-*d* and 2-methyl-1-butene-4-*d*, respectively. The structure of other deuterolysis products and their selectivity were also determined. Further, a kinetic study was carried out to elucidate the mechanism of the isoprene hydroalumination. Attempted Cp_2TiCl_2 -catalyzed hydroalumination of 1-alkynes with $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$ followed by deuterolysis gave rise exclusively to the deuterium incorporated 1-alkenes, which were a mixture of 1-alkene-1-*d* and 1-alkene-2-*d*.

Catalytic hydroalumination reactions of unsaturated hydrocarbons have been realized by the combined use of an inorganic aluminum hydride-type reagent such as LiAlH_4 and a catalytic amount of transition metal compound with high efficiency and selectivity under mild conditions.^{1, 2} Since the resulting organoaluminum compounds, organic groups of which possess a strong carbanion character, can act as powerful alkylating agents, these undergo facile intermolecular alkyl transfer reactions with various organic and inorganic electrophiles under mild conditions. The transition metal-catalyzed hydroalumination of conjugated dienes with complex aluminum hydrides has been reported to provide allylaluminum compounds,^{1d, 1i} which are more reactive and unique characteristic synthetic intermediates and reagents than their saturated counterparts.³ For example, the hydroalumination of isoprene with LiAlH_4 catalyzed by TiCl_4 , Cp_2TiCl_2 , or Ni compounds has been effected under mild conditions and it has become evident that 2-methyl-1-butene-3-*d* was produced predominantly by deuterolysis; it was contaminated, however, by mixtures of regioisomers and of mono- and dihydroalumination products,^{1d} and further investigations have not been reported. Accordingly, we should like to explore the further possibility of applying isoprene hydroalumination reaction for the selective generation of allylaluminum compound.



Initially, we examined various combination of transition metal catalysts (2.5 mol%) with LiAlH_4 (0.25 equiv) in THF for effecting hydroalumination of isoprene. After the hydroalumination at 30 °C for 24 h, the reaction was quenched with a saturated solution of NH_4Cl at 0 °C to monitor the catalytic activity and reaction selectivity by GLC analysis. As illustrated in Table 1, all of the transition metal catalysts provided a mixture of 2-methyl-1-butene (**1**), 2-methyl-2-butene (**2**), 2-methylbutane (**3**), and 3-methyl-1-butene (**4**). Among these, Cp_2TiCl_2 showed the highest catalytic activity and selectivity for the formation of the desired hydrolysis product **1** (76% selectivity, entry 1) even though it gave significant proportions of other products, **2—4**.^{1d} Hence,

determination of the factors affecting the selectivity of **1** in the Cp₂TiCl₂-catalyzed hydroalumination with LiAlH₄ was performed for obtaining information on the selective generation of allylaluminum compound.

Table 2 shows the relation between the hydrolysis product-selectivity and the concentration of LiAlH₄ in Cp₂TiCl₂-catalyzed hydroalumination. The selectivity of **1** decreased with an increase

Table 1. Catalytic Activity and Reaction Selectivity of Transition Metal Chlorides for Hydroalumination of Isoprene with LiAlH₄^a

entry	catalyst	yield/%				conv./%
						
		1	2	3	4	
1	Cp ₂ TiCl ₂ ^b	76	6	16	2	86
2	TiCl ₄	60	17	15	8	70
3	TiCl ₂ (acac) ₂	46	29	17	8	27
4	TiCl ₃ ^c	54	29	9	8	48
5	ZrCl ₄	50	50	0	0	2
6	VCl ₄	53	32	12	3	9
7	VCl ₃	38	43	14	5	11

^a Reaction conditions: [Catalyst] = 2.5 mmol·dm⁻³, [LiAlH₄] = 25 mmol·dm⁻³, [Isoprene] = 100 mmol·dm⁻³, [THF solution] = 0.05 dm³, 30 °C, 24 h. ^b [THF solution] = 0.10 dm³. ^c For 20 h.

in the concentration of LiAlH_4 (41% selectivity at $[\text{Isoprene}]/[\text{LiAlH}_4] = 1$) at a constant concentration of Cp_2TiCl_2 and isoprene (entries 1–3), while at a constant ratio of isoprene to LiAlH_4 ($[\text{Isoprene}]/[\text{LiAlH}_4] = 4$) it did not vary with LiAlH_4 concentration (entries 1, 4, and 5). Interestingly, even at $[\text{Isoprene}]/[\text{LiAlH}_4] = 4$, the selectivity of **1** was found to be very low (about 50% selectivity) in the region of less than 30% conversion yield, namely corresponding to $[\text{Isoprene}]/[\text{LiAlH}_4] \leq 1$, as shown in Figure 1. Furthermore, remarkable changes in the reactivity were observed by the successive addition of isoprene (1 equiv each) (Figure 2). The selectivity of **1** was very low in the first addition step ($[\text{Isoprene}]/[\text{LiAlH}_4] = 1$), but in the subsequent addition steps it was the exclusive and each addition step was slower than the preceding one.

Table 2. Effect of LiAlH_4 Concentration on Product-Selectivity^a

entry	$[\text{Cp}_2\text{TiCl}_2]$ molar ratio	$[\text{Isoprene}]$ $[\text{LiAlH}_4]$ molar ratio	yield/%				conv./%
			 1	 2	 3	 4	
1	10	4	76	6	16	2	86
2	20	2	44	20	34	2	95
3	40	1	41	26	29	3	100
4	20	4	75	4	18	3	82
5	40	4	73	16	8	3	67

^a Reaction conditions: $[\text{Cp}_2\text{TiCl}_2] = 2.5 \text{ mmol}\cdot\text{dm}^{-3}$, $[\text{THF solution}] = 0.10 \text{ dm}^3$, 30 °C, 24 h.

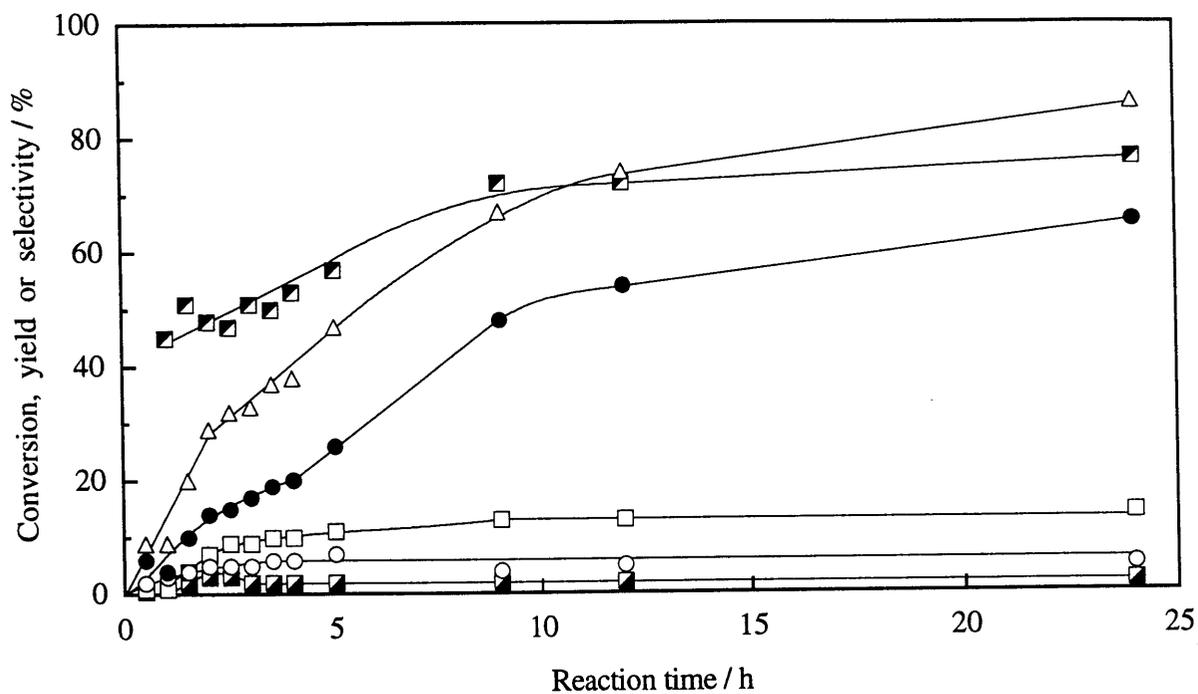


Figure 1. Cp_2TiCl_2 -Catalyzed Hydroalumination of Isoprene with LiAlH_4 at $[\text{Isoprene}] / [\text{LiAlH}_4] = 4$

$[\text{Cp}_2\text{TiCl}_2] = 2.5 \text{ mmol}\cdot\text{dm}^{-3}$, $[\text{LiAlH}_4] = 25 \text{ mmol}\cdot\text{dm}^{-3}$, $[\text{Isoprene}] = 100 \text{ mmol}\cdot\text{dm}^{-3}$, $[\text{THF solution}] = 0.10 \text{ dm}^3$, $30 \text{ }^\circ\text{C}$

- | | | | |
|---|-----------------------|---|-----------------------------------|
| ● | 2-Methyl-1-butene (1) | ■ | 3-Methyl-1-butene (4) |
| ○ | 2-Methyl-2-butene (2) | △ | Isoprene conversion |
| □ | 2-Methylbutane (3) | ▣ | 2-Methyl-1-butene (1) selectivity |

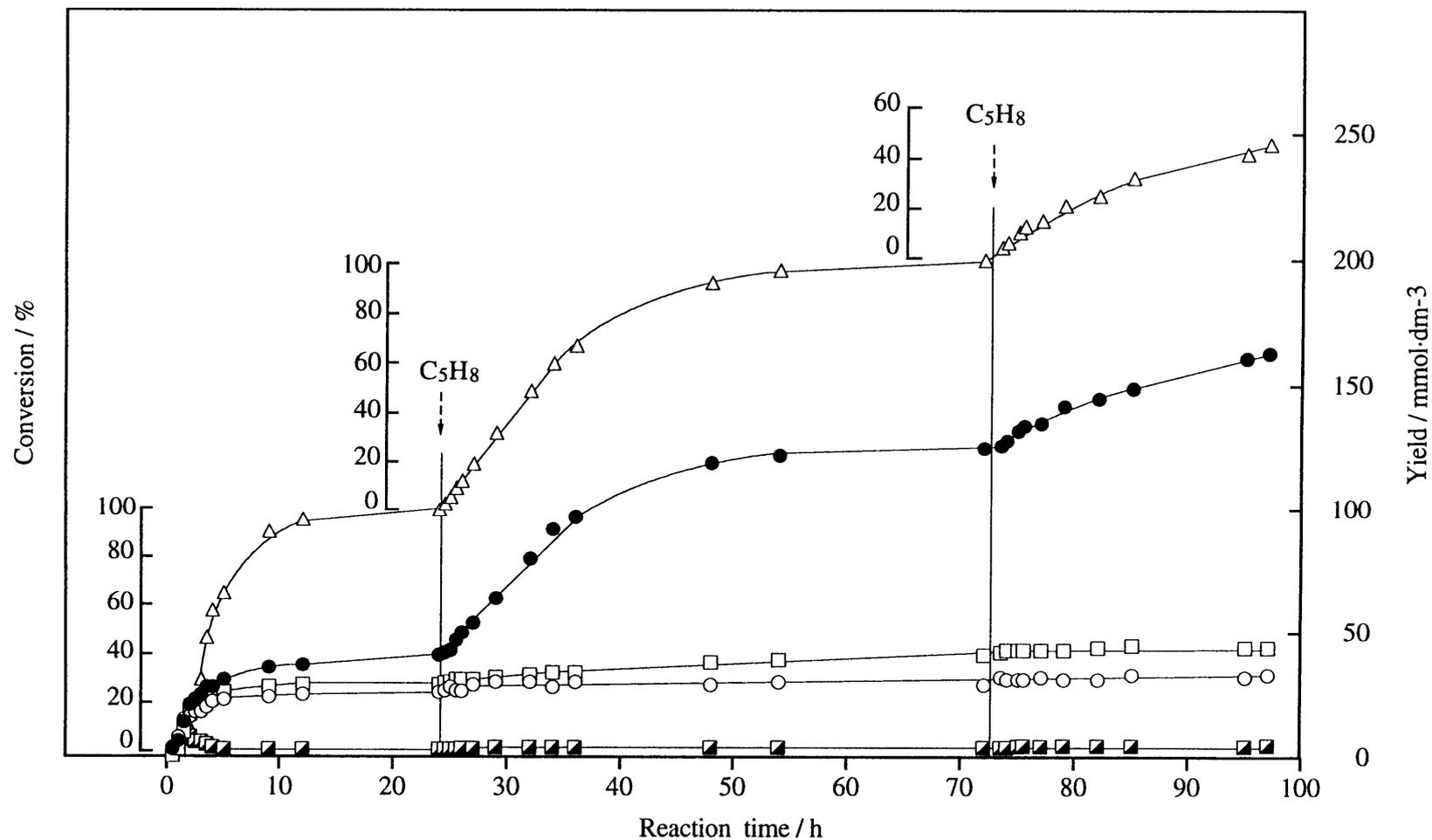
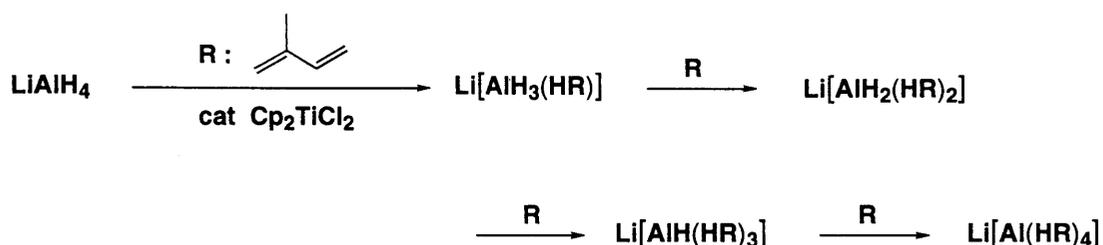


Figure 2. Successive Addition of Isoprene in Cp_2TiCl_2 -Catalyzed Hydroalumination

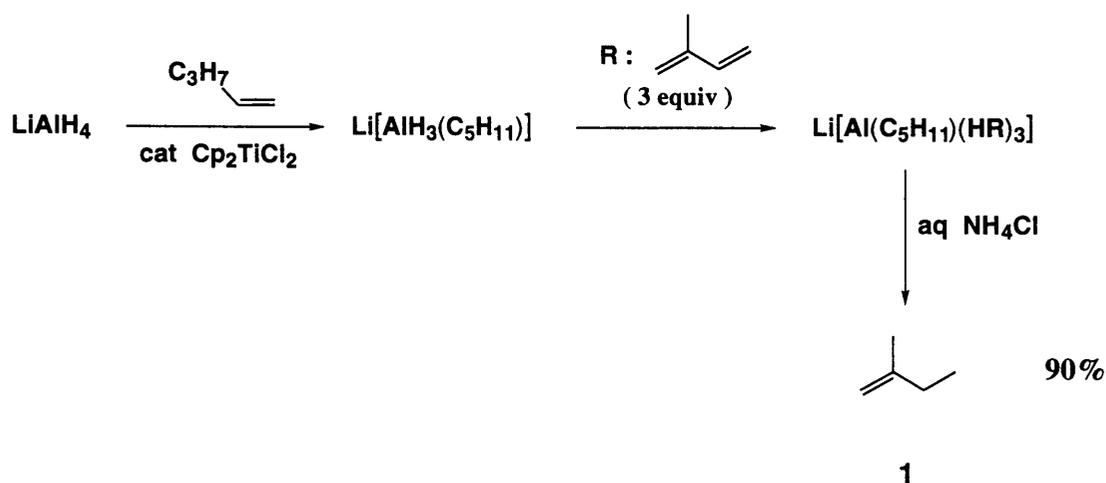
$[\text{Cp}_2\text{TiCl}_2] = 2.5 \text{ mmol}\cdot\text{dm}^{-3}$, $[\text{LiAlH}_4] = 100 \text{ mmol}\cdot\text{dm}^{-3}$, $[\text{THF solution}] = 0.10 \text{ dm}^3$, 30°C

- | | | | | | |
|---|-----------------------|---|-----------------------|---|--------------------|
| ● | 2-Methyl-1-butene (1) | ○ | 2-Methyl-2-butene (2) | □ | 2-Methylbutane (3) |
| ■ | 3-Methyl-1-butene (4) | △ | Isoprene conversion | | |

These results have been interpreted to mean that the hydroalumination with LiAlH_4 at $[\text{Isoprene}]/[\text{LiAlH}_4] = 4$ proceeded by a sequence of four successive addition steps, and that steric bulkiness of an organic group of lithium trihydridoaluminates ($\text{Li}[\text{AlH}_3(\text{HR})]$), which might be derived from the reaction of isoprene with LiAlH_4 in the first step, was responsible for the selective formation of **1** in the subsequent steps.



Indeed, Cp_2TiCl_2 -catalyzed hydroalumination of isoprene with the modified complex aluminum hydride, lithium trihydridopentylaluminate ($\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$), which can be readily prepared *in situ* by Cp_2TiCl_2 -catalyzed hydroalumination of 1-pentene with LiAlH_4 , afforded **1** with good selectivity even at $[\text{Isoprene}]/[\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]] = 1$ (Figure 3). Similarly, the treatment with lithium dihydridodipentylaluminate ($\text{Li}[\text{AlH}_2(\text{C}_5\text{H}_{11})_2]$) allowed the facile selective formation of **1** (Figure 4).



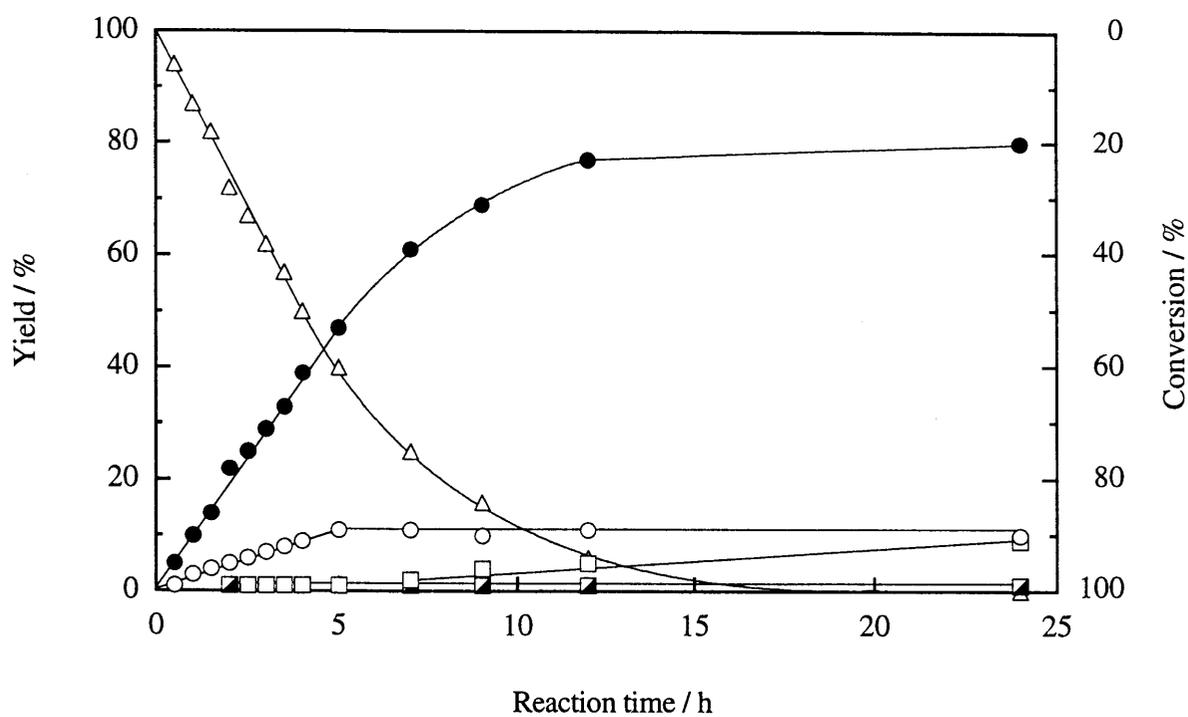


Figure 3. Cp₂TiCl₂-Catalyzed Hydroalumination of Isoprene with Li[AlH₃(C₅H₁₁)]

[Cp₂TiCl₂] = 2.5 mmol·dm⁻³, [Li[AlH₃(C₅H₁₁)]] = 100 mmol·dm⁻³, [Isoprene] = 100 mmol·dm⁻³, [THF solution] = 0.10 dm³, 30 °C

- | | | | |
|---|-----------------------|---|-----------------------|
| ● | 2-Methyl-1-butene (1) | ■ | 3-Methyl-1-butene (4) |
| ○ | 2-Methyl-2-butene (2) | △ | Isoprene conversion |
| □ | 2-Methylbutane (3) | | |

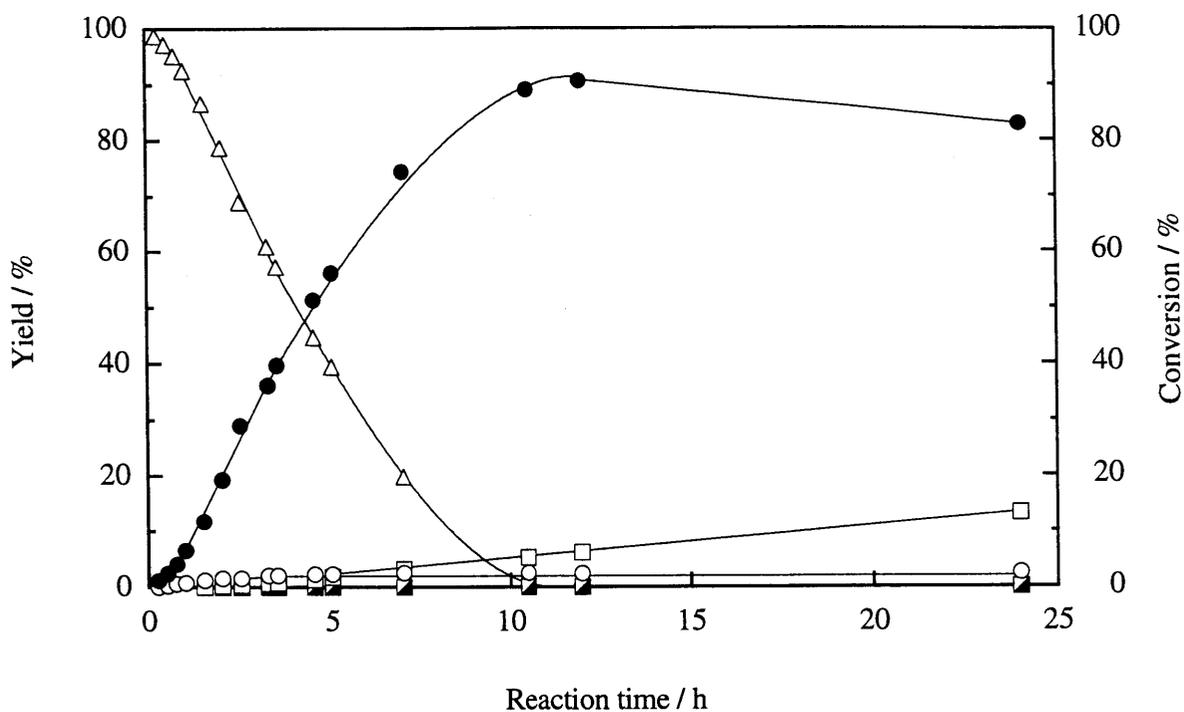


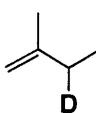
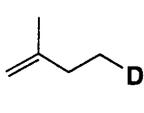
Figure 4. Cp_2TiCl_2 -Catalyzed Hydroalumination of Isoprene with $\text{Li}[\text{AlH}_2(\text{C}_5\text{H}_{11})_2]$

$[\text{Cp}_2\text{TiCl}_2] = 2.5 \text{ mmol}\cdot\text{dm}^{-3}$, $[\text{Li}[\text{AlH}_2(\text{C}_5\text{H}_{11})_2]] = 100 \text{ mmol}\cdot\text{dm}^{-3}$, $[\text{Isoprene}] = 100 \text{ mmol}\cdot\text{dm}^{-3}$, $[\text{THF solution}] = 0.10 \text{ dm}^3$, $30 \text{ }^\circ\text{C}$

- | | | | |
|---|-----------------------|---|-----------------------|
| ● | 2-Methyl-1-butene (1) | ■ | 3-Methyl-1-butene (4) |
| ○ | 2-Methyl-2-butene (2) | △ | Isoprene conversion |
| □ | 2-Methylbutane (3) | | |

A separate study quenching with D₂O was performed to determine the regioselectivity of Cp₂TiCl₂-catalyzed isoprene hydroalumination with LiAlH₄, Li[AlH₃(C₅H₁₁)], and Li[AlH₃(C₈H₁₇)] (Table 3). According to mass spectral analysis, the alkenes incorporated a high yield of deuterium (87—93%), but the 2-methylbutane (**3**) contained non-deuterated 2-methylbutane (2-methylbutane-*d*₀), 2-methylbutane-*d*₁, and 2-methylbutane-*d*₂. The ¹³C NMR (inverse gated decoupling⁴) study of the isolated 2-methyl-1-butene (**1**) indicated that the deuterium incorporated **1** obtained at [Isoprene]/[LiAlH₄] = 3.5 consisted of a mixture of 2-methyl-1-butene-3-*d* (**5**) and 2-methyl-1-butene-4-*d* (**6**) in a ratio of 87:13, in contrast to the result at [Isoprene]/[LiAlH₄] = 1 (100 : 0) (Table 4). Unfortunately, the hydroalumination with the modified complex aluminum hydrides, Li[AlH₃(C₅H₁₁)] and Li[AlH₃(C₈H₁₇)], also afforded a mixture of deuterated isomers, **5** and **6**, respectively (entries 3 and 4).

Table 4. Structure and Selectivity of Deuterated 2-Methyl-1-butene^a

entry	conditions	selectivity/% ^b		yield/% ^c	conv./%
					
		5	6		
1	LiAlH ₄ , 1.0	100	0	35 (90)	100
2	LiAlH ₄ , 3.5	87	13	76 (93)	99
3	Li[AlH ₃ (C ₅ H ₁₁)], 3.0	65	35	90 (89)	88
4	Li[AlH ₃ (C ₈ H ₁₇)], 3.0	60	40	90 (93)	86

^a Reaction conditions are given in Table 3. ^b Determined by ¹³C NMR (inverse gated decoupling) spectra of isolated products. ^c Values in parentheses are relative ratio/% of 2-methyl-1-butene-*d*₁ based on 2-methyl-1-butene-*d*₀ and 2-methyl-1-butene-*d*₁. Determined by mass spectra.

