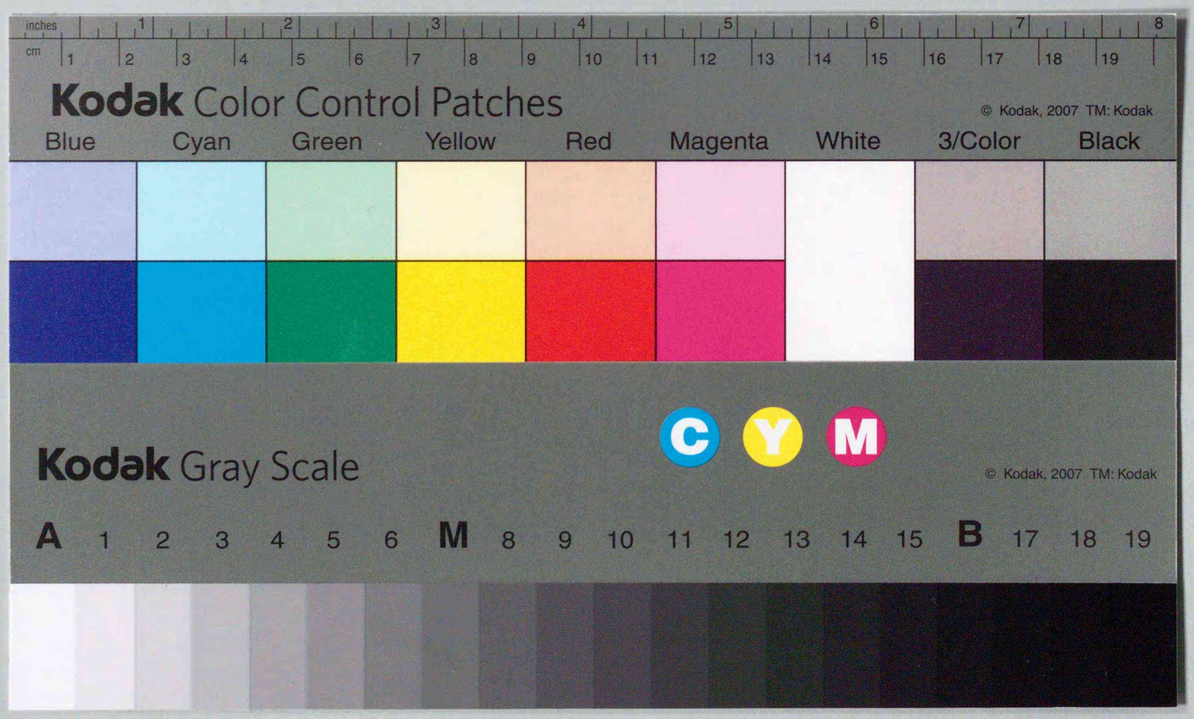
Development of New Aluminum Catalysis for Selective Transformation of Oxygen-Containing Functional Groups

Hayato Ichikawa



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Contents

Chapter 1

Introduction and General Summary

Organoaluminum compounds, although known over 100 years before, have become widely accepted and increasingly important, since Ziegler and co-workers discovered the direct synthesis of trialkylaluminums from aluminum metal, olefin and hydrogen and their brilliant application to the polymerization of olefins. The stream of intensive research on organoaluminums can be categorized into either the utilization of the nucleophilic center attached to the aluminum atom, which can be activated by the formation of the coordination complex with heteroatom-containing substrates, or their property to serve primarily as Lewis acidic reagents.[1-4]

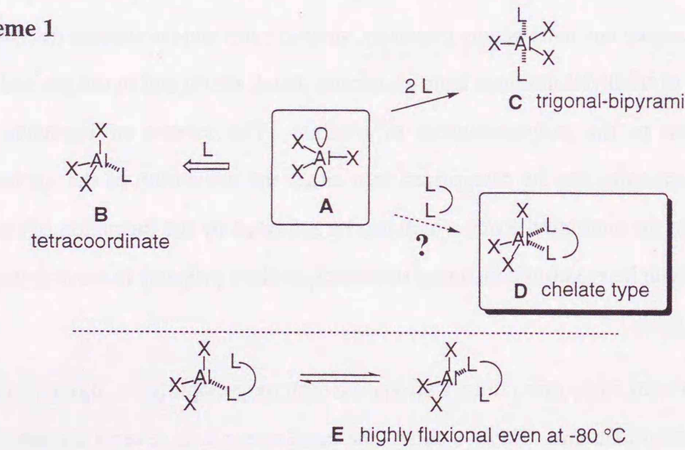
Aluminum, in addition to its well-known high oxigenophilicity, has an exceedingly high affinity toward fluorne. Table 1 shows the bond strength in several diatomic molecules of aluminum - second and third peridic elements.[5]

Table 1. Bond Strengths in Several Diatomic Molecular (kJ/mol)

Al - N	297.0±9.6
O	**511.0±3**
F	**663.6±6.3**
Si	229.3±30.1
P	216.7±12.6
S	373.6±7.9
Cl	511.3±0.8

Most of the chemistry of organoaluminum compounds (**A**, scheme 1) is readily understood in terms of the Lewis acidity of the organoaluminum monomers, which is directly related to the tendency of the aluminum atom to complete electron octets. Nearly all organoaluminum compounds react vigorously with oxygen or air. The strong Lewis acidity of organoaluminum compounds appeares to account for their great affinity for various heteroatoms in organic molecules, particularly oxygen. They generate 1:1 tetracoordinate complexes of type **B** even with neutral bases such as ethers as clearly observed in the single-crystal X-ray diffraction analysis of trimethylaluminum-1,4-dioxane complex.