Table 3. Cp₂TiCl₂-Catalyzed Hydroalumination of Isoprene with Complex Aluminum Hydrides^a

entry	conditions	yield/%				conv./%
						
		1	2	3	4	
1 ^b	LiAlH ₄ , 1.0 ^c	35 (90) ^d	23 (93) ^e	42 (3/54/43) ^f	trace	100
2 ^g	LiAlH ₄ , 3.5	76 (93)	6 (89)	16 (10/36/54)	2	99
3 ^h	Li[AlH ₃ (C ₅ H ₁₁)], 3.0	90 (89)	7 (90)	3	trace	88
4 ⁱ	Li[AlH ₃ (C ₈ H ₁₇)], 3.0	90 (93)	7 (87)	3	trace	86

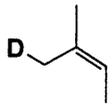
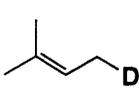
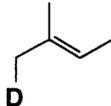
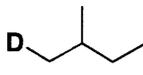
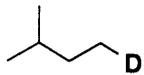
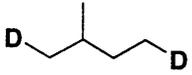
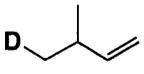
^a Reaction conditions: [Cp₂TiCl₂] = 9.5 mmol·dm⁻³, [Complex aluminum hydride] = 380 mmol·dm⁻³, [THF solution] = 0.10 dm³, 30 °C. Reaction was quenched with D₂O at 0 °C.

^b For 48 h. ^c Molar ratio of isoprene to LiAlH₄ ([Isoprene]/[LiAlH₄]). ^d Values in parentheses are relative ratio/% of 2-methyl-1-butene-*d*₁ based on 2-methyl-1-butene-*d*₀ and 2-methyl-1-butene-*d*₁. Determined by mass spectra. ^e Values in parentheses are relative ratio/% of 2-methyl-2-butene-*d*₁ based on 2-methyl-2-butene-*d*₀ and 2-methyl-2-butene-*d*₁.

^f Values in parentheses are relative ratio/% of 2-methylbutane-*d*₀, 2-methylbutane-*d*₁, and 2-methylbutane-*d*₂. ^g For 73 h. ^h For 92 h. ⁱ For 50 h.

In a similar manner, the structure of other deuterolysis products obtained by the hydroalumination with LiAlH_4 and their selectivity were determined, and the results are depicted in Tables 5. The deuterated 2-methyl-2-butene (2-methyl-2-butene- d_1) produced by the reaction at both $[\text{Isoprene}]/[\text{LiAlH}_4] = 1$ and 3.5 was a mixture of the allyl-deuterated alkenes, **7**, **8**, and **9**

Table 5. Structure and Selectivity of Other Deuterolysis Products^a

entry	conditions	structure and selectivity/%			yield/%	conv./%
						
		7	8	9		
1	LiAlH_4 , 1.0	71	23	6	23 (93)	100
2	LiAlH_4 , 3.5	74	14	12	6 (89)	99
						
		10	11	12		
3	LiAlH_4 , 1.0	25	31	44	42 (3/54/43)	100
4	LiAlH_4 , 3.5	21	19	60	16 (10/36/54)	99
						
			13			
5	LiAlH_4 , 1.0 ^b		100		18 (74/26)	79

^a Reaction conditions are given in Table 3. ^b For 0.5 h.

(entries 1 and 2). On the other hand, the saturated product, 2-methylbutane, was an approximately 50/50 mixture of 2-methylbutane- d_1 and 2-methylbutane- d_2 . This 2-methylbutane- d_1 contained a 1:1 mixture of the 2-methylbutane-1- d (**10**) and 2-methylbutane-4- d (**11**), while 2-methylbutane- d_2 was only 2-methylbutane-1,4- d_2 (**12**) (entries 3 and 4).

In studying the reaction at $[\text{Isoprene}]/[\text{LiAlH}_4] = 1$, a marked increase in the yield of the hydrolysis product, 3-methyl-1-butene (**4**), was observed (Figure 5); it continued for a period of approximately 0.5 h, and then by compensation of the yield of **4** the yield of 2-methylbutane (**3**) gradually increased. When the study quenching with D_2O after the reaction at $[\text{Isoprene}]/[\text{LiAlH}_4] = 1$ for 0.5 h was performed to determine the structure of deuterated species of **4** and their selectivity, 3-methyl-1-butene-4- d (**13**) was obtained solely. The deuterium incorporation of **4** was only 26%, however, the rest being non-deuterated **4** (3-methyl-1-butene- d_0) (entry 5 in Table 5).

On the basis of the structural consideration for the main resulting deuterated products, 2-methyl-1-butene-3- d (**5**), 2-methyl-1-butene-4- d (**6**), (*Z*)-2-methyl-2-butene-1- d (**7**), 2-methylbutane-1,4- d_2 (**12**), and 3-methyl-1-butene-4- d (**13**), the hydroalumination products have been assumed as follows (Scheme I). The homoallyl-deuterated products, **6** and **13**, would arise from the deuterolysis of the corresponding homoallylaluminum compounds, **19** and **20**, while the allyl-deuterated products, **5** and **7**, could be considered to derive from the deuterolysis involving the allylic rearrangement³ of allylaluminum intermediates, **15** and **16**, via the transmetallation of *syn*-1,2-dimethylallyltitanium complex **14**.⁵ The deuterolysis of dihydroalumination product **21**, which may be produced *in situ* by an additional hydroalumination reaction of the homoallylaluminum intermediates, **19** and **20**, led to the dideuterated product **12**. Hence, that no formation of the homoallyl-deuterated products **6** was observed at $[\text{Isoprene}]/[\text{LiAlH}_4] = 1$ may be attributable to this proposed dihydroalumination reaction for the formation of **21** via **19**. Since the use of the modified complex aluminum hydrides such as $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$ has efficiently controlled to give monohydroalumination products, which are probably **15** and **19**, the regiochemistry of isoprene hydroalumination should be determined in the transmetallation step, where alkenyl transfer reactions from titanium atom to aluminum atom would be restricted by a steric bulkiness of an organic group of aluminum hydrides.

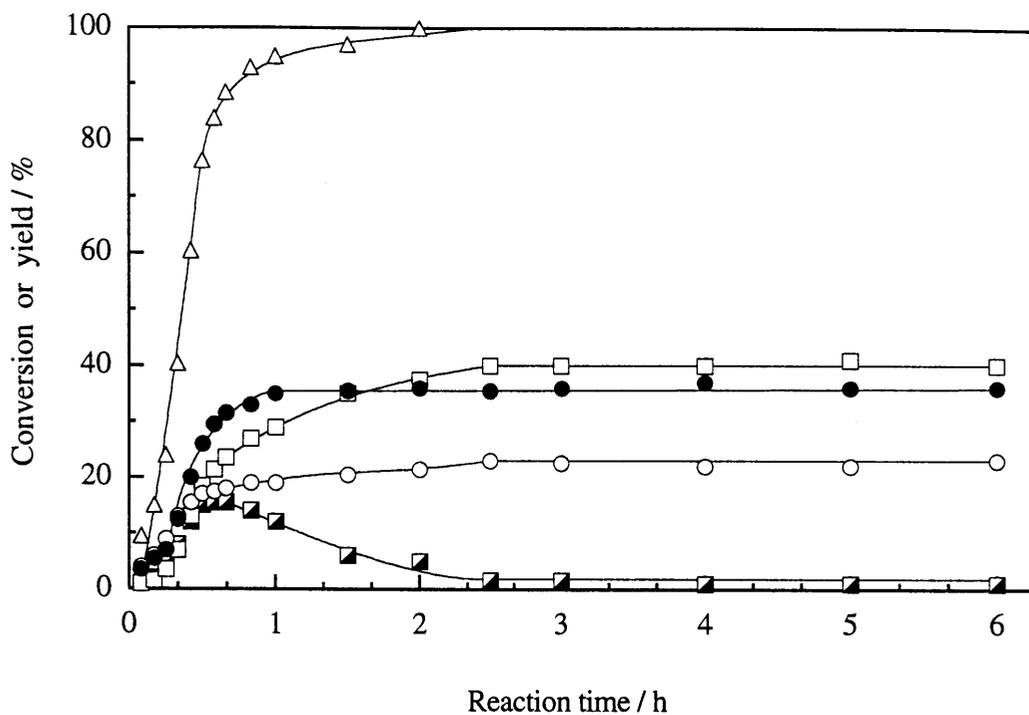
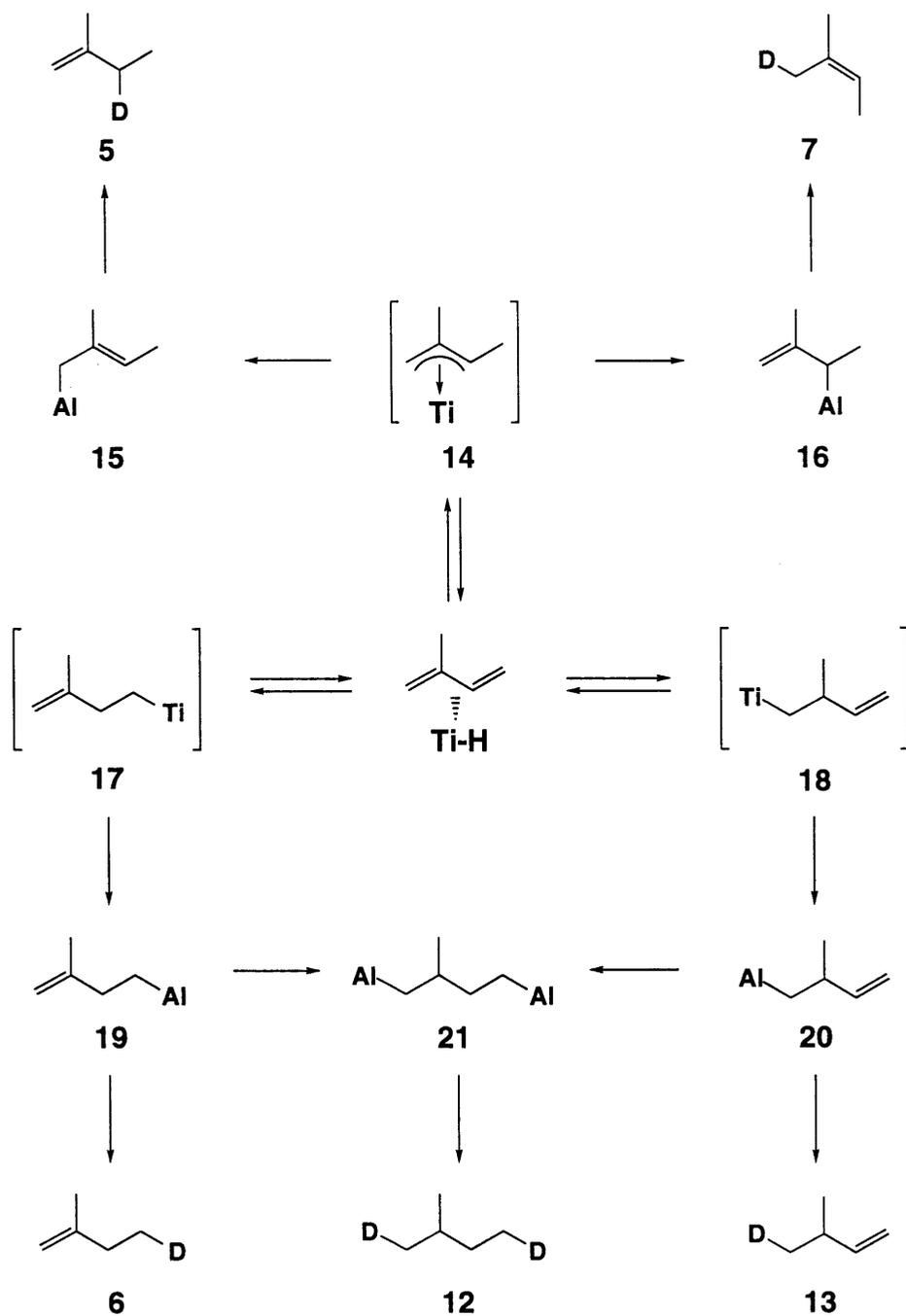


Figure 5. Cp₂TiCl₂-Catalyzed Hydroalumination of Isoprene at [Isoprene] / [LiAlH₄] = 1

[Cp₂TiCl₂] = 9.5 mmol·dm⁻³, [LiAlH₄] = 380 mmol·dm⁻³, [Isoprene] = 380 mmol·dm⁻³,
 [THF solution] = 0.05 dm³, 30 °C

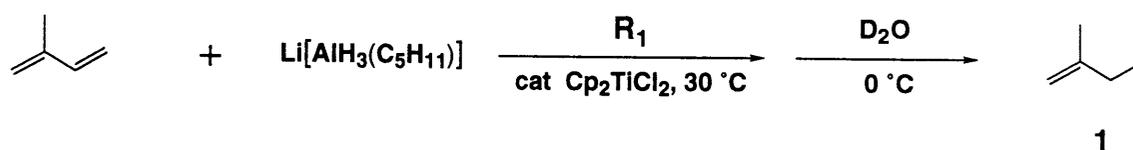
- | | | | |
|---|-----------------------|---|-----------------------|
| ● | 2-Methyl-1-butene (1) | ■ | 3-Methyl-1-butene (4) |
| ○ | 2-Methyl-2-butene (2) | △ | Isoprene conversion |
| □ | 2-Methylbutane (3) | | |

Scheme I

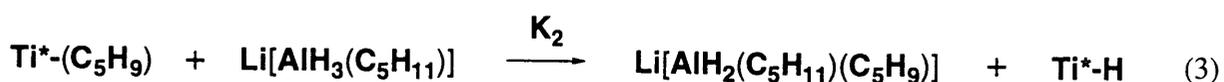
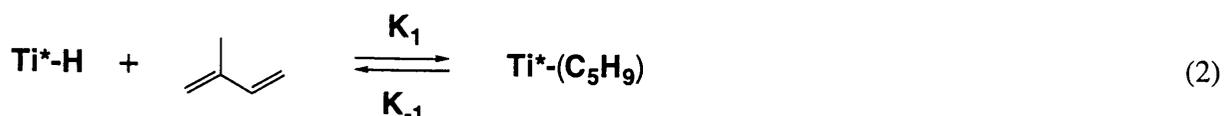


In order to elucidate the mechanism of the isoprene hydroalumination, a kinetic study of Cp_2TiCl_2 -catalyzed isoprene hydroalumination with $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$ was also examined. For example, time dependence of the yield of the resulting hydrolysis products at

$[\text{Isoprene}]/[\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]] = 3$ is shown in Figure 6. The yield of **1** produced selectively was proportional to the reaction time in the range of a low conversion of isoprene (less than 30% conversion), the appropriate plot passing through the origin. Thus, the initial rate, R_1 , for the formation of **1** under this condition was established to be $22.3 \text{ mmol}\cdot\text{dm}^{-3}\cdot\text{h}^{-1}$ (entry 1 in Table 6). Hydroalumination results obtained at 30°C under different conditions are listed in Table 6. That the product **1** was derived from the corresponding alkenylaluminum intermediates was confirmed



by deuterolysis of the reaction mixture after 24 h (85—90% deuterium incorporation). As revealed in Table 6, R_1 showed to be a first-order dependence on the concentration of Cp_2TiCl_2 (entries 1—3), as well as the concentration of $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$ (entries 4—9). In contrast, the effect of the isoprene concentration was independent of R_1 (entries 1, 7, 10, and 11). Consequently, the initial rate, R_1 , could be expressed by $R_1 = K[\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]][\text{Cp}_2\text{TiCl}_2]$, where $[\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]]$ and $[\text{Cp}_2\text{TiCl}_2]$ denote the initial concentration of complex aluminum hydride and Ti-catalyst, respectively. This experimental formula can be anticipated in terms of the mechanism^{1d} in which the isoprene hydroalumination proceeded by a sequence of two successive reactions: (1) the coordination and subsequent insertion of an isoprene to an active Ti-H bond as the fast step (Eq. 2);



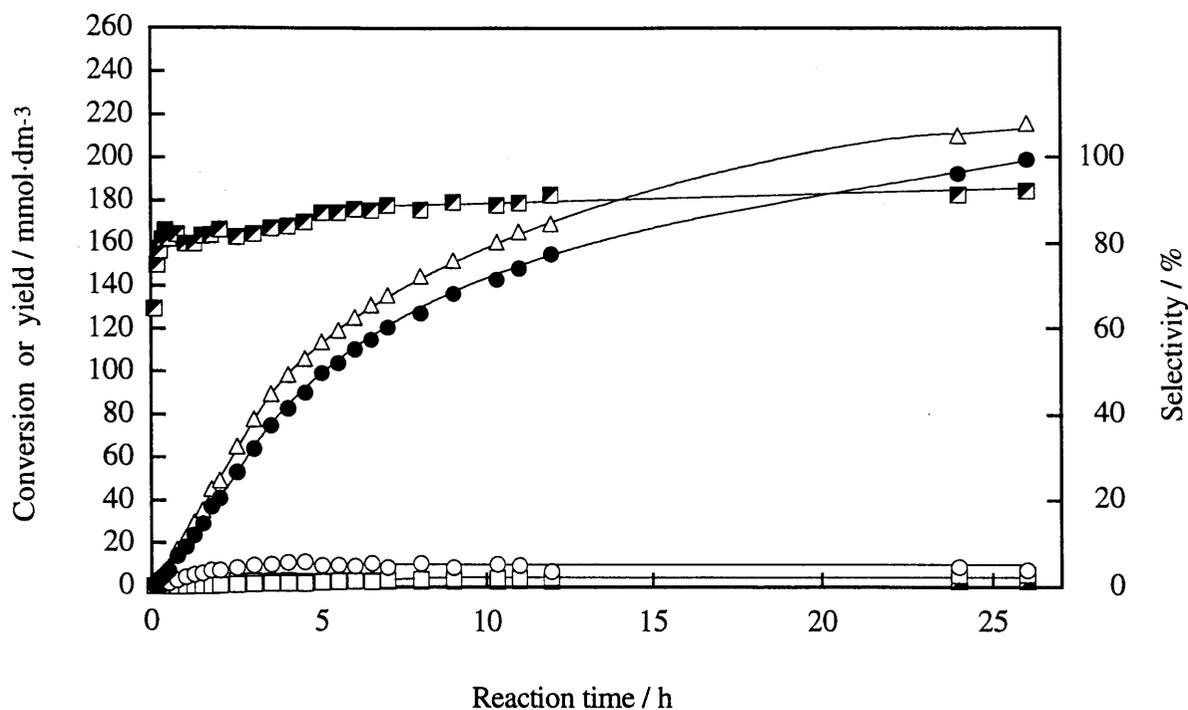


Figure 6. Cp_2TiCl_2 -Catalyzed Hydroalumination of Isoprene at $[\text{Isoprene}] / [\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]] = 3$

$[\text{Cp}_2\text{TiCl}_2] = 2.5 \text{ mmol}\cdot\text{dm}^{-3}$, $[\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]] = 100 \text{ mmol}\cdot\text{dm}^{-3}$, $[\text{Isoprene}] = 300 \text{ mmol}\cdot\text{dm}^{-3}$, $[\text{THF solution}] = 0.10 \text{ dm}^3$, $30 \text{ }^\circ\text{C}$

- | | | | |
|---|-----------------------|---|-----------------------------------|
| ● | 2-Methyl-1-butene (1) | ■ | 3-Methyl-1-butene (4) |
| ○ | 2-Methyl-2-butene (2) | △ | Isoprene conversion |
| □ | 2-Methylbutane (3) | ■ | 2-Methyl-1-butene (1) selectivity |

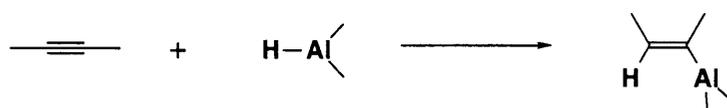
and (2) the transmetallation of the intermediary alkenyltitanium compound ($\text{Ti}^*(\text{C}_5\text{H}_9)$), thus generated, with $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$ involving regeneration of the active titanium hydride species ($\text{Ti}^*\text{-H}$) as the rate-determining step (Eq. 3).

Table 6. Initial Rate for Formation of 2-Methyl-1-butene in Cp_2TiCl_2 -Catalyzed Hydroalumination of Isoprene with $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$ ^a

entry	$[\text{Cp}_2\text{TiCl}_2]$ ($\text{mmol}\cdot\text{dm}^{-3}$)	$[\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]]$ ($\text{mmol}\cdot\text{dm}^{-3}$)	[Isoprene] ($\text{mmol}\cdot\text{dm}^{-3}$)	formation of 1 ^b	
				initial rate R_1 ($\text{mmol}\cdot\text{dm}^{-3}\cdot\text{h}^{-1}$)	selectivity (%)
1	2.5	100	300	22.3	92
2	5.0	100	300	45.0	90
3	10.0	100	300	92.0	93
4	2.5	50	300	13.0	95
5	2.5	150	300	30.0	91
6	2.5	50	600	14.0	94
7	2.5	100	600	22.3	95
8	2.5	150	600	33.8	93
9	2.5	200	600	45.8	94
10	2.5	100	200	22.5	91
11	2.5	100	800	22.0	90

^a Reaction was carried out in THF ([THF solution] = 0.1 dm^3) at $30 \text{ }^\circ\text{C}$ for 24 h, and was then quenched with D_2O at $0 \text{ }^\circ\text{C}$. ^b Deuterium incorporation was 85—90 % after reaction for 24 h.

Although hydroalumination of alkynes with organoaluminum hydrides (R_2AlH) such as *i*- Bu_2AlH has been a reasonably convenient and effective reaction for selective generation of vinylaluminum compounds,⁶ the Cp_2TiCl_2 -catalyzed hydroalumination of 1-alkynes with complex aluminum hydrides and dialkylaminoaluminum hydrides was reported to afford a mixture of mono- and dihydroalumination products.² In this context, catalytic hydroalumination of 1-alkynes with the modified complex aluminum hydride, $Li[AlH_3(C_5H_{11})]$ was examined in an attempt to produce vinylaluminum intermediates selectively. For example, Cp_2TiCl_2 -catalyzed hydroalumination of



1-hexyne with $Li[AlH_3(C_5H_{11})]$ followed by deuterolysis gave rise exclusively to 1-hexene (97% selectivity) incorporated high yield of deuterium (88%), as listed in Table 8 (entry 3). Results when $LiAlH_4$ was used are also included for comparison. The steric effect of the modified complex aluminum hydride, $Li[AlH_3(C_5H_{11})]$, is favorable in the hydroalumination of terminal alkynes for obtaining monohydroalumination products. Hence the structure of the resulting deuterated products, 1-alkene- d_1 , alkane- d_1 , and alkane- d_2 , and their selectivity were determined by

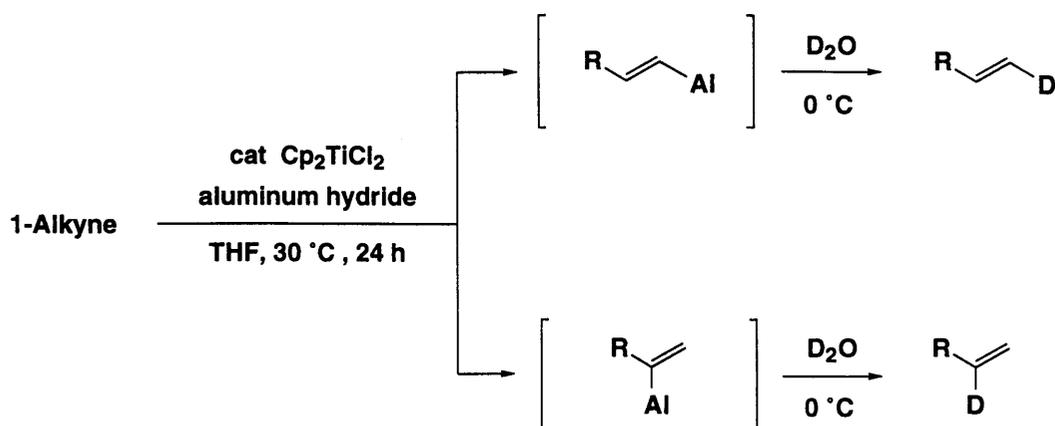


Table 8. Transition Metal-Catalyzed Hydroalumination of 1-Alkynes with Complex Aluminum Hydrides^a

entry	catalyst	conditions	yield/% ^b			conv./%	
			1-hexyne	hexane	1-hexene		2-hexene
1	Cp ₂ TiCl ₂	LiAlH ₄ , 1.0 ^c	50 (6/33/52/9) ^d	49 (96) ^e	1	100	
2		LiAlH ₄ , 4.0	17 (11/37/49/3)	82 (87)	1	58	
3		Li[AlH ₃ (C ₅ H ₁₁)], 3.0	3	97 (88)	0	60	
4	TiCl ₄	LiAlH ₄ , 4.0	46 (9/41/50/0)	54 (85)	0	38	
5	Ti(acac) ₂ Cl ₂	LiAlH ₄ , 4.0	33 (26/49/25/0)	67 (68)	0	28	
			1-octyne	octane	1-octene	2-octene	
6	Cp ₂ TiCl ₂	LiAlH ₄ , 1.0 ^c	45 (6/32/52/10) ^d	51 (93) ^e	4	100	
7		LiAlH ₄ , 4.0	18 (22/49/37/2)	80 (86)	2	58	
8		Li[AlH ₃ (C ₅ H ₁₁)], 3.0	2	96 (88)	2	56	

^a [Catalyst] = 10 mmol·dm⁻³, [Complex aluminum hydride] = 100 mmol·dm⁻³, [THF solution] = 0.05 dm³. Reaction was carried out at 30 °C for 24 h, and was then quenched with D₂O at 0 °C. ^b Determined by GLC analysis using the internal standard method. ^c Molar ratio of isoprene to complex aluminum hydride ([Isoprene]/[Complex aluminum hydride]). ^d Values in parentheses are relative ratio/% of alkane-*d*₀, alkane-*d*₁, alkane-*d*₂, and alkane-*d*₃. Determined by mass spectra. ^e Values in parentheses are relative ratio/% of 1-alkene-*d*₁ based on 1-alkene-*d*₀ and 1-alkene-*d*₁.

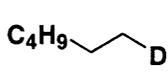
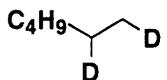
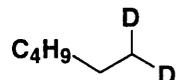
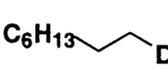
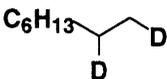
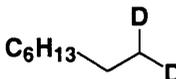
^{13}C NMR analysis, as shown in Tables 9 and 10. As revealed in Table 9, this catalytic method using $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$ ultimately revealed disappointing regioselectivity similar to that in the sole use of LiAlH_4 , the deuterated 1-alkene being found to be a mixture of 1-alkene-1-*d*, **22** or **24**, and 1-alkene-2-*d*, **23** or **25**.

Table 9. Structure and Selectivity of 1-Alkene-*d*^a

entry	conditions	structure and selectivity/% ^b		yield/% ^c	conv./%
1-hexyne					
		22	23		
1	LiAlH_4 , 1.0	72	28	49 (96)	100
2	LiAlH_4 , 4.0	72	28	82 (87)	58
3	$\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$, 3.0	68	32	97 (88)	60
1-octyne					
		24	25		
4	LiAlH_4 , 1.0	63	37	51 (93)	100
5	LiAlH_4 , 4.0	69	31	80 (86)	58
6	$\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$, 3.0	64	36	96 (88)	56

^a Reaction conditions are given in Table 8. ^b Determined by ^{13}C NMR (inverse gated decoupling) spectra of isolated products. ^c Values in parentheses are relative ratio/% of 1-alkene-*d*₁ based on 1-alkene-*d*₀ and 1-alkene-*d*₁.

Table 10. Structure and Selectivity of Alkane- d_1 and Alkane- d_2 ^a

conditions	structure and selectivity/% ^b			yield/% ^c	conv./%
					
	26	27	28		
LiAlH ₄ , 1.0	40	30	30	50 (6/33/52/9)	100
					
	29	30	31		
LiAlH ₄ , 1.0	40	30	30	45 (6/32/52/10)	100

^a Reaction conditions are given in Table 8. ^b Determined by ¹³C NMR (inverse gated decoupling) spectra of isolated products. ^c Values in parentheses are relative ratio/% of alkane- d_0 , alkane- d_1 , alkane- d_2 , and alkane- d_3 .

Experimental Section

General. The GLC analyses were performed with a Shimadzu 6A and 7A gas chromatograph equipped with Silicone DC-710 (6m) and VZ-7 (6m) columns (N₂ as carrier gas). The ¹H NMR and ¹³C NMR spectra were recorded on JEOL FX-60Q spectrometer, using tetramethylsilane (Me₄Si) as an internal standard. Splitting patterns are indicated as s, singlet; t, triplet; q, quartet; m, multiplet. The mass spectra were recorded with a Shimadzu GCMS-7000

mass spectrometer. Tetrahydrofuran (THF), isoprene, 1-pentene, and 1-octene were freshly distilled from LiAlH₄. All experiments were carried out under an atmosphere of dry argon. Other simple, inorganic and organic chemicals were purchased and used as such.

General Method of Transition Metal-Catalyzed Hydroalumination of Isoprene with LiAlH₄. To a clear filtered solution of LiAlH₄ in THF⁷ was added isoprene followed by a solution of transition metal halides in THF at 30 °C. The reaction mixture was stirred at 30 °C, and was then quenched at a given time with a saturated solution of NH₄Cl or D₂O. The amount of recovered isoprene and the resulting products were determined by GLC analysis. Each product was collected from a gas chromatograph and submitted for mass spectral analysis.¹ The regioselectivity of the reaction was monitored by ¹³C NMR spectroscopy applied *inverse gated decoupling*⁴ for resulting deuterated products by deuterolysis. This technique allows the quantitative evaluation of proton-decoupled ¹³C NMR spectra. For example, this ¹³C NMR measurement of deuterated 2-methyl-1-butene (a mixture of **5** and **6**) obtained by Cp₂TiCl₂-catalyzed hydroalumination at [Isoprene]/[LiAlH₄] = 3.5 (Table 4, entry 2) showed that the signals of deuterated C₃-D and C₄-D carbons split into triplet ($J_{C_3-D}=19.0$ Hz and $J_{C_4-D}=19.0$ Hz) and shifted upper field ($\Delta\delta_{C_3}=0.4$ ppm and $\Delta\delta_{C_4}=0.4$ ppm by comparison with the isotopic C₃-H (δ 30.6) and C₄-H (δ 12.4) carbon signals of 2-methyl-1-butene-*d*₀), respectively. Additionally, due to the ¹³C₃-C₄-D and ¹³C₄-C₃-D spin-spin coupling the broad triplet signals were observed by overlapping to C₃-H and C₄-H carbon signals ($^2J^{13}C-D=0.7$ Hz). By determining the integration ratio of C₃-D signal to ¹³C₃-C₄-D and C₃-H signals (81:19) and those of C₄-D to ¹³C₄-C₃-D and C₄-H (12:88), relative ratio of **5** based on **5** and **6** was established to be 87:13, as tabulated in Table 4. The deuterated products were identified by spectral comparison with authentic non-deuterated samples obtained commercially. The following characteristic ¹³C NMR data were observed ($\Delta\delta(\delta_{C-H} - \delta_{C-D})$ in ppm upper field from the corresponding isotopic C-H carbon signal).

2-Methyl-1-butene-3-*d* (5): C₃-D (δ 30.2, t, $J_{C-D}=19.0$ Hz, $\Delta\delta(\delta_{C-H} - \delta_{C-D})=0.4$).

2-Methyl-1-butene-4-*d* (6): C₄-D (δ 12.0, t, $J_{C-D}=19.0$ Hz, $\Delta\delta(\delta_{C-H} - \delta_{C-D})=0.4$).

(Z)-2-Methyl-2-butene-1-*d* (7): C₁-D (δ 17.0, t, $J_{C-D}=19.0$ Hz, $\Delta\delta(\delta_{C-H} - \delta_{C-D})=0.3$).

2-Methyl-2-butene-4-*d* (8): C₄-D (δ 13.1, t, $J_{C-D}=19.0$ Hz, $\Delta\delta(\delta_{C-H} - \delta_{C-D})=0.3$).

(E)-2-Methyl-2-butene-1-d (9): C₁-D (δ 25.3, t, J_{C-D} =19.0 Hz, $\Delta\delta(\delta_{C-H} - \delta_{C-D})=0.3$).

2-Methylbutane-1-d (10): C₁-D (δ 21.9, t, J_{C-D} =19.0 Hz, $\Delta\delta(\delta_{C-H} - \delta_{C-D})=0.4$).

2-Methylbutane-4-d (11): C₄-D (δ 11.5, t, J_{C-D} =19.0 Hz, $\Delta\delta(\delta_{C-H} - \delta_{C-D})=0.3$).

2-Methylbutane-1,4-d₂(12): C₁-D (δ 21.9, t, J_{C-D} =19.0 Hz, $\Delta\delta(\delta_{C-H} - \delta_{C-D})=0.4$), C₄-D (δ 11.5, t, J_{C-D} =19.0 Hz, $\Delta\delta(\delta_{C-H} - \delta_{C-D})=0.3$).

3-Methyl-1-butene-4-d (13): C₄-D (δ =21.6, t, J_{C-D} =19.0 Hz, $\Delta\delta(\delta_{C-H} - \delta_{C-D})=0.4$).

Preparation of Lithium Trihydridopentylaluminate (Li[AlH₃(C₅H₁₁)]). To a clear filtered solution of LiAlH₄ in THF was added 1-pentene (1 equiv) followed by a solution of Cp₂TiCl₂ (2.5 mol%) in THF at 30 °C. The reaction mixture was stirred at 30 °C for 24 h and used as a solution of Li[AlH₃(C₅H₁₁)] in THF without any purification. Other modified complex aluminum hydrides such as lithium dihydridodipentylaluminate (Li[AlH₂(C₅H₁₁)₂]) and lithium trihydridoctylaluminate (Li[AlH₃(C₈H₁₇)]) were prepared *in situ* from Cp₂TiCl₂-catalyzed hydroalumination of the corresponding olefins with LiAlH₄ in THF at 30 °C for 24 h.

General Method of Cp₂TiCl₂-Catalyzed Hydroalumination of Isoprene with Modified Complex Aluminum Hydrides. To a solution of modified complex aluminum hydride in THF was added isoprene (3 equiv). The mixture was stirred at 30 °C and was then quenched at a given time with D₂O or a saturated solution of NH₄Cl. Analysis of all products arising from the quenching of reactions was performed by the methods as described above.

General Method of Cp₂TiCl₂-Catalyzed Hydroalumination of 1-Alkynes with LiAlH₄. To a clear filtered solution of LiAlH₄ in THF was added an 1-alkyne followed by a solution of Cp₂TiCl₂ (10 mol%) in THF at 30 °C. The reaction mixture was stirred at 30 °C for 24 h, and was then quenched with D₂O. Analysis of all products arising from the quenching of reactions was performed by the methods as described above. The following characteristic ¹H and/or ¹³C NMR data were observed for the hydroalumination of 1-hexyne ($\Delta\delta(\delta_{C-H} - \delta_{C-D})$ in ppm upper field from the corresponding isotopic C-H carbon signal).

1-Hexene-1-d (22):

¹³C NMR (CDCl₃) C₁-D (δ 113.8, t, J_{C-D} =24.1 Hz, $\Delta\delta(\delta_{C-H} - \delta_{C-D})=0.2$);

¹H NMR (CDCl₃) C₁H (δ 4.96, d, $J=17.0$ Hz), C₂H (δ 5.80, dt, $J=17.0, 6.3$ Hz).

1-Hexene-2-*d* (23):

^{13}C NMR (CDCl_3) $\text{C}_2\text{-D}$ (δ 138.8, t, $J_{\text{C-D}}=23.1$ Hz, $\Delta\delta(\delta_{\text{C-H}} - \delta_{\text{C-D}})=0.3$);

^1H NMR (CDCl_3) C_1H (δ 4.96 and 4.92, broad).

Hexane-1-*d* (26): ^{13}C NMR (CDCl_3) $\text{C}_1\text{-D}$ (δ 13.7, t, $J_{\text{C-D}}=19.1$ Hz, $\Delta\delta(\delta_{\text{C-H}} - \delta_{\text{C-D}})=0.3$).

Hexane-1,2-*d*₂(27):

^{13}C NMR (CDCl_3) $\text{C}_1\text{-D}$ (δ 13.6, t, $J_{\text{C-D}}=19.1$ Hz, $\Delta\delta(\delta_{\text{C-H}} - \delta_{\text{C-D}})=0.4$),

$\text{C}_2\text{-D}$ (δ 22.3, t, $J_{\text{C-D}}=19.4$ Hz, $\Delta\delta(\delta_{\text{C-H}} - \delta_{\text{C-D}})=0.4$).

Hexane-1,1-*d*₂(28):

^{13}C NMR (CDCl_3) $\text{C}_1\text{-D}_2$ (δ 13.4, quintet, $J_{\text{C-D}}=19.1$ Hz, $\Delta\delta(\delta_{\text{C-H}} - \delta_{\text{C-D}})=0.6$).

General Method of Cp_2TiCl_2 -Catalyzed Hydroalumination of 1-Alkynes with Complex Aluminum Hydrides. To a solution of modified complex aluminum hydride in THF was added an 1-alkyne (3 equiv). The mixture was stirred at 30 °C for 24 h and was then quenched with D_2O . Analysis of all products arising from the quenching of reactions was performed by the methods as described above.

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Chapter 3

Organoborane-Catalyzed Hydroalumination with Dichloroaluminum Hydride

Abstract: The hydroalumination of a terminal allene, 1,2-nonadiene, with LiAlH_4 in THF using Cp_2TiCl_2 , TiCl_4 , TiCl_3 , ZrCl_4 , and Cp_2ZrCl_2 catalysts afforded a wide variety of deuterated species by quenching hydroalumination products with D_2O , while PhB(OH)_2 -catalyzed hydroalumination with AlHCl_2 in ether gave >95% pure 1-nonene-3-*d* as predominant product (92%) in high yield. The allylation of benzaldehyde using the PhB(OH)_2 -catalyzed hydroalumination product suggested that the resulting hydroalumination product may be the allylaluminum compound, 2-nonenylaluminum dichloride. Allylation of *trans*-cinnamaldehyde using this allylaluminum compound proceeded with high regioselectivity, leaving the ketone functionality intact. Allylative ring-opening reaction of epoxides was less regioselective. The combination of catalytic PhB(OH)_2 with AlHCl_2 also was effective for the regioselective hydroalumination of the disubstituted allenes, vinylidenecyclohexane and 1-trimethylsilyl-1,2-nonadiene, although the trisubstituted allene, 1-butenylidenecyclohexane, showed nonregioselective orientation results.

Although hydroalumination of allenes is a reasonably convenient method for the generation of allylaluminum compounds, only few studies have been made on this subject.¹ One recent study includes the hydroalumination of allenes with diisobutylaluminum hydride (DIBAH) which gives excellent yields of allylaluminum compounds regioselectively, but this system is not employable for subsequent functionalization due to its inertness towards carbonyl compounds.^{1a} In hydroalumination of alkenes, several successful examples have been reported which utilize transition metal catalysts² and organoborane catalysts³ by combining use of inorganic aluminum hydride-type reagents such as LiAlH₄ and AlHCl₂ to effect the smooth hydroalumination. In this context, we have been interested in the development of the regioselective hydroalumination of allenes with inorganic aluminum hydride under the influence of a certain catalyst and its potential application to selective organic synthesis. Here we report the details of the regioselectivity in the hydroalumination of allenes with inorganic aluminum hydrides using various transition metal and organoborane catalysts and the reaction of the regioselectively generated allylaluminum compound with various electrophiles such as carbonyl compounds and epoxides.⁴

Initially, we studied the hydroalumination of a simple terminal allene, 1,2-nonadiene, with LiAlH₄ (0.25 equiv) in the presence of various transition metal catalysts (2.5 mol%). After the catalytic hydroalumination at 30 °C or under reflux conditions, the reaction was quenched with D₂O at 0 °C to monitor the regioselectivity of reaction under these conditions. As illustrated in Table 1 (entries 1, 3—6, and 9—11), all of the transition metal catalysts provided a mixture of nonane, 1-nonene, and 2-nonenes. According to mass spectral analysis, the alkenes incorporated a high yield of deuterium (>90%), but the nonane contained non-deuterated nonane (nonane-*d*₀), monodeuteriononane (nonane-*d*₁), and dideuteriononane (nonane-*d*₂). The ¹³C NMR (inverse gated decoupling⁵) study of the isolated alkenes indicated that Ti-catalysts and Cp₂ZrCl₂ catalyst produced a wide variety of deuterated alkenes. A similar tendency of low regioselectivity was also observed in the Ti-catalyzed hydroalumination of conjugated dienes and terminal alkynes.^{2e,2i,2j,6} In contrast, ZrCl₄ catalyst showed a nearly quantitative yield (>95%) of the deuterium incorporation at the allyl position of each alkene, resulting in a mixture of 1-nonene-3-*d* (**1**), (*E*)-2-nonene-1-*d* (**3**), and (*Z*)-2-nonene-1-*d* (**5**) (entries 5 and 6). Accordingly, we studied some modifications of

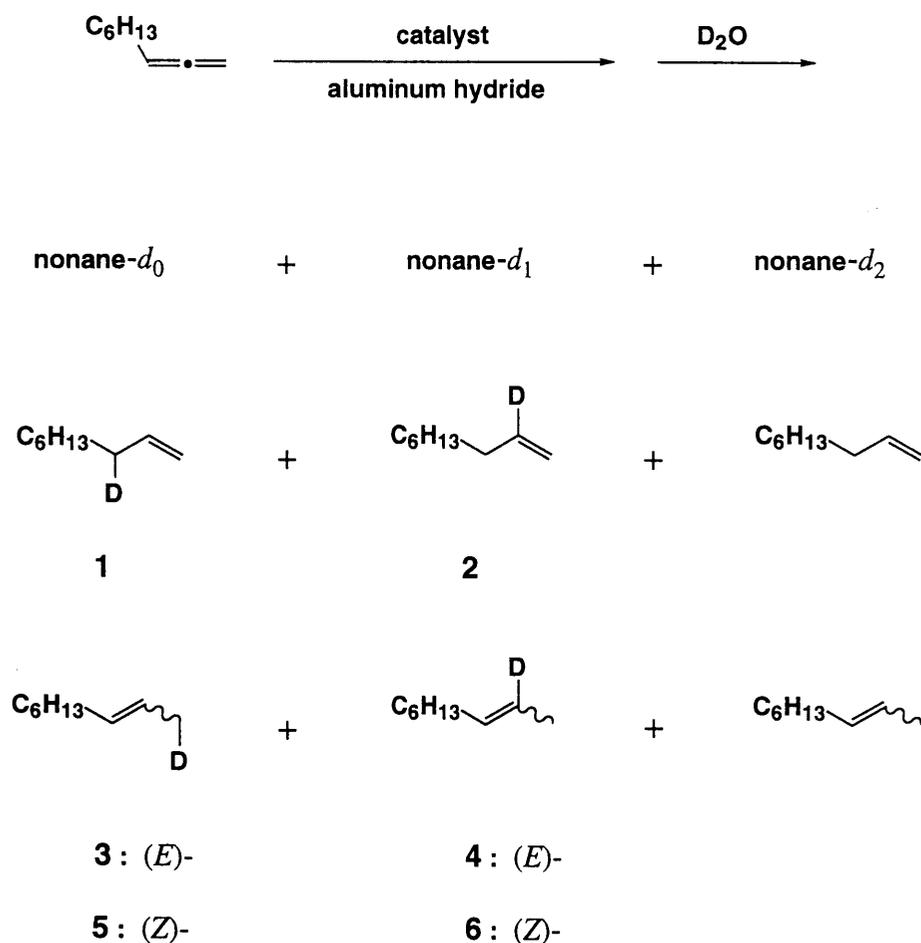
Table 1. Transition Metal-Catalyzed Hydroalumination of 1,2-Nonadiene^a

entry	catalyst	conditions	yield/% ^b				conv./% ^b
			nonane	1-nonene	(<i>E</i>)-2-nonene	(<i>Z</i>)-2-nonene	
1	Cp ₂ TiCl ₂	LiAlH ₄	16 (5/12/83) ^c	35 (62) ^d	14 (58) ^e	35 (29) ^f	92
2		AlHCl ₂ ^g	2	74 (60)	6	18	95
3	TiCl ₄	LiAlH ₄	23 (17/40/43)	48 (76)	15 (89)	14 (58)	88
4	TiCl ₃	LiAlH ₄	20 (14/51/35)	52 (77)	12 (89)	16 (51)	55
5	ZrCl ₄	LiAlH ₄	25 (11/77/12)	50 (>95)	15 (>95)	10 (>95)	50
6		LiAlH ₄ , reflux ^h	20	62 (>95)	10 (>95)	8 (>95)	72
7		Li[AlH ₃ (C ₅ H ₁₁)] ⁱ	13	64 (>95)	10	13	51
8		AlHCl ₂ ^g	21	75 (>95)	1	3	90
9	Cp ₂ ZrCl ₂	LiAlH ₄	31	48	13	8	10
10		LiAlH ₄ , reflux ^h	17	48 (59)	16 (82)	19 (46)	61
11	VCl ₃	LiAlH ₄	28 (36/48/16)	39	11	22	16

^a Unless otherwise noted, reaction was carried out in THF at 30 °C for 24 h using transition metal catalysts (2.5 mol%) with LiAlH₄ (0.25 equiv), and was then quenched with D₂O at 0 °C.

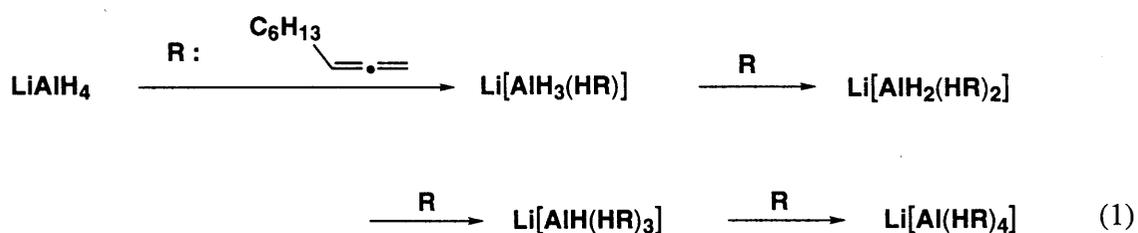
^b Determined by GLC analysis using the internal standard method. ^c Values in parentheses are relative ratio/% of nonane-*d*₀, nonane-*d*₁, and nonane-*d*₂. Determined by mass spectral analysis. ^d Relative ratio/% of allyl-deuterated isomer **1** based on **1** and **2**. Determined by ¹³C NMR (inverse gated decoupling) spectra of isolated products. ^e Relative ratio/% of allyl-deuterated isomer **3** based on **3** and **4**. ^f Relative ratio/% of allyl-deuterated isomer **5** based on **5** and **6**. ^g AlHCl₂ (1.2 equiv, prepared from LiAlH₄(0.3 equiv) and AlCl₃(0.9 equiv)). ^h At 30 °C for 1 h and was then refluxed for 24 h. ⁱ Li[AlH₃(C₅H₁₁)] (0.33 equiv, prepared by ZrCl₄-catalyzed hydroalumination of 1-pentene with LiAlH₄ in THF at 30 °C for 24 h) at 30 °C for 1 h and was then refluxed for 24 h.

aluminum hydride using ZrCl_4 -catalyzed hydroalumination to circumvent the problems of low product-selectivity. Use of lithium trihydridopentylaluminumate ($\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$), which was easily prepared *in situ* by ZrCl_4 -catalyzed hydroalumination of 1-pentene with LiAlH_4 , has efficiently



controlled to give monohydroalumination products and/or to gain regioselectivity in the catalytic hydroalumination of isoprene and 1-alkynes.⁶ The combination of ZrCl_4 catalyst with $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$, however, had no effect on the product ratios in this allene hydroalumination (entry 7). Hence we anticipated that the combination of ZrCl_4 catalyst with a certain aluminum monohydride might be suitable for effecting the selective hydroalumination if the low product-selectivity in hydroalumination with LiAlH_4 and $\text{Li}[\text{AlH}_3(\text{C}_5\text{H}_{11})]$ is attributable to the steric and

electronic requirements of each successive addition step (Eq. 1). Among various aluminum monohydrides, a stronger Lewis acid AlHCl_2 , which can be readily prepared from LiAlH_4 and AlCl_3 , might be expected to be a powerful aluminum hydride agent. When the ZrCl_4 -catalyzed hydroalumination with AlHCl_2 (1.2 equiv) was carried out at $30\text{ }^\circ\text{C}$ for 24 h, in fact, the yield of 1-nonene slightly increased (75%), as did the conversion of the hydroalumination (90%), although a significant proportion of nonane (21%) was produced (entry 8). It should be noted that a similar result was also observed in the Cp_2TiCl_2 -catalyzed hydroalumination (entry 2).



We then studied the possibility of organoborane catalysts with aluminum hydride-type reagents in diethyl ether (Et_2O).³ First, $\text{PhB}(\text{OH})_2$ -catalyzed hydroalumination of 1,2-nonadiene was carried out with a slight excess of the stronger Lewis acidic monohydride, AlHCl_2 (1.2 equiv) at room temperature for 4 h, giving 1-nonene (91%) as a major product and a small amount of the nonane and 2-nonenes in 55% conversion by protonolysis, as indicated in Table 2 (entry 1). With 2 equivalents of AlHCl_2 , the conversion yield increased with the longer reaction time without affecting the product selectivity (entries 2—4). When the reaction was allowed to continue for 7 h, however, the yield of nonane increased by compensation of the yield of 1-nonene (entry 5). Therefore, it seems reasonable that the nonane produced in this reaction was a result of dihydroalumination of alkenylaluminum intermediates. In contrast, the use of other aluminum hydrides, AlH_2Cl and AlH_3 , lowered the conversion of hydroalumination of 1,2-nonadiene even with a two-fold quantity of hydride and after a prolonged reaction time (24 h) (entries 6—9). Attempted Et_3B -catalyzed hydroalumination with AlHCl_2 (1.2 equiv) in 1,2-dichloroethane, which

has been an effective system for the hydroalumination of internal alkenes,³ resulted in unidentified side products with complete consumption of the starting 1,2-nonadiene (entry 10). A separate

Table 2. Organoborane-Catalyzed Hydroalumination of 1, 2-Nonadiene^a

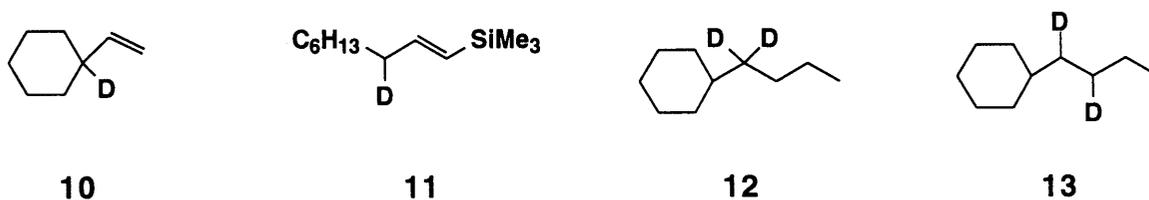
entry	catalyst	conditions	yield/%			conv./%
			nonane	1-nonene	2-nonenes	
1	PhB(OH) ₂	AlHCl ₂ ^b , 4 h	7	91	2	55
2		AlHCl ₂ ^c , 2 h	7	90	3	75
3		3 h	8	90	2	88
4		4 h	9	89	2	95
5		7 h	14	81	5	100
6		AlH ₂ Cl ^d , 4 h				4
7		24 h				12
8		AlH ₃ ^e , 4 h				0
9		24 h				4
10	Et ₃ B	AlHCl ₂ ^f , 1h				^g

^a Unless otherwise noted, reaction was carried out in Et₂O at room temperature using 5 mol% organoborane catalysts, and was then quenched with a saturated solution of NH₄Cl at 0 °C.

^b AlHCl₂ (1.2 equiv) was employed. ^c AlHCl₂ (2 equiv). ^d AlH₂Cl (2 equiv, prepared from LiAlH₄ (1 equiv) and AlCl₃ (1 equiv)). ^e AlH₃ (2 equiv, prepared from LiAlH₄ (1.5 equiv) and AlCl₃ (0.5 equiv)). ^f AlHCl₂ (1.2 equiv, prepared from DIBAH (1.2 equiv) and AlCl₃ (2.4 equiv)) in 1,2-dichloroethane. ^g Nonane, nonenes, and 1,2-nonadiene were not detected by GLC analysis. See also text.

study quenching with D₂O was performed to determine the regioselectivity of PhB(OH)₂-catalyzed hydroalumination with AlHCl₂ (2 equiv), and indicated that 89% of the isolated 1-nonene contained deuterium and this deuterated 1-nonene was >95% pure 1-nonene-3-*d* (**1**) without contamination of any deuterated isomers.

Other selected examples of the allene hydroalumination were studied under similar conditions and the results are depicted in Table 3. The disubstituted allenes, vinylidenecyclohexane (**7**) and 1-trimethylsilyl-1,2-nonadiene (**8**), were also successfully hydroaluminated using PhB(OH)₂ catalyst (5—20 mol%) with AlHCl₂, producing >95% pure 1-vinylcyclohexane-1-*d* (**10**) (88—93%) and >95% pure (*E*)-1-trimethylsilyl-1-nonene-3-*d* (**11**) (>99%), respectively (entries 2, 3, 5, and 6).⁷ However, trisubstituted allene, 1-butenylidenecyclohexane (**9**), afforded an approximately 50/50 mixture of corresponding alkane/alkenes (entries 9 and 10). The resulting saturated product, butylcyclohexane, was a mixture of monodeuteriobutylcyclohexane (butylcyclohexane-*d*₁) and dideuteriobutylcyclohexane (butylcyclohexane-*d*₂) in 18/82 proportions (entry 10). Interestingly, this butylcyclohexane-*d*₂ was a 3:1 mixture of the butyl-1,1-*d*₂ compound **12** and butyl-1,2-*d*₂ compound **13** which would have arisen from the dihydroalumination involving di- or monoaddition of aluminum atom on the central allene carbon followed by deuterolysis. These results can be interpreted as follows. According to the mechanism proposed for the transition metal-catalyzed hydroalumination,² an allene adds to B-H bond in a catalytic boron hydride species formed by the



reaction of PhB(OH)₂ with AlHCl₂.⁸ The intermediary alkenylboranes, thus generated, undergo the transmetalation with AlHCl₂ to yield the corresponding alkenylaluminum compounds with regeneration of the active boron hydride.⁹ Therefore, the regiochemistry of reaction may be

Table 3. Organoborane-Catalyzed Hydroalumination of Allenes^a

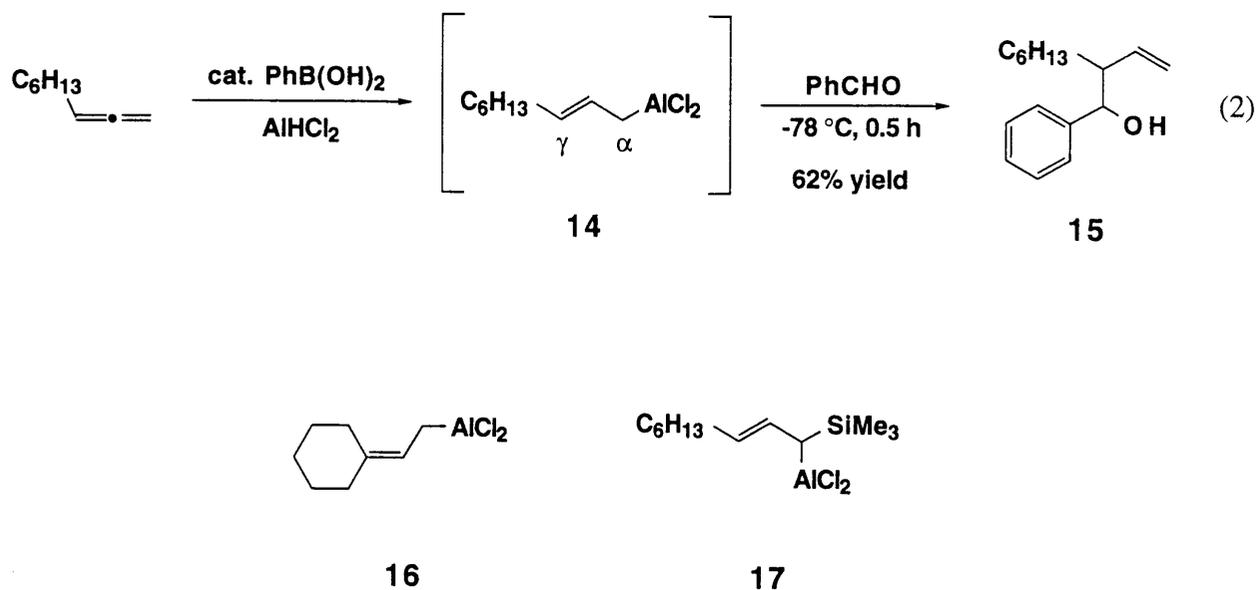
entry	conditions	yield/%			conv./%
		nonane	1-nonene	2-nonenenes	
1	PhB(OH) ₂ , 4h	6	92 (>95) ^b	2	75
	7				
2	PhB(OH) ₂ , 15 h	6	93 (>95)	1	87
3	PhB(OH) ₂ , 2 h ^c	10	88 (>95)	2	84
4	Et ₃ B, 0.5 h ^d	100			86
	8				
5	PhB(OH) ₂ , 24 h	>99 (>95)		<1 ^e	37
6	PhB(OH) ₂ , 24 h ^c	>99 (>95)		<1	53
7	Et ₃ B, 0.5 h ^d				<i>f</i>
8	Et ₃ B, 4 h ^g	>99 (>95)		<1	20
	9				
9	PhB(OH) ₂ , 6 h	48	32	20	19
10	PhB(OH) ₂ , 6 h ^c	45 (0/18/82) ^h	38	17	71
11	Et ₃ B, 0.5 h ^d	100			91

^a Unless otherwise noted, reaction was carried out in Et₂O at room temperature using 5 mol% organoborane catalysts with AlHCl₂ (2 equiv), and was then quenched with D₂O at 0 °C. ^b Values in parentheses are purity/% of allyl-deuterated isomer **1**, **10**, or **11**, respectively. ^c 20 mol% PhB(OH)₂ catalyst was employed. ^d AlHCl₂ (1.2 equiv) in 1,2-dichloroethane. ^e It was not detected by GLC analysis. ^f Nonane was observed. ^g AlHCl₂ (2 equiv) in Et₂O. ^h Values in parenthesis are relative ratio/% of butylcyclohexane-*d*₀, butylcyclohexane-*d*₁, and butylcyclohexane-*d*₂.

determined by the formation of the alkenylborane intermediates. Hydroalumination of 1,2-nonadiene and the disubstituted allenes, **7** and **8**, is considered as resulting in allylborane intermediates, which are observed from terminal attack of the boron atom at the more favored of the two sites of the allenic linkage; hence these exclusively and respectively gave the allyl-deuterated alkenes (deuterated on α -allylic position), **1**, **10**, and **11**, via the transmetallation followed by deuterolysis.

On the other hand, the trisubstituted allene **9** is more susceptible to central attack of the boron atom by the electronic and steric effects of pentamethylene and ethyl substituents on each terminal carbon of this allenyl system,¹⁰ thus this nature causing the nonregioselective hydroalumination due to the formation of a mixture of allyl- and vinylborane intermediates. In Et₃B-catalyzed hydroalumination of these allenes, unfavorable results were observed, that is, only the corresponding saturated products were provided as hydrolysis products (entries 4, 7, and 11).¹¹

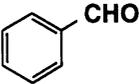
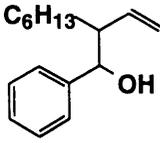
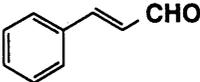
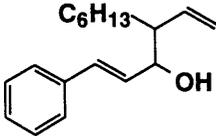
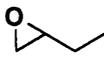
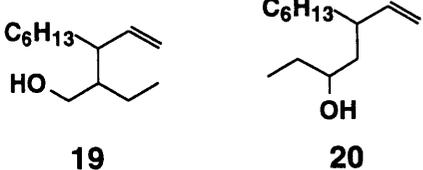
That the allyl-deuterated alkenes, **1**, **10**, and **11**, are derived from the deuterolysis of the corresponding, more hindered allylaluminum intermediates as hydroalumination products appears extremely doubtful. The reaction of allylic organometallics with electrophiles such as aldehydes and ketones is generally known to proceed through the S_E'-type substitution with a concomitant allylic rearrangement.¹² Accordingly, we carried out the reaction of PhB(OH)₂-catalyzed hydroalumination product with benzaldehyde to account for the regiochemical feature of hydroalumination products. As shown in Eq. 2, the allylation of benzaldehyde (2 equiv) using the hydroalumination product of 1,2-nonadiene in Et₂O at -78 °C for 0.5 h gave rise to the homoallylic alcohol **15** in 62% yield, suggesting that the intermediary allylaluminum compound **14** actually possesses C-Al bond at less hindered terminal carbon. Consequently, the deuterolysis of allylaluminum intermediates, **14** and **16**, led to the allyl-deuterated alkenes, **1** and **10**, respectively, with high γ -selectivity via the allylic rearrangement. Similarly, hydroalumination product of 1-trimethylsilyl-1,2-nonadiene (**8**) may be (1-trimethylsilyl-2-nonenyl)aluminum dichloride (**17**). In this case, our assumption is based on the trimethylsilyl group principally exerting the electronic effect, rather than the steric effect, which is the electron-donating ability comparable to vinylsilane compounds,¹³ the aluminum being located in the terminal carbon adjacent to the silicon atom.¹⁴



To apply this regioselective PhB(OH)_2 -catalyzed hydroalumination of allenes in organic synthesis, we carried out the C-C bond formation of the hydroalumination product **14** with various electrophiles. Selected examples are summarized in Table 4. The reaction of *trans*-cinnamaldehyde (2 equiv) with **14** at $-78\text{ }^\circ\text{C}$ for 1 h furnished only the corresponding 1,2-adducted homoallylic alcohol **18** with high γ -selectivity in 37% yield based on the starting 1,2-nonadiene (entry 2). The intermediate **14** also reacted with 1,2-epoxybutane in both of the two types of ring-opening reaction to produce an almost 1:1 mixture of *primary* and *secondary* δ , ϵ -unsaturated alcohols, **19** and **20**, in 40% yield (entry 3). It is noteworthy that this hydroalumination product **14** exhibited a high chemoselectivity, leaving the ketone functionality intact. For example, the reaction of **14** with acetone and acetophenone gave no addition products even at ambient temperature. In noncatalytic allene hydroalumination using DIBALH, however, the resulting allyldiisobutylaluminum intermediates is reported to be inert towards aldehydes and acid chlorides.^{1a} The high reactivity of allyldichloroaluminum intermediate **14** observed herein might be attributable to its lower steric bulkiness and stronger Lewis acidity.

In conclusion, the present method demonstrates a convenient and highly regioselective way to generate allylaluminum compounds, which can then be satisfactorily utilized for regioselective allylation of aldehydes.

Table 4. Reaction of Allylaluminum Compound **14** with Various Electrophiles^a

entry	electrophile	product	yield/% ^b
1		 15	62 ^c
2		 18	37 ^d
3		 19 20	40 ^e

19 : 20 = 60 : 40^f

^a Reaction was generally carried out at -78 °C for 0.5 h—1 h by adding an electrophile (2 equiv) to allylaluminum compound **14**, which was prepared *in situ* by PhB(OH)₂-catalyzed hydroalumination (entry 1 in Table 3). For experimental details, see text.

^b Isolated yield based on the starting 1,2-nonadiene. ^c *Erythro/threo* ratio is 3:2 or 2:3 by ¹H NMR analysis. ^d *Erythro/threo* ratio is 7:2 or 2:7 by ¹H NMR analysis. ^e The reaction was conducted at -20 °C for 0.5 h. ^f Determined by ¹H NMR analysis.

Experimental Section

General. The GLC analyses were performed with a Shimadzu 7A gas chromatograph equipped with Silicone DC-710 (6m) and VZ-7 (6m) columns (N₂ as carrier gas). The ¹H NMR and ¹³C NMR spectra were recorded on JEOL FX-60Q and Varian Gemini-200 spectrometers, using tetramethylsilane (Me₄Si) as an internal standard. Splitting patterns are indicated as s,

singlet; t, triplet; q, quartet; m, multiplet. The mass spectra were recorded with a Shimadzu GCMS-7000 mass spectrometer. The IR spectra were measured on a Perkin-Elmer 1600 Series FT IR spectrometer.

Diethyl ether (Et₂O) was freshly distilled from sodium metal using diphenylketyl as indicator. Tetrahydrofuran (THF) was freshly distilled from LiAlH₄. 1,2-Dichloroethane was freshly distilled before use. All experiments were carried out under an atmosphere of dry argon. Other simple, inorganic and organic chemicals were purchased and used as such, unless otherwise noted.

Preparation of Allenes. 1,2-Nonadiene,¹⁵ vinylidenecyclohexane (7),¹⁶ and 1-butenylidenecyclohexane (9)¹⁷ were available by the literature procedure. The allenes were identified by the following data.

1,2-Nonadiene: ¹H NMR (CDCl₃) δ 0.86 (3H, t, *J*=6.5 Hz, CH₃), 1.2—1.5 (8H, m, C₄H₈), 1.9—2.1 (2H, m, CH₂-C=), 4.62 (2H, dt, *J*=3.3 and 6.7 Hz, =CH₂), 5.07 (1H, tt, *J*=6.7 and 6.7 Hz, CH=); ¹³C NMR (CDCl₃) δ 14.12, 22.79, 28.47, 28.96, 29.32, 31.88, 74.41, 90.09, 208.68 (=C=); IR (neat) 2965, 2934, 2864, 1959, 1468, 1380, 844 cm⁻¹.

Vinylidenecyclohexane (7): ¹H NMR (CDCl₃) δ 1.4—1.7 (6H, m, C₃H₆), 2.0—2.2 (4H, m, (CH₂)₂-C=), 4.51 (2H, tt, *J*=2.4 and 2.4 Hz, =CH₂); ¹³C NMR (CDCl₃) δ 26.17, 27.21, 31.23, 72.36, 101.16, 203.49 (=C=); IR (neat) 2929, 2854, 1961, 1447, 1293, 842 cm⁻¹.

1-Butenylidenecyclohexane (9): ¹H NMR (CDCl₃) δ 0.98 (3H, t, *J*=7.3 Hz, CH₃), 1.3—2.1 (12H, m, C₅H₁₀ and =C-CH₂), 5.01 (1H, m, =CH); ¹³C NMR (CDCl₃) δ 13.51, 22.47, 26.36, 27.69, 32.01, 90.51, 103.07, 197.97 (=C=); IR (neat) 2963, 2928, 2853, 2359, 1965, 1447, 1316, 1265, 1238 cm⁻¹.

1-Trimethylsilyl-1,2-nonadiene (8). To a solution of 1,2-nonadiene (40 mmol) in THF (30 mL) was added a 1.4 M hexane solution of n-BuLi (28.6 mL, 40 mmol) at -20 °C. After 0.5 h, chlorotrimethylsilane (40 mmol) was added at this temperature. The resulting mixture was stirred at -20 °C for 0.5 h and poured into sat. NaHCO₃. Extraction with hexane followed by separation by column chromatography on silica gel (hexane as eluant) gave the title allene (20.6 mmol, 51.5%). The ¹³C NMR spectrum agreed with that reported in the literature¹⁸: ¹H NMR (CDCl₃) δ 0.09 (9H, s, Me₃Si), 0.89 (3H, t, *J*=7.0 Hz, CH₃), 1.26 (8H, m, C₄H₈), 1.9—2.0 (2H, m, CH₂-C=), 4.74

(1H, dt, $J=6.8$ and 7.0 Hz, CH=), 4.87 (1H, dt, $J=3.5$ and 7.0 Hz, =CH-Si); ^{13}C NMR (CDCl_3) δ -0.88 (Me₃Si), 14.12, 22.73, 27.92, 28.96, 29.77, 31.82, 82.36, 83.44, 210.08 (=C=); IR (neat) 2957, 2927, 2856, 1938, 1466, 1379, 1248, 855, 841, 760, 699 cm^{-1} .

Transition Metal-Catalyzed Hydroalumination of 1,2-Nonadiene with LiAlH₄. To a clear filtered solution of LiAlH₄ in THF¹⁹ (2.5 mmol in 25 mL of THF) was added 1,2-nonadiene (10 mmol) followed by a solution of transition metal halides in THF (0.25 mmol) at 30 °C. The reaction mixture was stirred at 30 °C for 24 h or 30 °C for 1 h followed by reflux for 24 h, and was then quenched with D₂O to produce the deuterated species. The amount of recovered 1,2-nonadiene and products was determined by GLC analysis. Each product was collected from a gas chromatograph and submitted for mass spectral analysis.^{2j} The regioselectivity of reaction was monitored by ^{13}C NMR spectroscopy applied *inverse gated decoupling*⁵ for resulting deuterated products. This technique allows the quantitative evaluation of proton-decoupled ^{13}C NMR spectra. For example, this ^{13}C NMR measurement of deuterated 1-nonene (a mixture of **1** and **2**) obtained by Cp₂TiCl₂-catalyzed hydroalumination (Table 1. entry 1) showed that the signals of deuterated C₃-D and C₂-D carbons split into triplet ($J_{\text{C}_3\text{-D}}=19.1$ Hz and $J_{\text{C}_2\text{-D}}=23.1$ Hz) and shifted upper field ($\Delta\delta_{\text{C}_3}=0.39$ ppm and $\Delta\delta_{\text{C}_2}=0.34$ ppm by comparison with the isotopic C₃-H and C₂-H carbon signals of 1-nonene-*d*₀), respectively. Additionally, due to the $^{13}\text{C}_3\text{-C}_2\text{-D}$ and $^{13}\text{C}_2\text{-C}_3\text{-D}$ spin-spin coupling the broad triplet signals were observed by overlapping to C₃-H and C₂-H carbon signals ($^2J_{\text{C-D}}$ could not be determined with certainty). By determining the integration ratio of C₃-D signal to $^{13}\text{C}_3\text{-C}_2\text{-D}$ and C₃-H signals (56:44) and those of C₂-D to $^{13}\text{C}_2\text{-C}_3\text{-D}$ and C₂-H (34:66), relative ratio of **1** based on **1** and **2** was established to be 62 %, as tabulated in Table 1. The deuterated products were identified by spectral comparison with authentic non-deuterated samples obtained commercially. The following characteristic ^{13}C NMR data were observed ($\Delta\delta(\delta_{\text{C-H}} - \delta_{\text{C-D}})$ in ppm upper field from the corresponding isotopic C-H carbon signal).

1-Nonene-3-*d* (1): C₃-D (δ 33.67, t, $J_{\text{C-D}}=19.1$ Hz, $\Delta\delta(\delta_{\text{C-H}} - \delta_{\text{C-D}})=0.39$).

1-Nonene-2-*d* (2): C₂-D (δ 138.64, t, $J_{\text{C-D}}=23.1$ Hz, $\Delta\delta(\delta_{\text{C-H}} - \delta_{\text{C-D}})=0.34$).

(*E*)-2-Nonene-1-*d* (3): C₁-D (δ 17.64, t, $J_{\text{C-D}}=19.4$ Hz, $\Delta\delta(\delta_{\text{C-H}} - \delta_{\text{C-D}})=0.24$).

(*E*)-2-Nonene-2-*d* (4): C₂-D (δ 124.17, t, $J_{\text{C-D}}=22.7$ Hz, $\Delta\delta(\delta_{\text{C-H}} - \delta_{\text{C-D}})=0.29$).

(Z)-2-Nonene-1-d (5): C₁-D (δ 12.47, t, $J_{C-D}=19.1$ Hz, $\Delta\delta(\delta_{C-H} - \delta_{C-D})=0.15$).

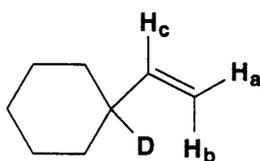
(Z)-2-Nonene-2-d (6): C₂-D (δ 123.24, t, $J_{C-D}=23.8$ Hz, $\Delta\delta(\delta_{C-H} - \delta_{C-D})=0.29$).

ZrCl₄-Catalyzed Hydroalumination of 1,2-Nonadiene with Li[AlH₃(C₅H₁₁)]. To a clear filtered solution of LiAlH₄ in THF (3.3 mmol in 25 mL of THF) was added 1-pentene (3.3 mmol) followed by a solution of ZrCl₄ in THF (0.25 mmol) at 30 °C. The reaction mixture was stirred at 30 °C for 24 h to prepare Li[AlH₃(C₅H₁₁)] (0.33 equiv, 3.3 mmol) where it was added 1,2-nonadiene (10 mmol). The mixture was stirred at 30 °C for 1 h and then refluxed for 24 h.

ZrCl₄-Catalyzed Hydroalumination of 1,2-Nonadiene with AlHCl₂. To a solution of anhydrous AlCl₃ (9 mmol) in THF (25mL) was added LiAlH₄ (3 mmol) at 0 °C. After 15 min, the resulting solution of AlHCl₂ (1.2 equiv, 12 mmol) was allowed to warm to 30 °C where it was successively added 1,2-nonadiene (10 mmol) and a THF solution of ZrCl₄ (0.25 mmol) and was then stirred for 24 h.

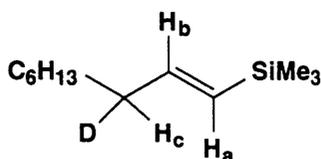
PhB(OH)₂-Catalyzed Hydroalumination of Allenes.³ To a solution of anhydrous AlCl₃ (1.5 mmol) in Et₂O (1 mL) was added LiAlH₄ (0.5 mmol) at 0 °C. After 15 min, PhB(OH)₂ (0.05 mmol) followed by an allene (1 mmol) was added at 0 °C. The resulting mixture was allowed to warm to room temperature where it was stirred for 4—24 h. The reaction was then quenched with D₂O or a saturated solution of NH₄Cl. Analysis of all products arising from the quenching of reactions was performed by the methods described above. The deuterated products were identified by spectral comparison with non-deuterated authentic samples obtained commercially. Authentic (*E*)-1-trimethylsilyl-1-nonene was prepared by the reduction of 1-trimethylsilyl-1,2-nonadiene (**8**) with DIBAH (5 equiv) in hexane at 60 °C for 15 h (73 % yield; vinylsilane/alkylsilane = 75:25).^{1a} The following characteristic ¹H NMR and/or ¹³C NMR data were observed ($\Delta\delta(\delta_{C-H} - \delta_{C-D})$ in ppm upper field from the corresponding isotopic C-H carbon signal).

1-Vinylcyclohexane-1-d (10):



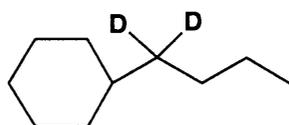
^1H NMR (CDCl_3) H_a (δ 4.92, 1H, dd, $J_{ab}=1.8$ and $J_{ac}=17.7$ Hz), H_b (δ 4.85, 1H, dd, $J_{ab}=1.8$ and $J_{bc}=10.7$ Hz), H_c (δ 5.75, 1H, dd, $J_{ac}=10.7$ and $J_{bc}=17.7$ Hz); ^{13}C NMR (CDCl_3) C-D (δ 41.19, t, $J_{\text{C-D}}=19.0$ Hz, $\Delta\delta(\delta_{\text{C-H}} - \delta_{\text{C-D}})=0.46$).

(E)-1-Trimethylsilyl-1-nonene-3-*d* (11):



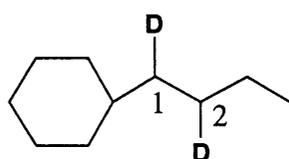
^1H NMR (CDCl_3) Me_3Si (δ 0.04, 9H), H_a (δ 5.62, 1H, dd, $J_{ab}=18.6$ and $J_{ac}=1.4$ Hz), H_b (δ 6.04, 1H, dd, $J_{ab}=18.6$ and $J_{bc}=6.2$ Hz), H_c (δ 2.0—2.2, 1H, m).

Butyl-1,1-*d*₂-cyclohexane (12):



^{13}C NMR (CDCl_3) C- D_2 (δ 36.60, quintet, $J_{\text{C-D}_2}=19.0$ Hz, $\Delta\delta(\delta_{\text{C-H}} - \delta_{\text{C-D}})=0.90$).

Butyl-1,2-*d*₂-cyclohexane (13):



^{13}C NMR (CDCl_3) $\text{C}_1\text{-D}$ (δ 36.91, t, $J_{\text{C-D}}=19.0$ Hz, $\Delta\delta(\delta_{\text{C-H}} - \delta_{\text{C-D}})=0.59$), $\text{C}_2\text{-D}$ (δ 28.85, t, $J_{\text{C-D}}=19.0$ Hz, $\Delta\delta(\delta_{\text{C-H}} - \delta_{\text{C-D}})=0.61$).

Et₃B-Catalyzed Hydroalumination of Allenes.³ To a vigorously stirred suspension of anhydrous AlCl_3 (2.4 mmol) in 1,2-dichloroethane (10 mL) was added a solution of DIBAH in hexane (1.2 mmol) at room temperature. After 30 min, a solution of Et_3B in hexane (0.05 mol) and

an allene (1 mmol) was successively added at 0 °C. The resulting mixture was allowed to warm to room temperature where it was stirred for 0.5 h. The reaction was then quenched with a saturated solution of NH₄Cl.

General Method for Reaction of Allylaluminum Compound 14 with Electrophiles. The hydroalumination product **14**, which was prepared *in situ* by PhB(OH)₂-catalyzed hydroalumination of 1,2-nonadiene (1 mmol) in Et₂O (1 mL) at room temperature for 4 h, was diluted with more Et₂O (5 mL) and cooled to -78 °C. To the resulting suspension was added an electrophile (carbonyl compounds or epoxides) (2 mmol) at -78 °C. The mixture was stirred for 0.5—1 h, poured into a saturated solution of NH₄Cl at 0 °C, and extracted with Et₂O. The combined extracts were dried, concentrated, and purified by column chromatography on silica gel (Et₂O/hexane as eluant) to give a mixture of isomeric alcohols as listed in Table 4. The isomeric ratio was determined by ¹H NMR analysis.

Homoallylic Alcohol 15: ¹H NMR (CDCl₃) δ 0.83 (3H, t, *J*=6.0 Hz, *erythro* and *threo* CH₃), 1.20 and 1.50 (10H, m, *erythro* and *threo* C₅H₁₀), 1.99 (1H, d, *J*=4.8 Hz, *erythro* or *threo* OH), 2.15 (1H, d, *J*=2.3 Hz, *erythro* or *threo* OH), 2.27 (1H, m, *erythro* or *threo* CH), 2.3—2.5 (1H, m, *erythro* or *threo* CH), 4.37 (1H, dd, *J*=2.3 and 8.0 Hz, *erythro* or *threo* CH-O), 4.59 (1H, dd, *J*=4.8 and 5.8 Hz, *erythro* or *threo* CH-O), 4.98 and 5.17 (1H, dd, *J*=2.0 and 17.0 Hz, *erythro* and *threo* =CH₂), 5.04 and 5.23 (1H, dd, *J*=2.0 and 10.4 Hz, *erythro* and *threo* =CH₂), 5.48 and 5.64 (1H, ddd, *J*=9.1, 10.4, and 17.0 Hz, *erythro* and *threo* CH=), 7.2—7.3 and 7.30 (5H, m, *erythro* and *threo* C₆H₅). Found: C, 82.69 H, 10.52%. Calcd for C₁₆H₂₄O: C, 82.70; H, 10.41%. The *erythro*/*threo* ratio of **15** is 3:2 or 2:3.

Homoallylic Alcohol 18: ¹H NMR (CDCl₃) δ 0.8—0.9 (3H, m, *erythro* and *threo* CH₃), 1.2—1.5 (10H, m, *erythro* and *threo* C₅H₁₀), 1.87 and 1.95 (1H, broad, *erythro* or *threo* OH), 2.1—2.2 (1H, m, *erythro* or *threo* CH), 2.2—2.4 (1H, m, *erythro* or *threo* CH), 3.92 (1H, dd, *J*=2.4 and 6.4 Hz, *erythro* or *threo* CH-O), 4.05 (1H, dd, *J*=7.0 and 7.2 Hz, *erythro* or *threo* CH-O), 5.12 and 5.15 (1H, dd, *J*=2.3 and 16.2 Hz, *erythro* and *threo* =CH₂), 5.16 and 5.21 (1H, dd, *J*=2.3 and 10.4 Hz, *erythro* and *threo* =CH₂), 5.5—5.8 (1H, m, *erythro* and *threo* CH=), 6.18 (1H, dd, *J*=7.2 and 16.0 Hz, *erythro* or *threo* Ph-C=CH), 6.20 (1H, dd, *J*=6.4 and 16.0 Hz, *erythro* or *threo* Ph-C=CH),

6.57 (1H, d, $J=16.0$, *erythro* or *threo* Ph-CH=), 6.58 (1H, d, $J=16.0$ Hz, *erythro* or *threo* Ph-CH=), 7.2—7.4 (5H, m, *erythro* and *threo* Ph). Found: C, 83.48; H, 10.42%. Calcd for $C_{18}H_{26}O$: C, 83.66; H, 10.14%. The *erythro*/*threo* ratio of **18** is 7:2 or 2:7.

Primary δ,ϵ -unsaturated alcohol 19: 1H NMR ($CDCl_3$) δ 0.8—1.0 (6H, m, CH_3), 1.2—1.5 (14H, m, CH, CH_2 , OH and C_5H_{10}), 2.0—2.2 (1H, m, CH-C=), 3.5—3.6 (2H, m, CH_2 -O), 4.9—5.1 (2H, m, = CH_2), 5.5—5.7 (1H, m, CH=). Found: C, 78.86; H, 13.16%. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21%.

Secondary δ,ϵ -unsaturated alcohol 20: 1H NMR ($CDCl_3$) δ 0.8—0.9 (6H, m, CH_3), 1.2—1.6 (15H, m, CH_2 , OH and C_5H_{10}), 1.9—2.0 (1H, m, CH-C=), 3.44 (1H, m, CH-O), 5.0—5.2 (2H, m, = CH_2), 5.5—5.7 (1H, m, CH=). Found: C, 78.71; H, 13.20%. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21%.

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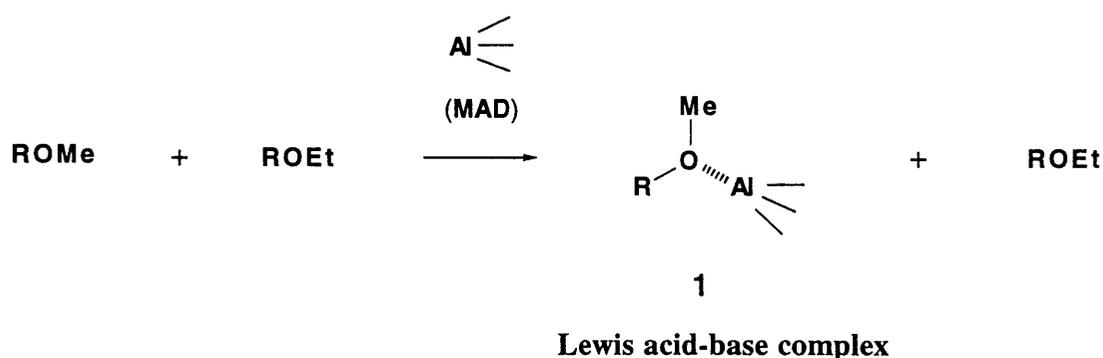
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Chapter 4

Molecular Recognition of Oxygen-Containing Substrates with Modified Organoaluminum Reagents

Abstract: The exceptionally bulky, oxygenophilic methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) can be successfully utilized for recognition of structurally or electronically similar ether substrates by the selective Lewis acid-base complex formation as ascertained by low-temperature ^{13}C NMR spectroscopy. The exceedingly high recognition ability of MAD is described in comparison with other Lewis acids such as *i*- Bu_3Al , SnCl_4 , and $\text{BF}_3\cdot\text{OEt}_2$. Furthermore, selective separation of the less hindered or electronically more labile of two different ethers has been accomplished with MAD by yielding precipitates as selective Lewis acid-base complexes. The binding behaviors of Lewis acidic MAD for various oxygen-containing substrates have been studied by low-temperature ^{13}C NMR analysis. Amides were found to more strongly coordinate to MAD than aldehydes, esters, or ketones, while coordination of ethereal oxygens was rather weak. This chemistry has been applied to a new type of complexation chromatography by using polymeric organoaluminum reagent **7** as a stationary phase which is readily obtainable from sterically hindered triphenol **6** and Me_3Al . This technique allows the surprisingly clean separation of structurally or electronically similar organic substrates such as ethers.

The chemistry of molecular recognition is a subject of current interest,¹ and a number of recognition systems capable of reversible binding interactions have been developed for this purpose.²⁻⁵ Most of these artificial enzymes utilize effective hydrogen-bonding interactions between substrate and receptor as also seen in natural enzymes. With organic substrates of weak hydrogen-bonding capability such as ethers, however, such tight binding behavior cannot be expected. Here we introduce exceptionally bulky, oxygenophilic methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)⁶ (hereafter, abbreviated to MAD) featuring a Lewis acidic molecular cleft for recognition of structurally or electronically similar ether substrates based on selective Lewis acid-base complex formation.⁷



We have examined the recognition ability of MAD with two different ether substrates by low-temperature ¹³C NMR spectroscopy. For example, the 125 MHz ¹³C NMR measurement of a mixture of 1 equiv each of MAD, methyl 3-phenylpropyl ether, and ethyl 3-phenylpropyl ether in CDCl₃ (0.4 M solution) at -50 °C showed that the original signal of methyl ether at δ 58.66 shifted downfield to δ 60.09, whereas the signal of the α-methylene carbon of ethyl ether remained unchanged. This result showed the virtually complete recognition between methyl and ethyl ethers with MAD giving Lewis acid-base complex **1** (R = (CH₂)₃Ph) exclusively. It should be noted that this remarkable selectivity can only be achieved with exceptionally bulky organoaluminum reagents as ascertained by comparison with other Lewis acids (Table 1). The use of two exceptionally bulky

Table 1. Recognition Ability of Various Lewis Acids with Two Different Ethers^a

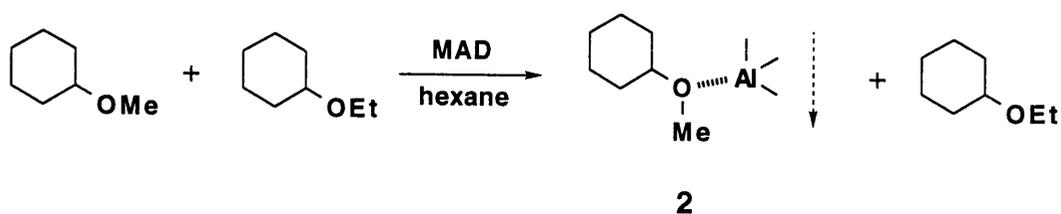
Lewis acid	complexation ratio: ^b Ph(CH₂)₃OMe + Ph(CH₂)₃OEt
MAD	100 : 0
methylaluminum bis(2,6-diisopropylphenoxide)	<i>c</i>
<i>i</i> -Bu ₃ Al	4 : 1
SnCl ₄	<i>d</i>
BEt ₃	<i>c</i>
BF ₃ ·OEt ₂	5 : 3

Lewis acid	complexation ratio: ^b CH₃CH₂CH₂OMe + EtOEt
MAD	96 : 4
BF ₃ ·OEt ₂	3 : 2

^a Two different ethers (1 mmol each) were mixed with 1 equiv of Lewis acid in CDCl₃ or CD₂Cl₂ (2 M solution) in a 5-mm NMR tube at 20–25 °C, and the 125 MHz ¹³C NMR spectra were taken at -50 to -100 °C. ^b The complexation ratio was determined by low-temperature ¹³C NMR analysis of ethereal α-carbons. ^c No complexation was observed. See also text. ^d Two equivalents of ethers coordinated to SnCl₄ to give a 2:1 complex.

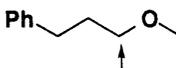
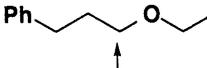
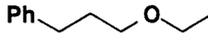
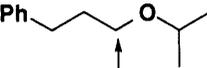
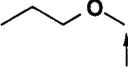
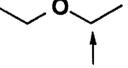
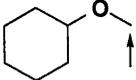
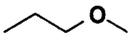
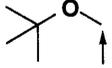
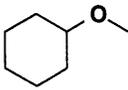
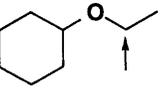
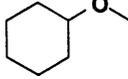
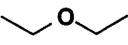
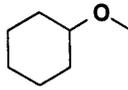
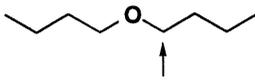
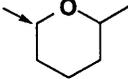
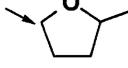
2,6-di-*tert*-butyl-4-methylphenoxy ligands in MAD is essential for providing one recognition site with the complementary size, shape, and coordination capacity. Furthermore, MAD exists as a monomeric species in solution,⁶ thereby exhibiting a high oxygenophilic character even with weak Lewis bases. In contrast, less bulky methylaluminum bis(2,6-diisopropylphenoxide) and methylaluminum bis(2,4,6-trimethylphenoxide) were found not to form any coordination complexes with ethers at low temperature, probably due to their strong self-association through electron deficient bonds. Other examples of selective complexation of two different ethers with MAD are listed in Table 2. Ethers possessing sterically less hindered alkyl substituents form coordination complexes more easily than their bulky counterparts (entries 1—11). The more basic ethereal oxygens coordinate more strongly to MAD than the less basic oxygens (entries 12—17).

Since the separation of structurally or electronically very similar ethers cannot be easily accomplished by ordinary separation technique such as distillation, recrystallization, and silica gel chromatography,⁸ we are interested in the possibility of effecting the purification of such ether substrates by applying our recognition chemistry. The ¹³C NMR measurement of a mixture of 1 equiv each of MAD, cyclohexyl methyl ether and cyclohexyl ethyl ether in CD₂Cl₂ (0.4 M solution) at -90 °C showed the virtually complete recognition between the methyl and ethyl ethers with MAD giving Lewis acid-base complex **2** exclusively. At higher temperature, however, facile decomplexation of **2** by ligand exchange with the ethyl ether was observed by ¹³C NMR spectroscopy. In contrast, when an equimolar mixture of cyclohexyl methyl ether and cyclohexyl ethyl ether was treated with MAD (1 equiv) in hexane at room temperature for 1 h, a white



**MAD-ether complex
as a white precipitate**

Table 2. Selective Complexation of Two Different Ethers with MAD

entry	ethers		complexation ratio ^a
1			100 : 0
2			100 : 0
3			96 : 4
4			92 : 8 ^b
5			100 : 0 ^c
6			100 : 0 ^c
7			47 : 53 ^b
8			68 : 32 ^b
9			100 : 0
10			81 : 19 ^b
11			100 : 0

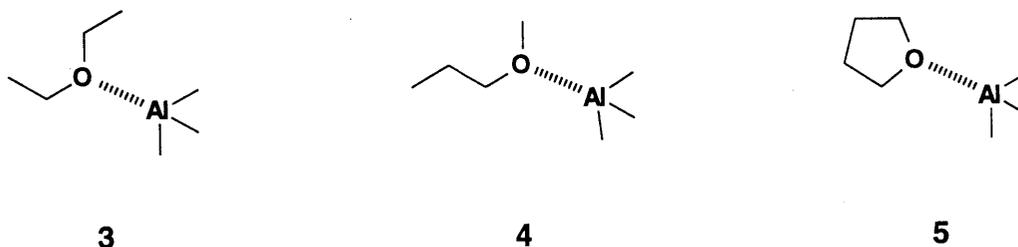
entry	ethers		complexation ratio ^a
12			100 : 0 ^c
13			100 : 0 ^c
14			56 : 44 ^b
15			90 : 10
16			100 : 0
17			100 : 0

^a The ratio of two MAD-ether complexes was determined in CDCl₃ at -50 °C by ¹³C NMR analysis of ethereal α -carbons at the indicated arrows. ^b Determined on the basis of the phenoxy carbons as well as ethereal α -carbons. ^c At -90 °C in CD₂Cl₂.

precipitate gradually formed.⁹ This precipitate was dissolved by addition of more hexane and recrystallized at room temperature for 5 h to furnish MAD-methyl ether complex **2** (68% yield) exclusively, which has been characterized by elemental analysis, ¹H and ¹³C NMR spectroscopy. This complex **2** shows downfield shifts in the ¹H NMR spectrum for the ethereal α -methyl and α -methine protons, when compared to the “free” ether, consistent with coordination of the ether to aluminum. The pure cyclohexyl methyl ether can be generated upon acid hydrolysis of **2**. Under

similar conditions, MAD-diethyl ether, MAD-methyl propyl ether, and MAD-THF complexes, **3**—**5**, can be selectively generated as white crystals from the combination of two different ethereal substitutes: diethyl ether and ethyl vinyl ether, methyl propyl ether and *tert*-butyl methyl ether, tetrahydrofuran and 2-methyltetrahydrofuran, or tetrahydrofuran and tetrahydropyran.

The present method demonstrates an effective way to purify not only these simple ethers but also a variety of structurally or electronically very similar ether substrates in the segment synthesis of polyether natural products.¹⁰



Organoaluminum compounds have a great tendency with various heteroatoms in organic molecules, particularly oxygen, to generate 1:1 coordination complexes.¹¹ Therefore, we are interested in the binding behavior of MAD for various oxygen-containing substrates. As oxygen-containing substrates, we utilized both aliphatic and aromatic aldehydes, amides, esters, ethers, and ketones with similar structural substituents. First, we took the low-temperature ¹³C NMR spectra of these substrates and their coordination complexes with MAD in CDCl₃. For carbonyl and ethereal substrates, characteristic signals of carbonyl carbons and ethereal α -carbons can be measured, respectively. These data are listed in Table 3.¹² The differences in the downfield shifts of carbonyl carbons of amides and esters by coordination to MAD were much smaller than those of aldehydes and ketones. This may be attributed to an electron releasing effect of the additional heteroatom (N, O) attached to the carbonyl groups which, in part, compensates for electron withdrawal of the complexed carbonyl oxygen. We then examined the binding behavior of MAD for combinations of other two different substrates by low-temperature ¹³C NMR spectroscopy, and these results are summarized in Scheme I. For example, the 125 MHz ¹³C NMR measurement of a mixture of 1 equiv each of MAD, *N,N*-dimethylpropionamide, and *N,N*-dimethylbenzamide in

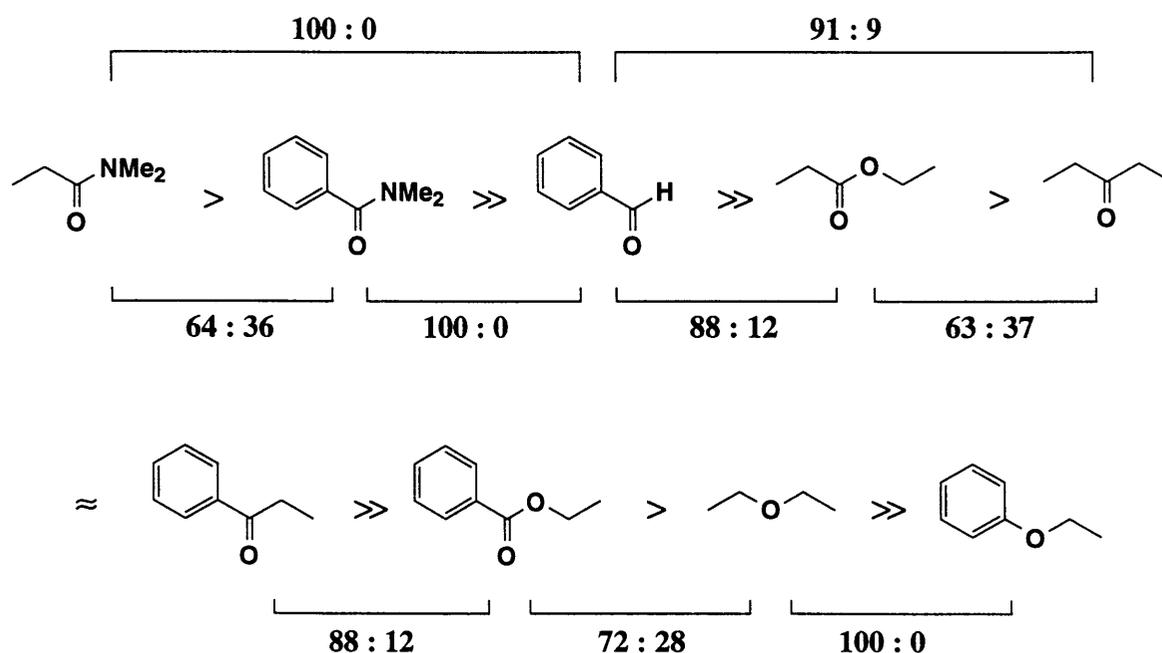
Table 3. Characteristic ^{13}C NMR Data for Free Substrates and Their Complexes with MAD^a

substrate	δ (free) / ppm ^b	δ (complex) / ppm	$\Delta\delta$ / ppm ^{c,d}	$\Delta\delta_{\text{Al-Me}}$ / ppm ^{c,e}
	carbonyl carbon			
PhCHO	192.97	201.68	8.71	2.60
CH ₃ CH ₂ COCH ₂ CH ₃	213.10	236.04	22.94	4.60
PhCOCH ₂ CH ₃	201.06	216.99	15.93	5.33
CH ₃ CH ₂ CONMe ₂	173.70	176.39	2.69	5.18
PhCONMe ₂	171.46	172.18	0.72	3.94
CH ₃ CH ₂ COOCH ₂ CH ₃	174.86	184.53	9.67	4.36
CH ₃ CH ₂ COOPh	173.44	184.83	11.39	4.07
PhCOOCH ₂ CH ₃	166.67	171.69	5.02	5.40
	α -methylene carbon			
CH ₃ CH ₂ OCH ₂ CH ₃	66.19	64.67	-1.52	5.62
PhOCH ₂ CH ₃	62.88	64.27	1.39	0.82

^a Unless otherwise noted, oxygen-containing substrate (0.5 mmol) was mixed with 1 equiv of MAD in CDCl₃ (0.5 M solution) in a 5-mm NMR tube at 20–25 °C and the 125 MHz ^{13}C NMR spectrum was taken at -50 °C. ^b The term " δ (free)" refers to the chemical shift for free carbonyl carbons or free ethereal α -carbons. ^c In ppm downfield from free substrates. ^d $\Delta\delta = \delta(\text{complex}) - \delta(\text{free})$. ^e $\Delta\delta_{\text{Al-Me}} = \delta_{\text{Al-Me}}(\text{complex}) - \delta_{\text{Al-Me}}(\text{free MAD})$. $\delta_{\text{Al-Me}}(\text{free MAD}) = -9.09$ ppm. In every cases, the downfield shifts were observed.

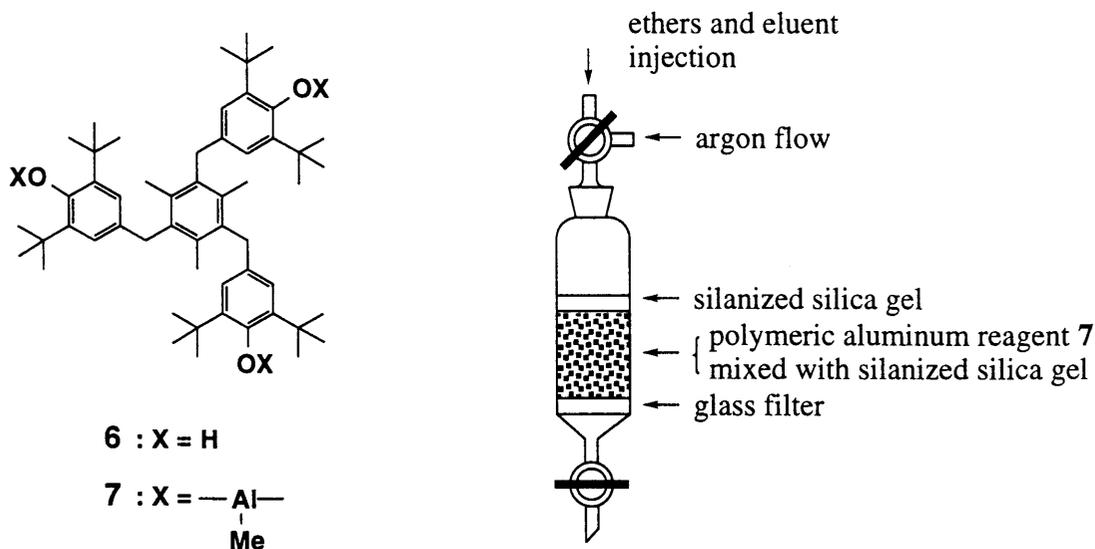
CDCl₃ (0.5 M solution) at -50 °C showed that the original signals of propionamide and benzamide at δ 173.70 and δ 171.46 shifted downfield to δ 176.39 and δ 172.18, respectively, in a ratio of 64:36. This ratio was also calculated based on the phenoxy carbons of free MAD and its complexes with amides.¹³ The other complexation ratios for two different substrates were determined in a similar manner. As revealed in Scheme I, amides more strongly coordinate to Lewis acidic MAD than aldehydes, esters, and ketones, while coordination of ethereal oxygens is rather weak.¹⁴ The order in Scheme I implies that even the same functional groups showed different binding behaviors to Lewis acidic MAD depending on the types of substituents (aliphatic or aromatic) and their steric requirements.

Scheme I



The ready availability of various types of hindered polyphenols enables the molecular designing of various polymeric organoaluminum reagents, implying the widespread potential of this molecular recognition chemistry. For example, this chemistry allows the realization of complexation chromatography, i.e., separation of heteroatom-containing solutes by complexation

with stationary, insolubilized organoaluminum reagents.¹⁵ Accordingly, treatment of sterically hindered triphenol **6**¹⁶ (2 mmol) in CH₂Cl₂ with Me₃Al (3 mmol) at room temperature for 1 h gave



polymeric aluminum reagent

polymeric organoaluminum column

rise to the polymeric monomethylaluminum reagent **7**. After evaporation of solvent, the residual solid was ground to a powder and mixed with silanized silica gel (1.7 g) in an argon box.¹⁷ This was packed in a short-path glass column (10 mm i.d. \times 150 mm) as a stationary phase and washed once with dry, degassed hexane to remove unreacted free triphenol **6**. Then a solution of methyl 3-phenylpropyl ether and ethyl 3-phenylpropyl ether (0.5 mmol each) in degassed hexane was charged on this short-path column. As shown in Figure 1, this technique allows the surprisingly clean separation of structurally similar ether substrates.¹⁸ Ethyl 3-phenylpropyl ether and isopropyl 3-phenylpropyl ether or the THF and THP ethers of 4-(*tert*-butyldiphenylsiloxy)-1-butanol can be separated equally well with this short-path column chromatography (Figures 2 and 3). The latter case would demonstrate an effective way to purify structurally or electronically similar ethers in the segment synthesis of polyether antibiotics. With these examples at hand, it appears feasible to separate the wide range of ethers listed in Table 2 by complexation chromatography. Although a variety of complexation chromatographies have been advanced,¹⁹ the use, as a stationary phase, of

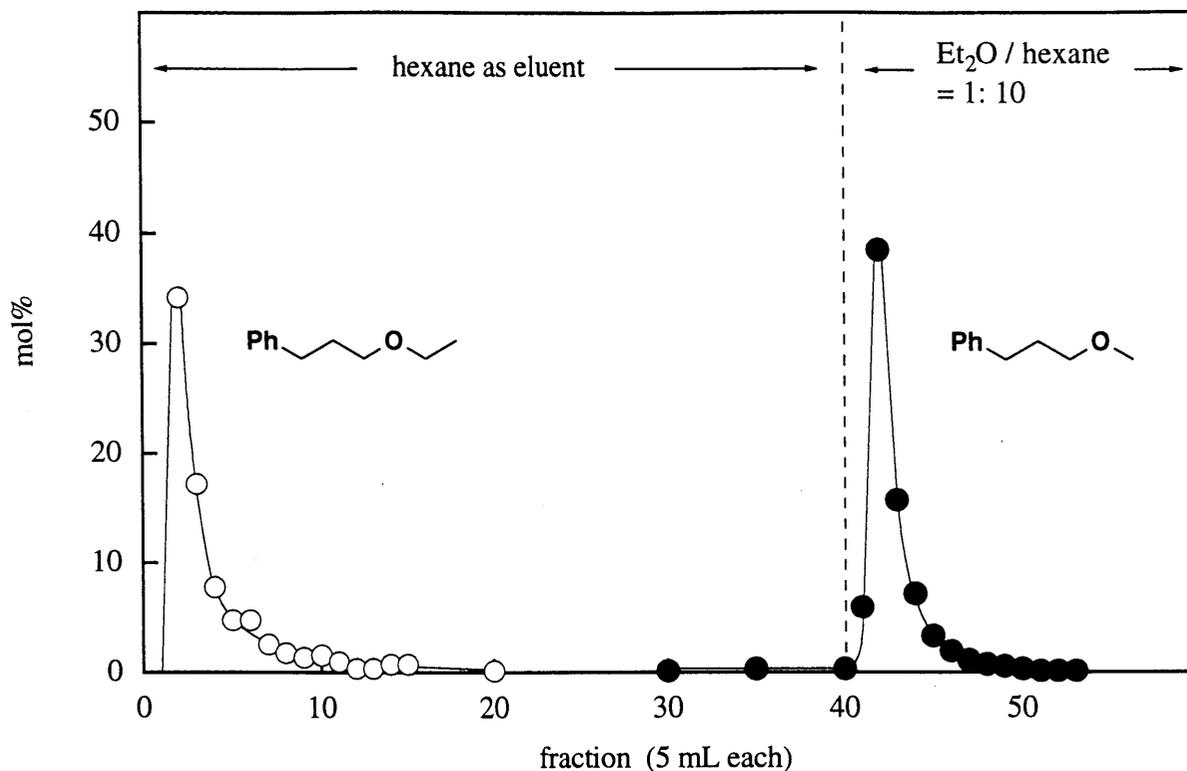


Figure 1. Separation of Methyl 3-Phenylpropyl Ether (●) and Ethyl 3-Phenylpropyl Ether (○) by Complexation Chromatography.

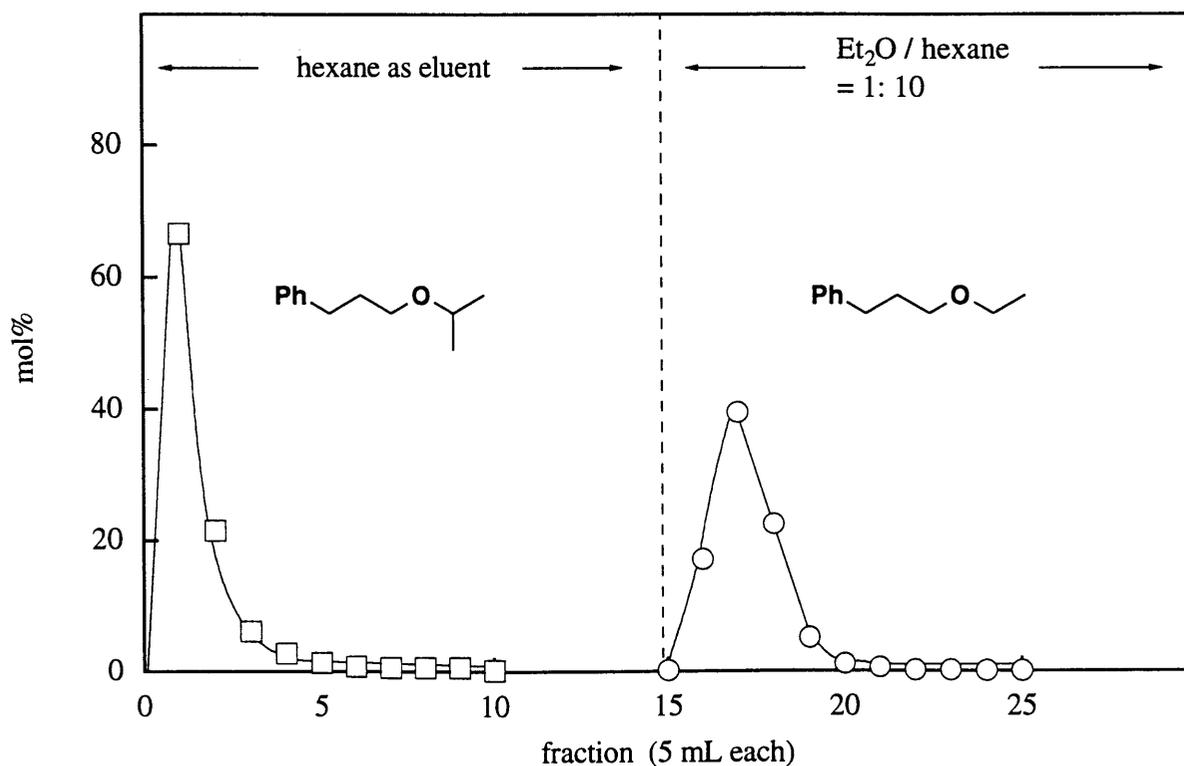


Figure 2. Separation of Ethyl 3-Phenylpropyl Ether (○) and Isopropyl 3-Phenylpropyl Ether (□) by Complexation Chromatography.

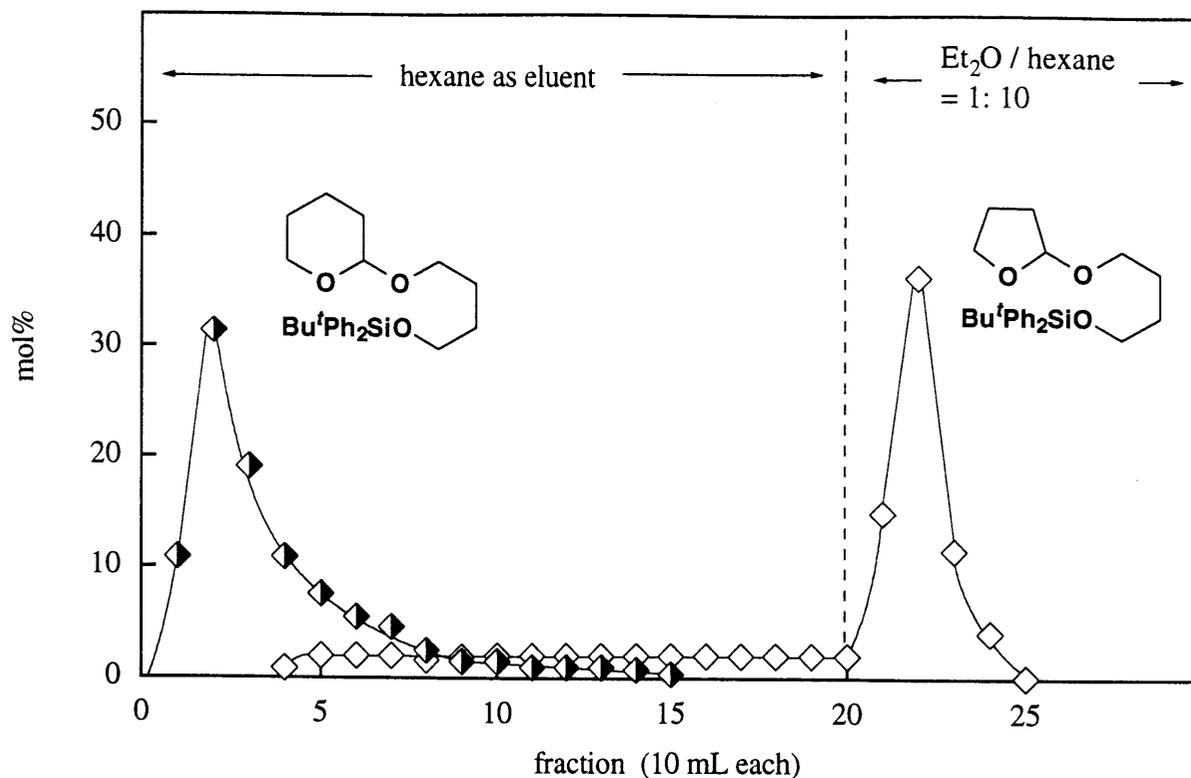


Figure 3. Separation of THF Ether of 4-(*tert*-Butyldiphenylsilyloxy)-1-butanol (◇) and THP Ether of 4-(*tert*-Butyldiphenylsilyloxy)-1-butanol (◆) by Complexation Chromatography.

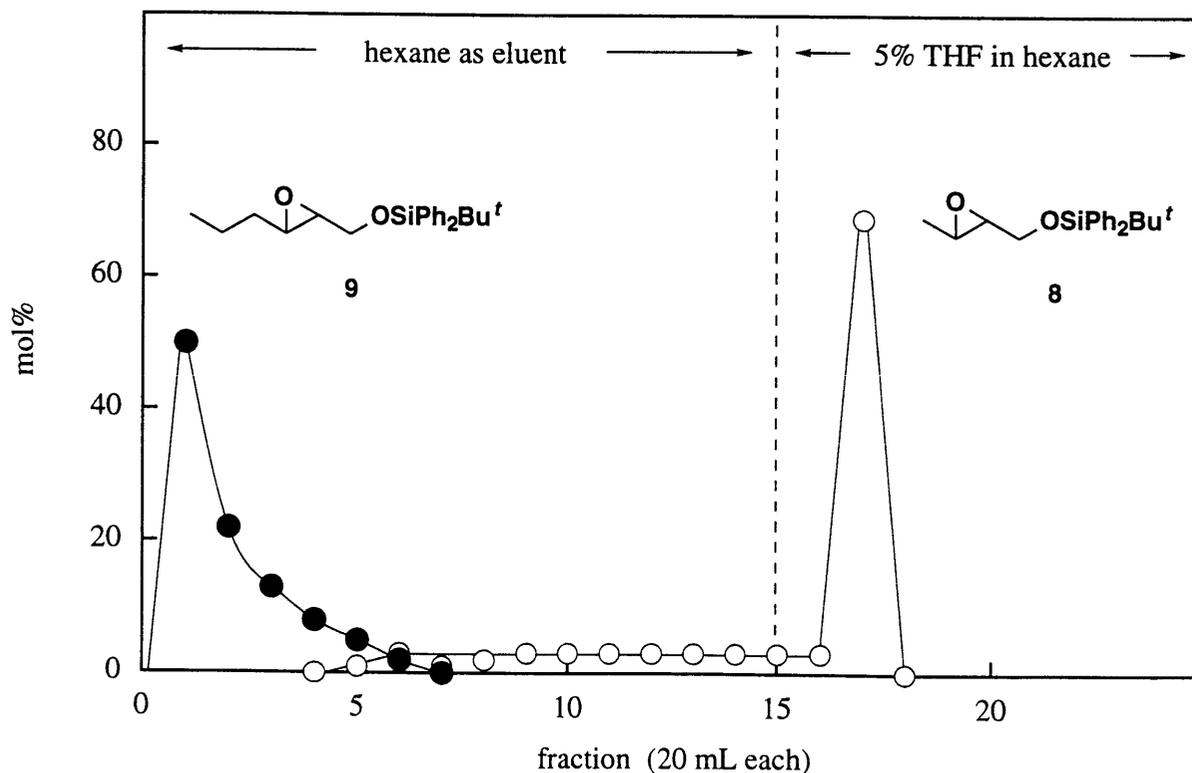
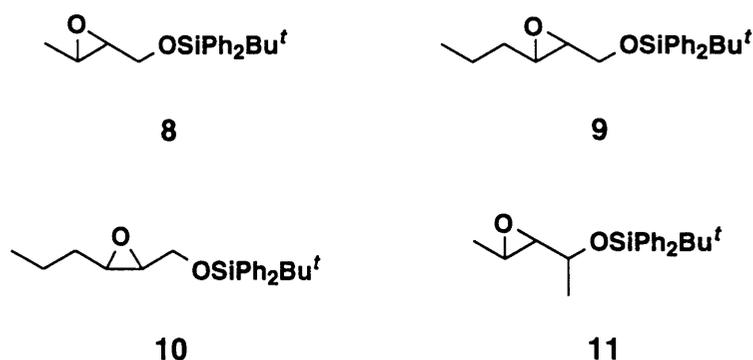


Figure 4. Separation of *trans*-3-Methyloxiranemethanol *tert*-Butyldiphenylsilyl Ether (○) and *trans*-3-Propyloxiranemethanol *tert*-Butyldiphenylsilyl Ether (●) by Complexation Chromatography at -15 °C

exceptionally bulky aluminum reagents, which possess exceedingly high recognition ability, is crucial in effecting the clean separation of structurally and/or electronically similar organic substrates.

This present complexation chromatography also allowed the effective separation of various structurally similar α,β -disubstituted epoxy silyl ethers. The polymeric organoaluminum column for complexation chromatography of epoxy silyl ethers was prepared as described previously with slight modification. Treatment of sterically hindered triphenol **6** (1 mmol) in CH_2Cl_2 (10 mL) with Me_3Al (1.5 mmol) at room temperature for 1 h gave rise to the polymeric organoaluminum reagent **7**. After evaporation of solvent, the residual solid was ground to a powder and mixed with silanized silica gel (10 g) in an argon box. This was packed in a short-path glass column (15 mm i.d. \times 250 mm) as a stationary phase and washed once with dry, degassed hexane (50 mL) to remove unreacted free triphenol **6**. Then, a solution of *trans*-3-methyloxiranemethanol *tert*-butyldiphenylsilyl ether (**8**) and *trans*-3-propyloxiranemethanol *tert*-butyldiphenylsilyl ether (**9**) (1 mmol each) in degassed hexane (2 mL) was charged on this short-path column at about $-15\text{ }^\circ\text{C}$. Degassed hexane was continuously passed through under the pressure of argon (0.3—0.4 kg/cm²). Each fraction (20 mL) was concentrated and analyzed by ¹H NMR. The more hindered *trans*-3-propyloxiranemethanol *tert*-butyldiphenylsilyl ether (**9**) was found to elute first. After collection of 15 fractions (i.e., 15 \times 20 mL), eluent was changed to 5% THF in hexane to elute the remaining *trans*-3-methyloxiranemethanol *tert*-butyldiphenylsilyl ether (**8**) as shown in Figure 4, which indicates the clean separation of structurally similar epoxy substrates.



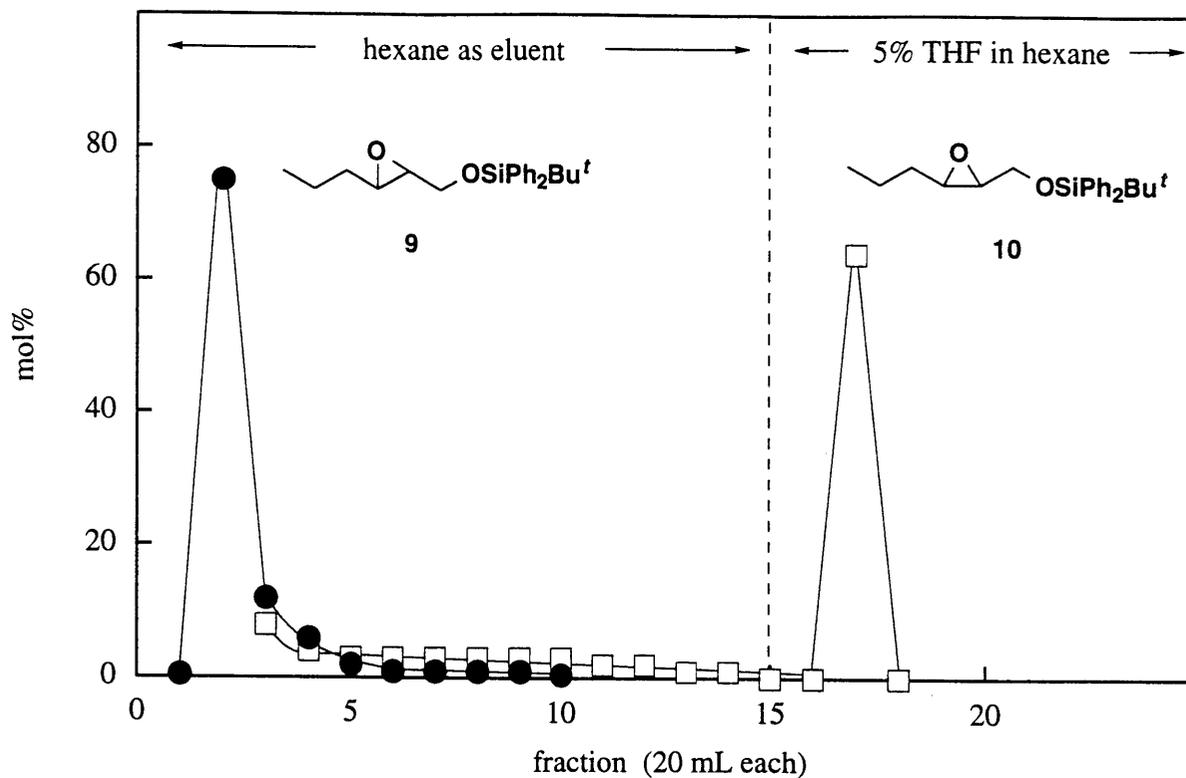


Figure 5. Separation of *cis*-3-Propyloxiranemethanol *tert*-Butyldiphenylsilyl Ether (□) and *trans*-3-Propyloxiranemethanol *tert*-Butyldiphenylsilyl Ether (●) by Complexation Chromatography at $-15\text{ }^{\circ}\text{C}$

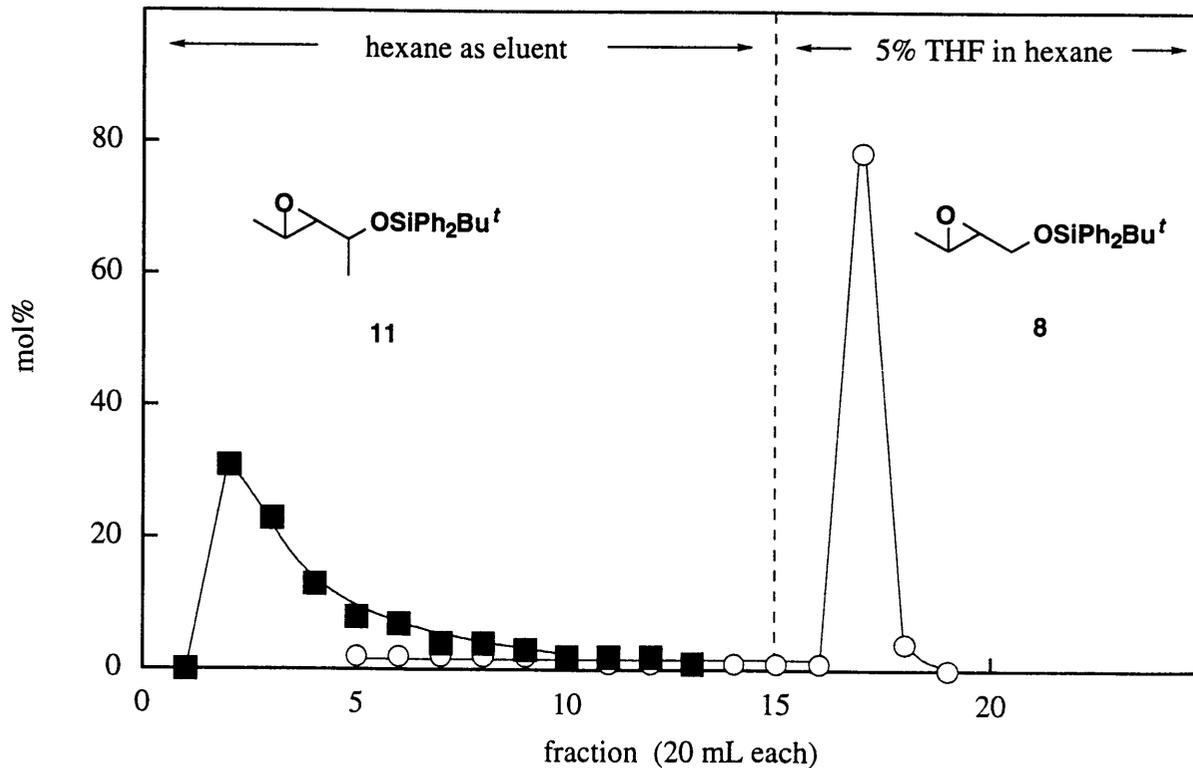


Figure 6. Separation of *trans*-3-Methyloxiranemethanol *tert*-Butyldiphenylsilyl Ether (○) and α -Methyl-(*trans*-3-Methyloxirane)methanol *tert*-Butyldiphenylsilyl Ether (■) by Complexation Chromatography at $-15\text{ }^{\circ}\text{C}$

In a similar manner, the chromatographic separation of geometrical isomers of epoxy silyl ethers such as *cis*- and *trans*-3-propyloxiranemethanol *tert*-butyldiphenylsilyl ethers, (**10**) and (**9**) (*cis/trans* ratio = 1:1) can be accomplished equally well by the present complexation chromatography (Figure 5). An additional example is illustrated in Figure 6. It should be noted that attempted separation of *erythro* and *threo* isomers of epoxy silyl ether **11** (*erythro/threo* ratio = 61:39) gave unsatisfactory results. Furthermore, cyclic epoxide, 2,3-epoxy cyclohexanol *tert*-butyldiphenylsilyl ether, which possesses the more basic, yet reactive epoxy oxygen, is susceptible to gradual decomposition at -15 °C on the polymeric organoaluminum reagent **7** as a stationary phase.

Although *gem*-disubstituted and trisubstituted epoxy silyl ethers are prone to be partially susceptible to the rearrangement on polymeric organoaluminum reagent **7**, the present technique allows the effective separation of various structurally similar α,β -disubstituted epoxy silyl ethers by discrimination of their structural environment such as the configuration of epoxides and the size of epoxide substituents.

Experimental Section

General. The IR spectra were measured on a Hitachi 260-10 spectrometer. The ¹H and ¹³C NMR spectra were recorded on Varian Gemini-200 and VXR 500 spectrometers, using tetramethylsilane (Me₄Si) as an internal standard. Splitting patterns are indicated as s, singlet; t, triplet; q, quartet; m, multiplet. Melting points are not corrected. The microanalysis was performed at the Elemental Analyses Center of Kyoto University and the Faculty of Agriculture, Nagoya University. All experiments were carried out under an atmosphere of dry argon.

In experiments requiring dry solvents, dichloromethane, hexane, and toluene were freshly distilled before use. Diethyl ether (Et₂O), tetrahydrofuran (THF), and tetrahydropyran (THP) were freshly distilled from sodium metal using diphenylketyl as indicator. Trimethylaluminum (Me₃Al) was obtained from Toso-Akzo Chemical Co., Ltd., Japan. Other simple, inorganic and organic chemicals were purchased and used as such.

Preparation and Purification of Methylaluminum Bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD).⁶ To a solution of 2,6-di-*tert*-butyl-4-methylphenol (13.22 g, 60 mmol) in degassed hexane (40 mL) was added a 2 M hexane solution of Me₃Al (15 mL, 30 mmol) at room temperature. The white precipitate appeared immediately. After 1 h, this mixture was heated until the precipitate redissolved in hexane. The resulting solution was stood for 3 h, yielding colorless crystal which was filtered in an argon box. Since the crystal includes some impurities such as 2,6-di-*tert*-butyl-4-methylphenol and inorganic aluminum salts, this was further recrystallized from hexane (45 mL) at -20 °C to give essentially pure MAD (7.83 g, 54% yield): ¹H NMR (CDCl₃) δ 7.04 (4H, s, C₆H₂), 2.28 (6H, s, CH₃), 1.53 (36H, s, C(CH₃)₃), -0.35 (3H, s, Al-CH₃); ¹³C NMR (CDCl₃) δ 152.02, 138.19, 127.71, 125.94, 34.94, 31.56, 21.40, -9.09 (Al-CH₃).

Preparation of Ethers. Methyl 3-phenylpropyl ether, ethyl 3-phenylpropyl ether, methyl cyclohexyl ether, and ethyl cyclohexyl ether were prepared by treatment of 3-phenylpropanol or cyclohexanol with methyl or ethyl iodide, sodium hydride, and HMPA in THF at room temperature for several hours. Isopropyl 3-phenylpropyl ether was prepared by treatment of isopropyl alcohol with 3-phenylpropyl bromide, sodium hydride, and HMPA in THF at room temperature for overnight. Other ethers were purchased and used as such.

Methyl 3-Phenylpropyl Ether: ¹H NMR (CDCl₃) δ 7.16—7.31 (5H, m, C₆H₅), 3.37 (2H, t, *J* = 6.4 Hz, CH₂-O), 3.33 (3H, s, O-CH₃), 2.67 (2H, t, *J* = 7.7 Hz, Ph-CH₂), 1.87 (2H, tt, *J* = 6.4, 7.7 Hz, CH₂); ¹³C NMR (CDCl₃) δ 142.10, 128.58, 128.43, 125.89, 72.05, 58.66, 32.44, 31.38.

Ethyl 3-Phenylpropyl Ether: ¹H NMR (CDCl₃) δ 7.16—7.31 (5H, m, C₆H₅), 3.46 (2H, q, *J* = 7.0 Hz, O-CH₂), 3.41 (2H, t, *J* = 6.5 Hz, CH₂-O), 2.68 (2H, t, *J* = 7.7 Hz, Ph-CH₂), 1.88 (2H, tt, *J* = 6.5, 7.7 Hz, CH₂), 1.20 (3H, t, *J* = 7.0 Hz, CH₃); ¹³C NMR (CDCl₃) δ 142.16, 128.57, 128.39, 125.83, 69.84, 66.20, 32.50, 31.45, 15.34.

Isopropyl 3-Phenylpropyl Ether: ¹H NMR (CDCl₃) δ 7.15—7.30 (5H, m, C₆H₅), 3.54 (1H, q, *J* = 6.0 Hz, O-CH), 3.39 (2H, t, *J* = 6.4 Hz, CH₂-O), 2.67 (2H, t, *J* = 7.2 Hz, Ph-CH₂), 1.86 (2H, tt, *J* = 6.4, 7.2 Hz, CH₂), 1.14 (6H, d, *J* = 6.0 Hz, CH₃); ¹³C NMR (CDCl₃) δ 142.26, 128.61, 128.38, 125.80, 71.48, 67.33, 32.54, 31.79, 22.30.

Cyclohexyl Methyl Ether: ¹H NMR (CDCl₃) δ 3.31 (3H, s, O-CH₃), 3.11 (1H, m, CH-O),

1.89 (2H, m, CH₂), 1.70 (2H, m, CH₂), 1.52 (1H, m, CH₂), 1.22 (5H, m, CH₂); ¹³C NMR (CDCl₃) δ 79.13, 55.70, 31.95, 25.99, 24.18.

Cyclohexyl Ethyl Ether: ¹H NMR (CDCl₃) δ 3.47 (2H, q, *J* = 7.2 Hz, O-CH₂), 3.18 (1H, m, CH-O), 1.89 (2H, m, CH₂), 1.69 (2H, m, CH₂), 1.53 (1H, m, CH₂), 1.22 (5H, m, CH₂), 1.16 (3H, t, *J* = 7.2 Hz, CH₃); ¹³C NMR (CDCl₃) δ 77.60, 62.57, 32.60, 26.05, 24.53, 15.91.

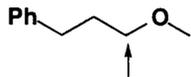
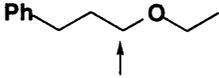
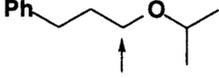
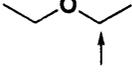
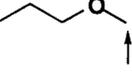
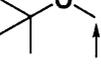
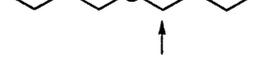
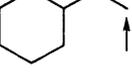
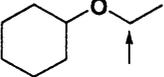
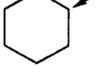
Determination of Recognition Ability of MAD with Two Different Ethers by Low-Temperature ¹³C NMR Analysis. Two different ethers (0.4 mmol each) were mixed with 1 equiv of MAD in CDCl₃ or CD₂Cl₂ (1 mL) in a 5-mm NMR tube at 20–25 °C, and the 125 MHz ¹³C NMR spectra were taken at -50 to -90 °C. The complexation ratio was determined by ¹³C NMR analysis of ethereal α-carbons of free ethers and their MAD complexes. This ratio was also calculated based on the phenoxy carbons of free MAD and its complexes with ethers. The characteristic ¹³C NMR data for free ethers and their complexes with MAD are summarized in Table 4.

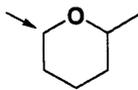
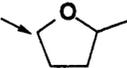
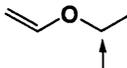
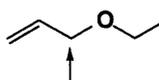
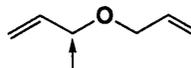
Determination of Recognition Ability of Various Lewis Acids with Two Different Ethers by Low-Temperature ¹³C NMR Analysis. Two different ethers (1 mmol each) were mixed with 1 equiv of Lewis acids in CDCl₃ or CD₂Cl₂ (0.5 mL) in a 5-mm NMR tube at 20–25 °C, and the 125 MHz ¹³C NMR spectra were taken at -50 to -100 °C. The complexation ratio was determined by ¹³C NMR analysis of ethereal α-carbons of free ethers and their complexes with Lewis acids.

Selective Synthesis of Cyclohexyl Methyl Ether-MAD Complex (2) from a Mixture of Cyclohexyl Methyl Ether and Cyclohexyl Ethyl Ether with MAD. A mixture of cyclohexyl methyl ether and cyclohexyl ethyl ether (0.4 mmol each) was added to MAD (0.4 mmol) in hexane (0.5 mL) at room temperature. A white precipitate gradually formed over a period of 1 h. This mixture was heated and diluted with more hexane (1.5 mL) until the precipitate redissolved. The resulting solution was allowed to stand at room temperature for 3 h to furnish, after filtration, cyclohexyl methyl ether-MAD complex (2) (158 mg, 68% yield) as white crystals: mp 36–38 °C; ¹H NMR (CDCl₃) δ 6.95 (4H, s, C₆H₂), 4.2–4.4 (1H, m, CH-O), 3.54 (3H, s, OCH₃), 2.23 (6H, s, CH₃), 1.11–2.05 (10H, m, CH₂), 1.36 (36H, s, C(CH₃)₃), -0.28 (3H, s, Al-CH₃); ¹³C NMR (CDCl₃ at -50 °C) δ 154.56, 137.95, 125.76, 125.41, 84.66, 53.07, 35.05, 32.48, 31.13,

29.03, 24.78, 21.20, -3.44 (Al-CH₃). Anal. Calcd for C₃₈H₆₃O₃Al: C, 76.72; H, 10.67%. Found: C, 75.80; H, 10.89%.

Table 4. Characteristic ¹³C NMR Data for Free Ethers and Their Complexes with MAD

ether	δ (free) / ppm ^a	δ (complex) / ppm ^b	δ (phenoxy) / ppm ^c
	72.05	75.32	154.47
	69.84	68.12	154.50
	67.33	67.31	152.62
	66.19	64.67	154.42
	58.82	59.97	154.44
	49.21	55.22	broad
	70.78	69.79	154.48
	55.70	53.07	154.56
	62.57	65.31	154.37
	68.71	73.73	154.36

ether	δ (free) / ppm ^a	δ (complex) / ppm ^b	δ (phenoxy) / ppm ^c
	68.45	65.89	153.28, 155.65
	68.18	73.23	154.47
	67.84	72.89	154.29, 155.33
	62.79	68.23	153.97
	71.97	70.63	154.38
	71.25	71.57	154.32
	75.70	79.50	154.49
	69.70	74.77	153.95

^a The term " δ (free)" refers to the chemical shift for ethereal α -carbons of free ethers at the indicated arrows. ^b The term " δ (complex)" refers to the chemical shift for ethereal α -carbons of MAD-ether complexes at the indicated arrows. ^c The term " δ (phenoxy)" denotes the chemical shift of phenoxy carbons of MAD-ether complexes, and in every case the downfield shifts were observed (phenoxy carbon of free MAD : δ 152.02 ppm).

Selective Synthesis of Diethyl Ether-MAD Complex (3) from a Mixture of Diethyl Ether and Ethyl Vinyl Ether with MAD. To MAD (0.4 mmol) in hexane (0.5 mL) was added a

mixture of diethyl ether and ethyl vinyl ether (0.4 mmol each) at room temperature. A white precipitate gradually formed over a period of 1 h. This mixture was heated and diluted with more hexane (0.5 mL) until the precipitate redissolved. This was allowed to stand at room temperature for 3 h to furnish, after filtration, diethyl ether-MAD complex (**3**) (178 mg, 80% yield) as white crystals: mp 60 °C; ¹H NMR (CDCl₃) δ 6.98 (4H, s, C₆H₂), 4.18 (4H, q, *J*=6.9 Hz, CH₂-O), 2.25 (6H, s, CH₃), 1.39 (36H, s, C(CH₃)₃), 1.27 (6H, t, *J*=6.9 Hz, O-C-CH₃), -0.27 (3H, s, Al-CH₃); ¹³C NMR(CDCl₃ at -50 °C) δ 154.42, 137.89, 125.79, 125.42, 64.67, 35.00, 31.04, 21.24, 11.38, -3.47 (Al-CH₃). Anal. Calcd for C₃₅H₅₉O₃Al: C, 75.77; H, 10.72%. Found: C, 74.98; H, 10.92%.

Selective Synthesis of Methyl Propyl Ether-MAD Complex (4) from a Mixture of Methyl Propyl Ether and *tert*-Butyl Methyl Ether with MAD. To MAD (0.4 mmol) in hexane (0.5 mL) was added a mixture of methyl propyl ether and *tert*-butyl methyl ether (0.4 mmol each) at room temperature. A white precipitate gradually formed over a period of 1 h. This mixture was heated until the precipitate redissolved. On standing at room temperature for 3 h, methyl propyl ether-MAD complex (**4**) was formed in 60% yield (133 mg) as white crystals after filtration: mp 51—52 °C; ¹H NMR (CDCl₃) δ 6.96 (4H, s, C₆H₂), 4.03 (2H, t, *J*=6.9 Hz, CH₂-O), 3.64 (3H, s, OCH₃), 2.24 (6H, s, CH₃), 1.75 (2H, m, CH₃CH₂), 1.36 (36H, s, C(CH₃)₃), 0.85 (3H, t, *J*=7.5 Hz, CH₃), -0.27 (3H, s, Al-CH₃); ¹³C NMR(CDCl₃ at -50 °C) δ 154.44, 137.80, 125.83, 125.45, 76.87, 59.97, 35.00, 30.95, 21.21, 19.02, 9.24, -3.82 (Al-CH₃). Anal. Calcd for C₃₅H₅₉O₃Al: C, 75.77; H, 10.72%. Found: C, 74.08; H, 10.85%.

Selective Synthesis of THF-MAD Complex (5) from a Mixture of THF and 2-Methyl-tetrahydrofuran with MAD. To MAD (0.4 mmol) in hexane (0.5 mL) was added a mixture of THF and 2-methyltetrahydrofuran (0.4 mmol each) at room temperature. A white precipitate gradually formed over a period of 1 h. This mixture was heated and diluted with more hexane (4.5 mL) until the precipitate redissolved. This was allowed to stand at room temperature for 3 h to furnish, after filtration, THF-MAD complex (**5**) (138 mg, 63% yield) as white crystals: mp 56—57 °C; ¹H NMR (CDCl₃) δ 6.97 (4H, s, C₆H₂), 4.25 (4H, m, CH₂-O), 2.24 (6H, s, CH₃), 1.98 (4H, m, CH₂), 1.38 (36H, s, C(CH₃)₃), -0.31 (3H, s, Al-CH₃); ¹³C NMR(CDCl₃ at -50 °C) δ 154.47,

137.78, 125.87, 125.28, 73.23, 35.07, 30.98, 25.10, 21.30, -3.97 (Al-CH₃). Anal. Calcd for C₃₅H₅₇O₃Al: C, 76.04; H, 10.39%. Found: C, 75.82; H, 10.59%.

Selective Synthesis of THF-MAD Complex (5) from a Mixture of THF and THP with MAD. To MAD (0.4 mmol) in hexane (0.5 mL) was added a mixture of THF and THP (0.4 mmol each) at room temperature. A white precipitate gradually formed over a period of 1 h. This mixture was heated with more hexane (4.5 mL) until the precipitate redissolved. This was allowed to stand at room temperature for 3 h to furnish, after filtration, THF-MAD complex (5) (114 mg, 53% yield) as white crystals. The analytical and physical data are listed above.

Determination of Recognition Ability of MAD with Two Different Oxygen-Containing Substrates by Low-Temperature ¹³C NMR Analysis. Two different oxygen-containing substrates (0.5 mmol each) were mixed with 1 equiv of MAD in CDCl₃ (1 mL) in a 5-mm NMR tube at 20–25 °C, and the 125 MHz ¹³C NMR spectra were taken at -50 °C. The complexation ratio was determined by ¹³C NMR analysis of free carbonyl carbons or ethereal α-carbons of oxygen-containing substrates and their MAD complexes. This ratio was also calculated based on the phenoxy carbons of free MAD and its complexes with substrates.

Preparation of THF and THP Ethers of 4-(*tert*-Butyldiphenylsiloxy)-1-butanol. To a solution of 1,4-butanediol (30 mmol) in CH₂Cl₂ were added a catalytic amount of p-TsOH, and 2,3-dihydrofuran (30 mmol) or 3,4-dihydro-2*H*-pyran (30 mmol) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and for 1 h at room temperature, poured into sat. Na₂CO₃, extracted with CH₂Cl₂, and dried over Na₂SO₄. Evaporation of solvents and purification of the residue by column chromatography on silica gel (ether/hexane as eluant) gave 4-(tetrahydro-2-furyloxy)-1-butanol or 4-(tetrahydro-2-pyranyloxy)-1-butanol.

tert-Butyldiphenylsilyl ethers of 4-(tetrahydro-2-furyloxy)-1-butanol and 4-(tetrahydro-2-pyranyloxy)-1-butanol were obtained by treatment of these alcohols with *tert*-butyldiphenylsilyl chloride (1.5 equiv) and imidazole (2 equiv) in DMF at -20 °C for several hours.

THF Ether of 4-(*tert*-Butyldiphenylsiloxy)-1-butanol: ¹H NMR (CDCl₃) δ 7.3–7.7 (10H, m, C₆H₅), 5.07 (1H, m, O-CH-O), 3.3–3.9 (6H, m, CH₂-O), 1.5–2.0 (8H, m, CH₂), 1.02 (9H, s, C(CH₃)₃).

THP Ether of 4-(*tert*-Butyldiphenylsiloxy)-1-butanol: ^1H NMR (CDCl_3) δ 7.3—7.7 (10H, m, C_6H_5), 4.53 (1H, m, O-CH-O), 3.3—3.9 (6H, m, $\text{CH}_2\text{-O}$), 1.4—1.9 (10H, m, CH_2), 1.02 (9H, s, $\text{C}(\text{CH}_3)_3$).

Preparation of Polymeric Organoaluminum Column for Complexation Chromatography of Ethers. To a solution of triphenol **6** (1.55 g, 2 mmol) in dry, degassed CH_2Cl_2 (20 mL) was added a 2M hexane solution of Me_3Al (1.5 mL, 3 mmol) at room temperature. After 1 h, 6.2 mmol of methane gas (i.e., nearly 2 equiv of methane gas per 1 equiv of Me_3Al) evolved, showing the formation of polymeric organoaluminum reagent **7**. Then the solvent was evaporated to dryness affording solid **7** (1.64—1.70 g). Attempted recrystallization of **7** was unsuccessful. Hence, the residue was ground to a powder and mixed with silanized silica gel (1.64—1.70 g), which was dried at 60—80 °C for 1 h under vacuum before use. Mixing of the polymeric organoaluminum reagent **7** with silanized silica gel is recommended for obtaining efficient separation and reproducibility in column chromatography. This was packed in a short-path glass column (10 mm i.d. \times 150 mm) as a stationary phase. These operations were carried out in an argon box. Then the stationary phase was washed once with dry, degassed hexane (50 mL) to remove unreacted free triphenol **6**.

Triphenol 6: ^1H NMR (CDCl_3) δ 6.88 (6H, s, C_6H_2), 4.96 (3H, s, OH), 4.03 (6H, s, CH_2), 2.25 (9H, s, CH_3), 1.34 (54H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR(CDCl_3) δ 151.61, 135.58, 134.25, 130.98, 124.54, 36.30, 34.42, 30.56, 17.34.

Polymeric Organoaluminum Reagent 7: ^1H NMR (CD_2Cl_2) δ 6.98 (C_6H_2), 4.03 (CH_2), 2.22 (CH_3), 1.47 ($\text{C}(\text{CH}_3)_3$), -0.36 (Al-CH_3); ^{13}C NMR(CD_2Cl_2) δ 153.19, 139.06, 135.80, 130.90, 125.06, 36.65, 35.34, 32.30, 17.14, -8.95 (Al-CH_3).

General Method for Separation of Two Different Ethers by Complexation Chromatography on Polymeric Organoaluminum Column. A Solution of two different ethers (0.5 mmol each) in degassed hexane (1 mL) was introduced on to the top of the column and degassed hexane was continuously passed through under the pressure of argon (0.3—0.4 kg/cm^2). Each fraction (5 mL) was concentrated and analyzed by ^1H NMR analysis. Sterically more hindered or electronically less basic ether was found to elute first. After collection of 15—40

fractions (i.e., 15—40 × 5 mL), eluent was changed to Et₂O in hexane (Et₂O/hexane = 1:10) to elute the remaining other ether as shown in Figure 1—3.

Preparation of Epoxy Silyl Ethers. Epoxy alcohols were prepared by VO(acac)₂-catalyzed epoxidation of allylic alcohols with *tert*-BuOOH. *tert*-Butyldiphenylsilyl ethers of epoxy alcohols were obtained by treatment of the epoxy alcohols with *tert*-butyldiphenylsilyl chloride (1.5 equiv) and imidazole (2 equiv) in DMF at -20—0 °C for several hours.

***trans*-3-Methyloxiranemethanol *tert*-Butyldiphenylsilyl Ether (8):** ¹H NMR (CDCl₃) δ 7.64—7.69 (4H, m, Ph), 7.36—7.39 (6H, m, Ph), 3.72—3.75 (2H, m, CH₂-OSi), 2.83 (2H, m, CH-O), 1.26 (3H, d, *J* = 5.0 Hz, CH₃), 1.03 (9H, s, C(CH₃)₃).

***trans*-3-Propyloxiranemethanol *tert*-Butyldiphenylsilyl Ether (9):** ¹H NMR (CDCl₃) δ 7.64—7.67 (4H, m, Ph), 7.36—7.38 (6H, m, Ph), 3.71—3.74 (2H, m, CH₂-OSi), 2.86 (1H, m, CH-O), 2.77 (1H, m, CH-O), 1.41—1.48 (4H, m, CH₂-CH₂), 1.03 (9H, s, C(CH₃)₃), 0.92 (3H, t, *J* = 6.6 Hz, CH₃).

***cis*-3-Propyloxiranemethanol *tert*-Butyldiphenylsilyl Ethers (10):** ¹H NMR (CDCl₃) δ 7.66—7.71 (4H, m, Ph), 7.35—7.41 (6H, m, Ph), 3.73—3.78 (2H, m, CH₂-OSi), 3.13 (1H, m, CH-O), 2.94 (1H, m, CH-O), 1.2—1.5 (4H, m, CH₂-CH₂), 1.05 (9H, s, C(CH₃)₃), 0.90 (3H, t, *J* = 6.6 Hz, CH₃).

***α*-Methyl-(*trans*-3-Methyloxirane)methanol *tert*-Butyldiphenylsilyl Ether (11):** ¹H NMR (CDCl₃) δ 7.63—7.78 (4H, m, *erythro* and *threo* Ph), 7.36—7.43 (6H, m, *erythro* and *threo* Ph), 3.66 (1H, dq, *J* = 6, 6 Hz, *threo* CH-OSi), 3.48 (1H, dq, *J* = 6.2, 6.4 Hz, *erythro* CH-OSi), 2.81 (1H, dq, *J* = 2.2, 5.2 Hz, *threo* C-CH-O), 2.77 (1H, dd, *J* = 2.2, 5.6 Hz, *threo* CH-C-OSi), 2.58 (1H, dd, *J* = 2.2, 6.2 Hz, *erythro* CH-C-OSi), 2.41 (1H, dq, *J* = 2.2, 5.2 Hz, *erythro* C-CH-O), 1.26 (3H, d, *J* = 5.2 Hz, *threo* CH₃-C-OSi), 1.21 (3H, d, *J* = 6.4 Hz, *erythro* CH₃-C-OSi), 1.10 (3H, d, *J* = 5.2 Hz, *erythro* CH₃-C-O), 1.08 (3H, d, *J* = 6.4 Hz, *threo* CH₃-C-O), 1.06 (9H, s, *threo* C(CH₃)₃), 1.04 (9H, s, *erythro* C(CH₃)₃). The *erythro*/*threo* ratio of 11 is 61:39.

Preparation of Polymeric Organoaluminum Column for Complexation Chromatography of Epoxy Silyl Ethers. To a solution of triphenol 6 (0.78 g, 1 mmol) in dry, degassed CH₂Cl₂ (10 mL) was added a 2M hexane solution of Me₃Al (0.75 mL, 1.5 mmol) at room temperature. After 1

h, the solvent was evaporated to dryness affording solid **7**. Then, the residue was ground to a powder and mixed with silanized silica gel (10 g), which was dried at 60—80 °C for 1 h under vacuum before use. Mixing of the polymeric organoaluminum reagent **7** with silanized silica gel is recommended for obtaining efficient separation and reproducibility in column chromatography. This was packed in a short-path glass column (15 mm i.d. × 250 mm) as a stationary phase. These operations were carried out in an argon box. Then the stationary phase was washed once with dry, degassed hexane (50 mL) to remove unreacted free triphenol **6**.

General Method for Separation of Two Different Epoxy Silyl Ethers by Complexation Chromatography on Polymeric Organoaluminum Column. A Solution of two different epoxy silyl ethers (1 mmol each) in degassed hexane (2 mL) was introduced on to the top of the column at -15 °C and degassed hexane was continuously passed through under the pressure of argon (0.3—0.4 kg/cm²) at this temperature. Each fraction (20 mL) was concentrated and analyzed by ¹H NMR analysis. After collection of 15 fractions (i.e., 15 × 20 mL), eluent was changed to 5% THF in hexane as shown in Figure 4—6.

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- (12) Unreproducible results were obtained in the case of aliphatic aldehydes such as propanal.

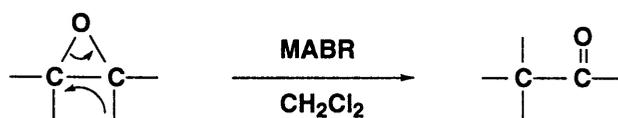
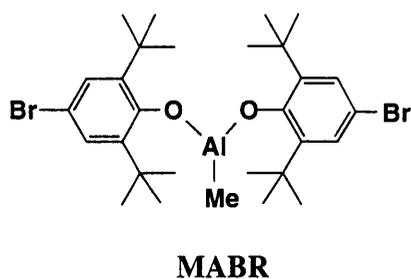
- (13) Two *N*-methyl carbons of amides can also be utilized to determine the complexation ratios. The 125 MHz ¹³C NMR signals for free *N*-methyl carbons and their MAD complexes in CDCl₃ at -50 °C follow: *N,N*-dimethylpropionamide [$\delta_{\text{N-Me}}$ (free) = 35.20 and 36.99 ppm; $\delta_{\text{N-Me}}$ (complex) = 38.24 and 38.88 ppm]; *N,N*-dimethylbenzamide [$\delta_{\text{N-Me}}$ (free) = 35.11 and 39.57 ppm; $\delta_{\text{N-Me}}$ (complex) = 38.16 and 40.91 ppm].
- (14) Phenyl propionate has a similar binding capability to ethyl benzoate (complexation ratio = 52:48).
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- (16) Kindly provided by Adeka Argus Chemical Co., Ltd.
- (17) Silanized silica gel was dried at 60–80 °C for 1 h under vacuum before use. Mixing of the polymeric organoaluminum reagent **7** with silanized silica gel (weight ratio = 1:1) is recommended for obtaining efficient separation and reproducibility in column chromatography.
- (18) It should be noted that the separation of methyl 3-phenylpropyl ether and its ethyl analogue cannot be readily accomplished by ordinary silica gel chromatography.
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Chapter 5

Synthetic Application of Complexation Chromatography on Polymeric Organoaluminum Column

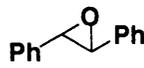
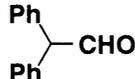
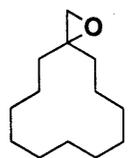
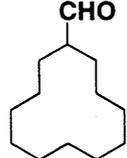
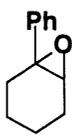
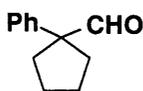
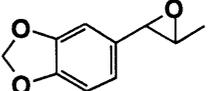
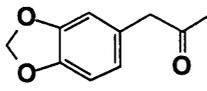
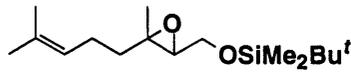
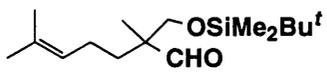
Abstract: The complexation chromatography on polymeric organoaluminum column can be successfully utilized for the facile workup-free catalytic rearrangement of various epoxides to carbonyl compounds at room temperature. The polymeric organoaluminum reagent **4** on the column exhibits its high efficiency not only as a catalyst for the epoxy rearrangement, but also as a filter for the selective removal of the resulting polar by-products based on the Lewis acid-base complex formation.

While the acid-catalyzed rearrangement of epoxides to carbonyl compounds is certainly a well-known transformation, only a few reagents have been employable for this purpose with respect to the efficiency and selectivity of the reaction.¹ Recently, Yamamoto *et al.* reported that the exceptionally bulky, oxygenophilic methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (abbreviated to MABR)² can be utilized as a stoichiometric reagent and a catalyst for the stereocontrolled rearrangement of optically active epoxy silyl ethers to optically active β -siloxy aldehydes under mild conditions.^{3,4} Therefore, we examined catalytic rearrangement of simple epoxides using MABR to produce carbonyl compounds selectively.



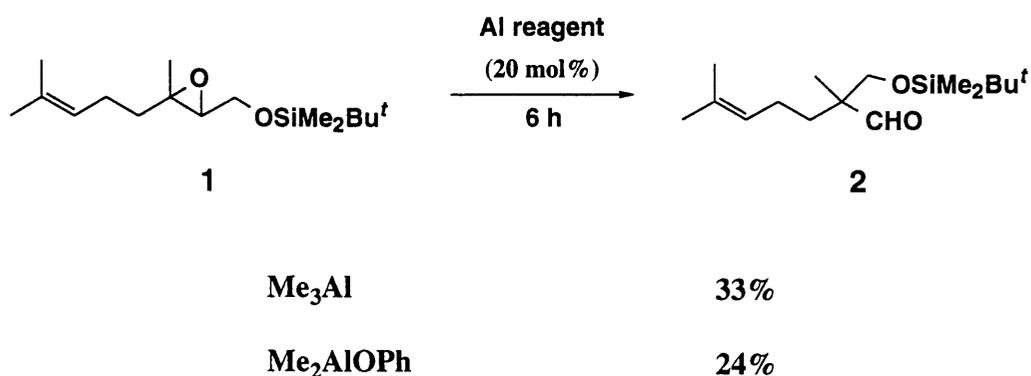
Reaction of *trans*-stilbene oxide with the catalytic amount (10 mol%) of MABR in CH_2Cl_2 at $-20\text{ }^\circ\text{C}$ was complete within 30 min to furnish the desired diphenylacetaldehyde in 95% yield. Also, treatment of *tert*-butyldimethylsilyl ether of epoxy geraniol (**1**) gave rise to the rearranged β -siloxy aldehyde **2** in 82% yield under the same conditions. Several examples are listed in Table 1. The amount of the catalyst varies from 5 to 30 mol% depending on the epoxy substrate. Yields when MABR is used stoichiometrically are also included for comparison. As revealed in Table 1, this catalytic method is applicable to various epoxides with high selectivity.⁵ Neither epoxides derived from monosubstituted olefins or internal dialkyl-substituted olefins are employable, however, even with a two-fold quantity of MABR.

Table 1. Organoaluminum-Catalyzed Rearrangement of Epoxides to Carbonyl Compounds^a

entry	epoxide	MABR ^b (mol%)	conditions (°C, h)	product	yield/% ^c
1		10	-20, 0.3		95
2		200	-78, 0.5		93
3		20	-20, 0.5		58
4		30	-20, 0.5		77
5		200	-78, 2; -20, 0.3		94
6		5	-20, 1		91
7		10	-20, 1		96
8		200	-78, 0.5		98
9		5	-20, 0.2		84
10		10	-20, 0.5		90
11		200	-78, 0.3		87
					
	1			2	
12		20	-78, 0.1; 0, 0.3		82
13		200	-78, 1; -20, 0.5		99

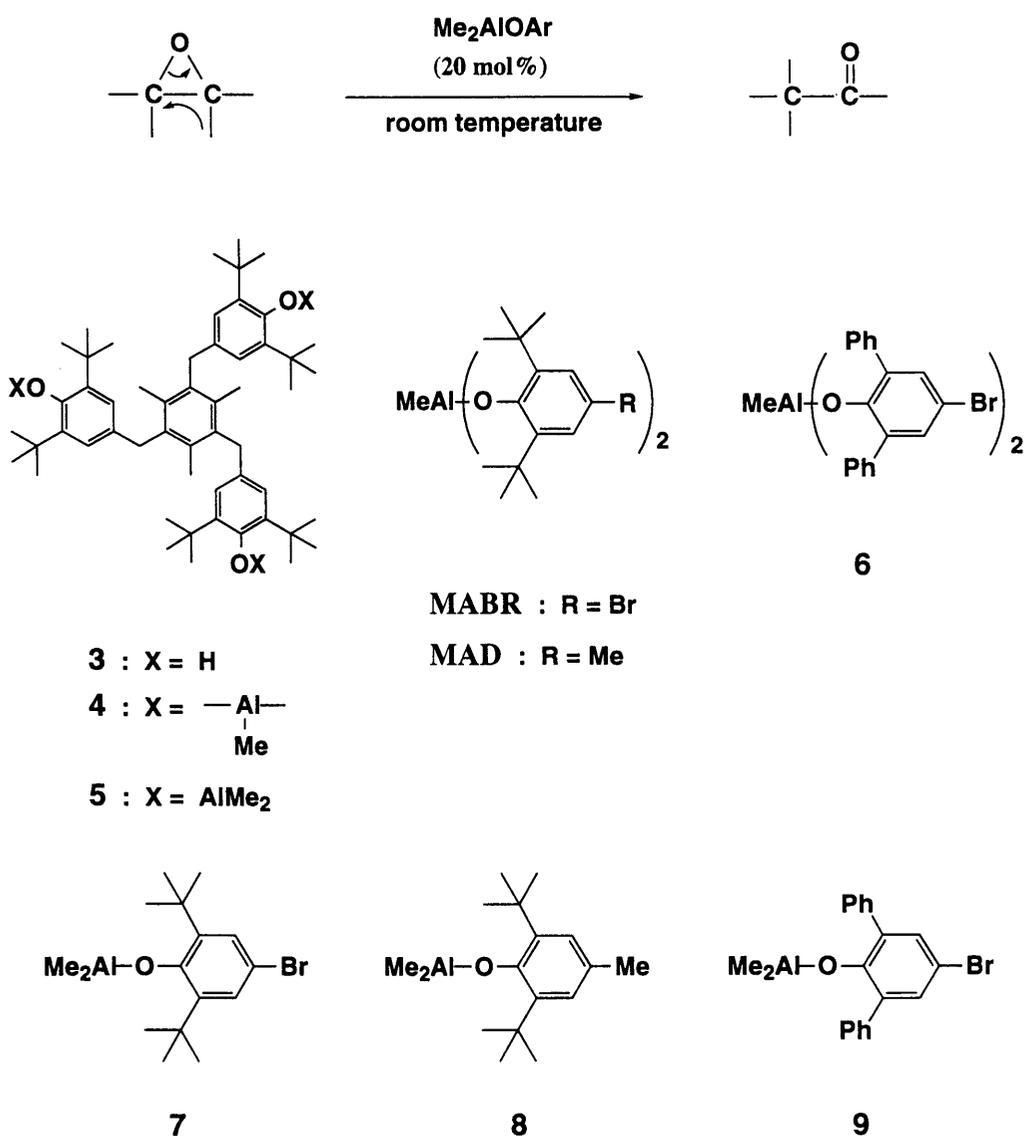
^a The rearrangement was carried out in degassed CH₂Cl₂ by using 0.05–2 equiv of the aluminum reagent MABR per epoxide under the indicated conditions. The reaction mixture was worked up by the NaF-H₂O method, see experimental section. ^b Prepared from Me₃Al and 4-bromo-2,6-di-*tert*-butylphenol (2 equiv) in degassed CH₂Cl₂ at room temperature for 1 h. ^c Isolated yield by column chromatography.

The exceptionally bulky MABR and methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (abbreviated to MAD)⁶ exist as a monomeric species in solution,⁷ whereas simple trialkylaluminums such as Me₃Al are generally themselves dimeric, bridged complexes in equilibrium with the monomer.⁸ Even in a solution of dimethylaluminum phenoxide (Me₂AlOPh) several species such as a cyclic dimer and trimer coexist.⁹ Self-association of less hindered organoaluminum compounds through electron deficient bonds results in decreasing of inherent Lewis acidity and heterogenophilicity including oxygenophilicity of aluminum atom. In fact, attempted rearrangement of *tert*-butyldimethylsilyl ether of epoxy geraniol (**1**) with Me₃Al and Me₂AlOPh catalysts (20 mol%) proceeded very slowly and virtually stopped after achieving only low yield of the desired β -siloxy aldehyde **2** (24—33% for 6 h) at room temperature.



In this context, we thought that certain dimethylaluminum compounds introduced one bulky aryloxy ligand would become selective catalysts for epoxy rearrangement even at room temperature because of their moderate Lewis acidity which might be at least stronger than that of Me₂AlOPh. Hence, the rearrangement of epoxide **1** using 20 mol% of various dimethylaluminum aryloxy reagents (Me₂AlOAr) in CH₂Cl₂ at room temperature was examined (Table 2). As aryloxy ligands, commercially available triphenol **3**, 2,6-di-*tert*-butylphenol, 2,6-diphenylphenol, and their derivatives were chosen for their steric bulkiness and versatility. Thus, the dimethylaluminum aryloxy reagents such as tris(dimethylaluminum)aryloxy (**5**), dimethylaluminum 4-bromo-2,6-di-*tert*-butylphenoxide (**7**), dimethylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide (**8**),

dimethylaluminum 4-bromo-2,6-diphenylphenoxide (**9**) could be utilized as mild Lewis acidic catalysts for the selective rearrangement of epoxides to carbonyl compounds at room temperature. Although the dimethylaluminum catalyst **9** showed low yield of the reaction (50% for 0.5 h), the unrearranged epoxide **1** could be entirely recovered without being changed by other side reactions. It should be noted that epoxide **1** is susceptible to gradual decomposition at room temperature with strong Lewis acidic reagents: the rearrangement with the corresponding monomethylaluminum reagents, polymeric aluminum reagent **4**, MABR, MAD, and methylaluminum bis(4-bromo-2,6-diphenylphenoxide) (**6**) afforded unidentified side products, and thus it revealed disappointing yields (25—70%) (Table 2).



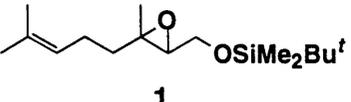
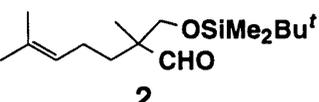
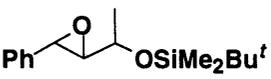
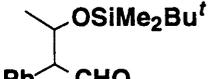
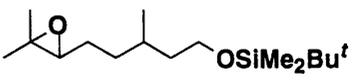
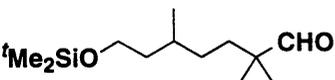
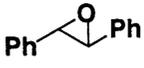
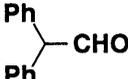
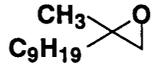
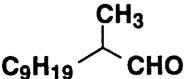
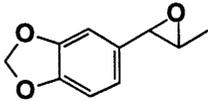
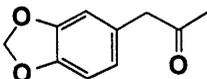
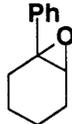
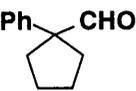
Other selected examples of epoxy rearrangement (Table 3) clearly indicate the effectiveness of this approach, i.e., catalytic rearrangement of epoxides at room temperature using mild Lewis acidic dimethylaluminum reagents. Among these, tris(dimethylaluminum)aryloxide (**5**) was highly effective for epoxy silyl ether substrates such as *tert*-butyldimethylsilyl ether of epoxy geraniol, while dimethylaluminum 4-bromo-2,6-diphenylphenoxide (**9**) was useful for simple epoxides such as *trans*-stilbene oxide.

Table 2. Catalytic Rearrangement of **1** to **2** with Various Aluminum Reagents^a

aluminum reagent	yield/% ^b
3	92 (70) ^c
7	84 (67)
8	85 ^d (57)
9	50 ^{e,f} (25)
Me ₃ Al	33 ^g
Me ₂ AlOPh	24 ^g

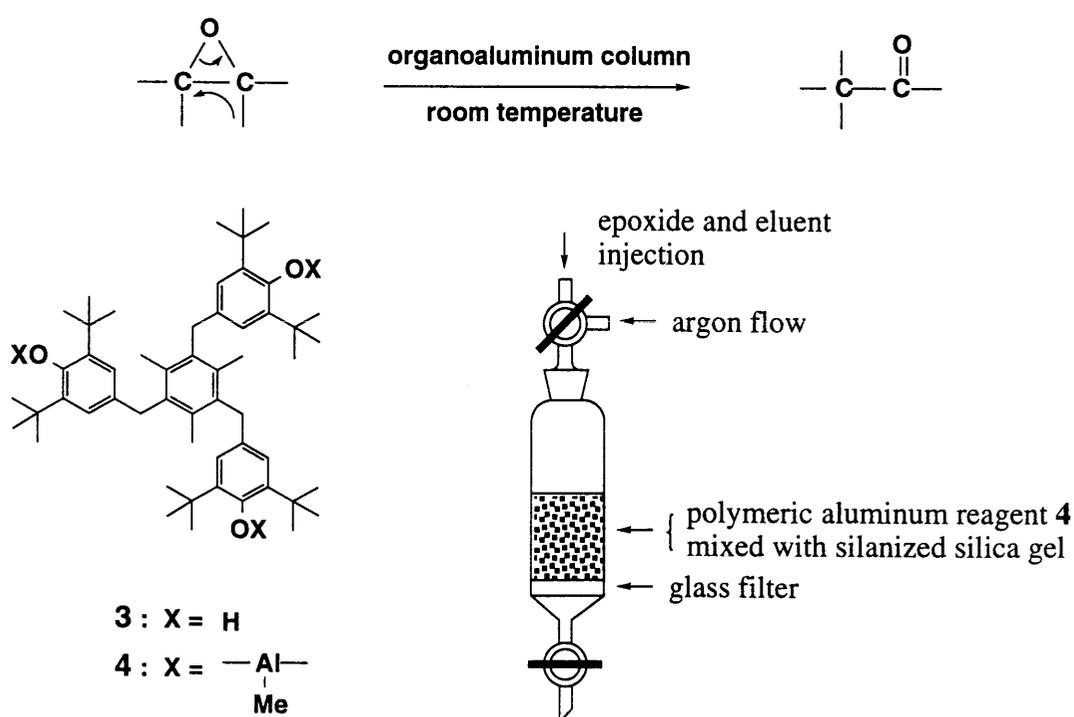
^a Unless otherwise noted, the rearrangement was carried out in CH₂Cl₂ using 20 mol% of various aluminum reagents at room temperature for 0.1 h. The reaction mixture was then worked up by the NaF-H₂O method, see experimental section. ^b Isolated yield by column chromatography on silica gel. ^c Values in parentheses are yields for the rearrangement with the corresponding monomethylaluminum reagents, **4**, MABR, MAD, and **6**, respectively. ^d For 0.3 h. ^e For 0.5 h. ^f Unrearranged epoxides could be entirely recovered without being changed by other side reactions. ^g For 6 h.

Table 3. Catalytic Rearrangement of Epoxides with Various Dimethylaluminum Reagents at Room Temperature

entry	epoxide	product	yield/%			
			5	7	8	9
1			92	84	85 ^a	50 ^{b,c}
2 ^{d,e}			88	89	79	49 ^{b,c}
3 ^f			0 ^c	0 ^c	0 ^c	66
4			52	70	47	96
5 ^g			21	30	22	0 ^c
6 ^h			74	66	62	84
7			94	92	98	98

^a For 0.3 h. ^b For 0.5 h. ^c Unrearranged epoxides could be entirely recovered without being changed by other side reactions. ^d *Erythro/threo* = 3:2 for the starting epoxy silyl ether. ^e The *erythro/threo* ratio of the β -siloxy aldehydes is 2:3 by ¹H NMR analysis. ^f For 2 h. ^g For 4 h. ^h (*E*)/(*Z*) = 1:2 for the starting epoxide.

We recently developed complexation chromatography¹⁰ on the polymeric aluminum reagent **4** possessing high recognition ability in complexation with several Lewis-basic substrates.¹¹ Based on the selective Lewis acid-base complex formation, this flow method has realized a surprisingly clean separation of structurally very similar ether substrates, which cannot be accomplished by ordinary silica gel or alumina chromatography.¹² Apart from its obvious utility in separation mixtures of structurally or electronically very similar ether substrates, complexation chromatography on polymeric organoaluminum column can be expected to become a very useful synthetic procedure for various organoaluminum-mediated reactions. In studying the separation mixtures of α,β -disubstituted epoxy silyl ethers using polymeric aluminum column, *gem*-disubstituted and trisubstituted epoxy silyl ethers were prone to be partially susceptible to the rearrangement on the stationary, polymeric aluminum reagent **4**.^{11b} This finding and the study of convenient procedure for epoxy rearrangement using the various organoaluminum catalysts mentioned above have prompted us to develop the synthetic application of polymeric organoaluminum column as a workup-free reactor to catalytic rearrangement of epoxides.



First, we studied the epoxide rearrangement with the polymeric aluminum reagent **4** (20 mol%) in a conventional batch method as a test of its applicability to the flow method on a column. For example, rearrangement of the *tert*-butyldimethylsilyl ether of epoxy geraniol (**1**) (1 mmol), which is a challenging substrate due to its susceptibility to various side reactions,⁵ at room temperature for 0.1 h yielded the desired β -siloxy aldehyde **2** in 70% yield, in addition to some by-products with complete consumption of the starting epoxy silyl ether (condition A). By lowering reaction temperature, however, the rearrangement proceeded very slowly with \approx 40% recovery of the starting material (53% yield after 0.5 h at -20 °C).¹³ Hence, the use of room temperature seems appropriate for a flow method.

With these results in hand, we tried the rearrangement of this epoxide in the flow method as follows (condition B): The organoaluminum column for catalytic rearrangement was prepared as described previously with some modification for *in situ* preparation.¹¹ Accordingly, the solution of polymeric aluminum reagent **4** (0.5 mmol) in CH₂Cl₂ (10 mL) was charged on a short-path glass column (15 mm i.d. \times 250 mm) packed with silanized silica gel (15 g).¹⁴ After evaporation of solvent under vacuum followed by mixing of the residual **4** and silanized silica gel, the stationary phase was washed once with dry, degassed hexane (50 mL) to remove unreacted free triphenol **3** under the pressure of argon (0.3–0.4 kg/cm²). Under the operating condition, the amount of the immobilized polymeric aluminum reagent **4** as the stationary phase was found to be 0.15–0.25 mmol based on the recovered triphenol **3**. Then, a solution of epoxide **1** (1 mmol) in degassed hexane (1 mL) was introduced on to the top of this organoaluminum column at room temperature. Degassed hexane (50 mL) was continuously passed through the column for 10 min, and then \approx 150 mL more was rapidly forced through until no further elution of desired aldehyde **2** was observed. Further purification of the concentrated eluates by short-path silica gel chromatography to remove trace triphenol **3** (aluminum ligand) gave the pure β -siloxy aldehyde **2** in 67% yield. It should be noted that the eluate by the flow method contained only a trace of by-products. Presumably, the polar by-products coordinated strongly to the stationary phase, polymeric aluminum reagent **4**. In fact, the remaining by-products could be eluted with 5% THF in hexane.

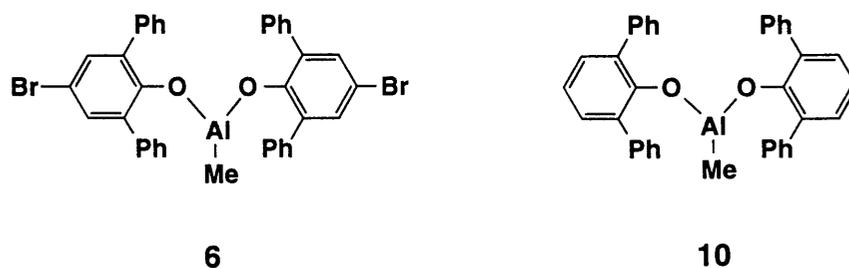
Other examples of epoxy silyl ethers and simple epoxides are given in Table 4. The yields in

Table 4. Catalytic Rearrangement of Epoxides on Immobilized Organoaluminum Columns

entry	epoxide	conditions ^a	product	yield/% ^b
1		4, A		70
2		4, B		67
3		10, A		18
4	1	6, A	2	25
5		4, A		58 ^{c,d}
6		4, B		55 ^{c,d}
7		10, A		16 ^{c,d}
8		6, A		33 ^{c,d}
9		4, A		20
10		4, B		35
11		10, A		52
12		10, B		63
13		6, A		70
14		6, B		72
15		4, A		74
16		4, B		90 ^e
17		10, A		75
18		10, B		83 ^e
19		6, A		81
20		6, B		90 ^e
21		4, A		98
22		4, B		85
23		10, A		94
24		10, B		82
25		6, A		94
26		6, B		85

^a Condition A: In batch method, use of 20 mol% organoaluminum reagents in degassed CH₂Cl₂ at room temperature for 0.1–0.5 h. B: In flow method eluting with degassed hexane (≈200 mL), use of 15–25 mol% organoaluminum reagents at room temperature. ^b Isolated yield. ^c *Erythro/threo* = 3:2 for the starting epoxy silyl ether. ^d The *erythro/threo* ratio of the β-siloxy aldehyde is 2:3 by ¹H NMR analysis. ^e Eluted with degassed hexane (100 mL) followed by 5% THF in hexane (50 mL).

the batch method are also included for comparison. Unfortunately, the reaction of the simple epoxide, *trans*-stilbene oxide, afforded the rearranged diphenylacetaldehyde in low yield (entries 9 and 10). Hence, we examined the possibility of using other organoaluminums such as methylaluminum bis(2,6-diphenylphenoxide) (**10**)¹⁵ and more Lewis acidic methylaluminum bis(4-bromo-2,6-diphenylphenoxide) (**6**), both of which are nearly insoluble in developing solvents. Indeed, treatment of *trans*-stilbene oxide with **6** (20 mol%) afforded the desired aldehyde in good yield under the same flow conditions (entry 14). Furthermore, the organoaluminum reagents, **10** and **6**, were employed successfully for the clean rearrangement of other simple epoxides (entries 18, 20, 24, and 26), though the transformation of epoxy silyl ethers gave less satisfactory results (entries 3, 4, 7, and 8).



Experimental Section

General. The IR spectra were measured on Perkin-Elmer 1600 Series FT IR spectrometer and Hitachi 260-10 spectrometer. The ¹H and ¹³C NMR spectra were recorded on JEOL FX-60Q and Varian Gemini-200 spectrometers, using tetramethylsilane (Me₄Si) as an internal standard. Splitting patterns are indicated as s, singlet; t, triplet; q, quartet; m, multiplet. All experiments were carried out under an atmosphere of dry argon.

Diethyl ether (Et₂O) was freshly distilled from sodium metal using diphenylketyl as indicator. Dichloromethane was freshly distilled before use. Trimethylaluminum (Me₃Al) was obtained from Toso-Akzo Chemical Co., Ltd., Japan. Triphenol **3** kindly provided by Adeka Argus Chemical Co., Ltd. Other simple, inorganic and organic chemicals were purchased and used as such.

Preparation of Epoxides. Various epoxides were prepared according to one of the following procedures: (1) simple epoxidation of olefins with MCPBA; (2) VO(acac)₂-catalyzed epoxidation of allylic alcohols with *tert*-BuOOH.

Preparation of Epoxy Silyl Ethers. *tert*-Butyldimethylsilyl ethers of various epoxy alcohols were obtained by treatment of the epoxy alcohols with *tert*-butyldimethylsilyl chloride (1.1—2 equiv) and imidazole (2—3 equiv) in DMF at -20—0 °C for several hours.

Silyl Ether of Epoxy Geraniol 1: ¹H NMR (CDCl₃) δ 5.08 (1H, t, *J*=7.5 Hz, C=CH), 3.72 (2H, d, *J*= 5 Hz, CH₂-OSi), 2.88 (1H, t, *J*=5 Hz, CH-O), 2.06 (2H, q, *J*=10 Hz, C=C-CH₂), 1.58 and 1.67 (6H, s, (CH₃)₂C=), 1.42 (2H, m, C-CH₂-C), 1.23 (3H, s, CH₃-C-O), 0.89 (9H, s, *t*-Bu), 0.07 (6H, s, Me₂Si); IR (liquid film) 2960, 2940, 2865, 1450, 1380, 1250, 1130, 1090, 830, 770 cm⁻¹.

1-Phenylcyclohexene Oxide: ¹H NMR (CDCl₃) δ 7.20—7.41 (5H, m, Ph), 3.05 (1H, t, *J*=2 Hz, CH-O), 1.93—2.35 (4H, m, 2CH₂), 1.18—1.68 (4H, m, 2CH₂).

3-(*tert*-Butyldimethylsiloxy)-1,2-epoxy-1-phenylbutane: ¹H NMR (CDCl₃) δ 7.21—7.37 (5H, m, Ph), 3.87 (1H, dq, *J*=4.2, 8 Hz, CH-OSi), 3.80 (1H, d, *J*=2 Hz, Ph-CH), 2.90 (1H, dd, *J*=2, 4.2 Hz, CH-O), 1.26 (3H, d, *J*=8 Hz, CH₃), 0.88 (9H, s, *t*-Bu), 0.07 (6H, s, Me₂Si); IR (liquid film) 2980, 2945, 2880, 1455, 1250, 1145, 1110, 1095, 830, 770, 685 cm⁻¹.

Preparation of MABR. To a solution of 4-bromo-2,6-di-*tert*-butylphenol (2 equiv) in CH₂Cl₂ was added at room temperature a 2 M hexane solution of Me₃Al (1 equiv). The methane gas evolved immediately. The resulting colorless solution was stirred at room temperature for 1 h and used as a solution of MABR in CH₂Cl₂ without any purification.

Preparation of Other Methylaluminum Reagents. Other methylaluminum reagents such as MAD, methylaluminum bis(4-bromo-2,6-diphenylphenoxide) (**6**), and methylaluminum bis(2,6-diphenylphenoxide) (MAPH) (**10**) were prepared *in situ* from Me₃Al (1 equiv) and the corresponding phenols (2 equiv) in CH₂CH₂ at room temperature for 1 h. Polymeric aluminum reagent **4** was prepared *in situ* from Me₃Al (1.5 equiv) and triphenol **3** (1 equiv) in CH₂CH₂ at room temperature for 1 h.

Preparation of Dimethylaluminum Aryloxy Reagents (Me₂AlOAr). Dimethylaluminum aryloxy reagents such as tris(dimethylaluminum)aryloxy (**5**), dimethylaluminum 4-bromo-2,6-

di-*tert*-butylphenoxide (**7**), dimethylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide (**8**), and dimethylaluminum 4-bromo-2,6-diphenylphenoxide (**9**) were prepared *in situ* from Me₃Al and the corresponding phenols in CH₂Cl₂ at room temperature for 1 h.

Stoichiometric Procedure for Rearrangement of Epoxides with MABR. To a solution of the MABR (1 mmol) in CH₂CH₂ (5 mL) was added an epoxide (0.5 mmol) at -78 °C and the resulting mixture was stirred under the indicated conditions in Table 1. The solution was then poured into diluted HCl and extracted with CH₂CH₂. The combined extracts were washed with saturated NaHCO₃ and dried over Na₂SO₄. Evaporation of solvents and purification of the residue by column chromatography (ether/hexane as eluant) gave carbonyl compounds in the yields shown in Table 1.

General Procedure for Catalytic Rearrangement of Epoxides with Modified Organoaluminum Reagents. To a solution of modified mono- or dimethylaluminum reagent (0.05—0.2 mmol) in degassed CH₂Cl₂ (5—10 mL) was added a solution of epoxide (1 mmol) in CH₂CH₂ (0.5 mL). The mixture was stirred under the indicated conditions in Table 1—3. Then the mixture was treated with NaF (17 mg, 0.4 mmol) followed by water (5.4 μL, 0.3 mmol) at -20—0 °C.¹⁶ The entire mixture was vigorously stirred at -20—0 °C for 20 min and filtered with the aid of CH₂Cl₂. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (ether/hexane as eluant) gave carbonyl compounds in the yields shown in Table 1—3.

Preparation of Polymeric Organoaluminum Column for Catalytic Rearrangement. To a solution of triphenol **3** (0.256 g, 0.33 mmol) in dry, degassed CH₂Cl₂ (10 mL) was added a 2 M hexane solution of Me₃Al (0.25 mL, 0.5 mmol) at room temperature. After 1 h, the solution of polymeric aluminum reagent **4** was charged on a short-path glass column (15 mm i.d. × 250 mm) packed with silanized silica gel (15 g). After evaporation of solvent under vacuum followed by mixing of the residual **4** and silanized silica gel, the stationary phase was washed once with dry, degassed hexane (50 mL) to remove unreacted free triphenol **3** under the pressure of argon (0.3—0.4 kg/cm²). Under the operating condition, the amount of the immobilized polymeric aluminum reagent **4** as the stationary phase was found to be 0.15—0.25 mmol based on the recovered triphenol **3**.

Preparation of Other Immobilized Organoaluminum Columns for Catalytic Rearrangement. Modified monomethylaluminum reagents, methylaluminum bis(2,6-diphenylphenoxide) (**10**) and methylaluminum bis(4-bromo-2,6-diphenylphenoxide) (**6**) were prepared *in situ* from Me₃Al and the corresponding phenols (2 equiv) in CH₂Cl₂ at room temperature for 1 h. Then immobilized organoaluminum columns were prepared according to the preparation procedure for the polymeric monomethylaluminum column.

General Procedure for Catalytic Rearrangement of Simple Epoxides on Immobilized Organoaluminum Columns. A solution of epoxide (1 mmol) in degassed hexane (1 mL) was introduced on to the top of immobilized organoaluminum column at room temperature. Degassed hexane (50 mL) was continuously passed through the column for 10 min, and then ≈150 mL more was rapidly forced through until no further elution of desired carbonyl compound was observed. Further purification of the concentrated eluates by short-path silica gel chromatography to remove trace triphenol **3** (aluminum ligand) gave the pure carbonyl compound as shown in Table 4.

β-Siloxy Aldehyde 2: ¹H NMR (CDCl₃) δ 9.53 (1H, s, CHO), 5.03 (1H, br, t, J=6.5 Hz, C=CH), 3.67 (1H, d, J=10 Hz, CH-OSi), 3.54 (1H, d, J=10 Hz, CH-OSi), 1.88 (2H, m, C=C-CH₂), 1.55 and 1.64 (6H, s, (CH₃)₂C=), 1.02 (3H, s, CH₃), 0.85 (9H, s, *t*-Bu), 0.02 (6H, s, Me₂Si); IR (liquid film) 2950, 2920, 2850, 1730, 1455, 1255, 1100, 840, 775 cm⁻¹.

α-Phenylcyclopentanecarboxaldehyde: ¹H NMR (CDCl₃) δ 9.39 (1H, s, CHO), 7.19—7.41 (5H, m, Ph), 2.43—2.59 (2H, m, CH₂), 1.50—1.95 (6H, m, 3CH₂).

3-(tert-Butyldimethylsiloxy)-2-phenylbutanal: ¹H NMR (CDCl₃) δ 9.84 (1H, s, CHO), 7.16—7.39 (5H, m, Ph), 4.48 (1H, dq, J=5.5, 8.5 Hz, CH-OSi), 3.50 (1H, dd, J=3.4, 8.5 Hz, CH-C=O), 1.03 (3H, d, J=5.5 Hz, CH₃), 0.85 (9H, s, *t*-Bu), 0.05 and 0.07 (6H, s, Me₂Si); IR (liquid film) 2946, 2924, 1724, 1268, 1137, 1094, 988, 837, 771, 695 cm⁻¹.

7-(tert-Butyldimethylsiloxy)-2,2,5-trimethylheptanal: ¹H NMR (CDCl₃) δ 9.42 (1H, s, CHO), 3.59 (2H, m, CH₂-OSi), 1.00 (6H, s, (CH₃)₂C), 0.86 (9H, s, *t*-Bu), 0.85 (3H, d, J=7 Hz, CH₃), 0.02 (6H, s, Me₂Si).

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Publication List

I. Part of the present thesis have been published in the following journals.

Chapter 2 The Regioselectivity of Catalytic Hydroalumination of Isoprene with LiAlH_4

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III. Review.

Molecular Recognition using Lewis Acidic Receptors

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