Scheme 1

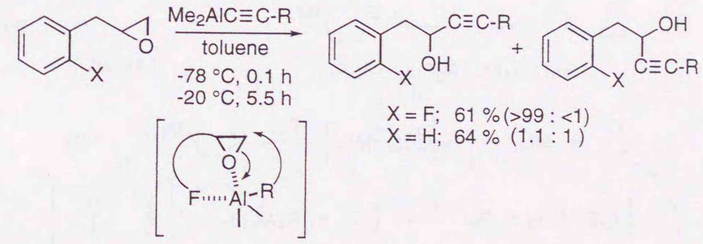


These complexes are usually stable enough to be purified by distillation under reduced pressure, though they could dissociate or decompose on heating or on treatment with strong Lewis base.

As evident from the ether complexes, organoaluminums (**A**) react readily with a variety of neutral or negatively charged Lewis bases (L) to form the corresponding tetracoordinate complexes of type **B**.[6] Recently, several restricted examples on neutral pentacoordinate, trigonal-bipyramidal aluminum complexes of type **C** (X = halogen, hydrogen, alkyl; L = nitrogen or phosphine), where ligands L occupy two axial positions, have been isolated and characterized.[7] However, little is known about the existence of another pentacoordinate organoaluminum complex **D**, and its nature still remains elusive. Although pentacoordination of type **D** (X = Et; L = phosphine) in 1:1 Et_3Al/diphosphine complexes has been previously claimed with Ph_2PPPh_2, $MeN(PPh_2)_2$, and $EtN(PPh_2)_2$, recent evidence obtained on the $Me_3Al/Ph_2PCH_2PPh_2$ complex only points to a highly fluxional molecule in solution with tetracoordinate aluminum species of type **E** even at -80 °C.[8] Hence, trivalent aluminum compounds **A** have long been regarded as non-chelating Lewis acids.

In this context, Maruoka and co-workers paved the way of forming a hitherto uncertain pentacoordinate organoaluminum complex **D** and successfully presented its synthetic application to fluorine-assisted selective alkylation of fluoro epoxides by taking advantage of high affinity of aluminum toward fluorine as well as its inherent oxygenophilicity (Scheme 2). The origin of the selectivity crucially depends on the intervention of a pentacoordinate trialkylaluminum chelate complex, which was verified by low temperature ^{13}C and ^{27}Al NMR study of fluoro epoxide-trimethylaluminum complexes.[9]

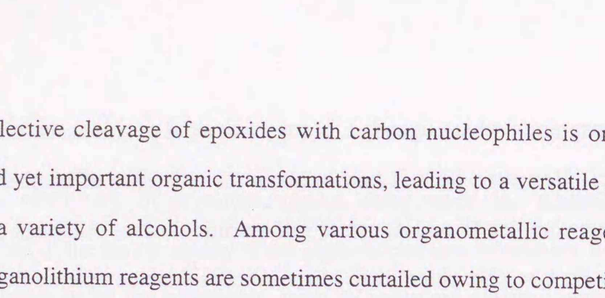
Scheme 2



Aiming at the development of new, catalytic transformation of oxygen-containing organic molecules with eminent selectivity by the utilization of inherent property of organoaluminum compounds, the author first focused his attention on the reactivity of pentacoordinate trialkylaliminum complexes. In chapter 2, the amphiphilic alkylation of heteroatom-containing epoxides is described .

The regioselective cleavage of epoxides with carbon nucleophiles is one of the most fundamental and yet important organic transformations, leading to a versatile method for the preparation of a variety of alcohols. Among various organometallic reagents as carbon nucleophiles, organolithium reagents are sometimes curtailed owing to competing β-hydrogen abstractions arising from their Lewis basicity. Accordingly, these reagents are transformed to the corresponding diorganocuprates or organoaluminates to ensure a smooth epoxide opening (eq 1). Recently, addition of $BF_3 \cdot OEt_2$ was reported to cause the enhancement of reactivity for the epoxide cleavage with organolithium reagents (eq 2).[10] However, this type of alkylation (*i.e.*, amphiphilic alkylation) has never been realized by combining use of highly oxygenophilic organoaluminum reagents with organolithiums because of the preferable formation of organoaluminate complexes. In this context, the author has been interested in the possibility of forming chelation complexes (**F**) of organoaluminums with certain epoxy substrates possessing adjacent hetero-substituents preferentially rather than the ate complex formation with organolithiums, which could enable regio- and stereocontrolled amphiphilic alkylation of such hetero-substituted epoxides under mild conditions.

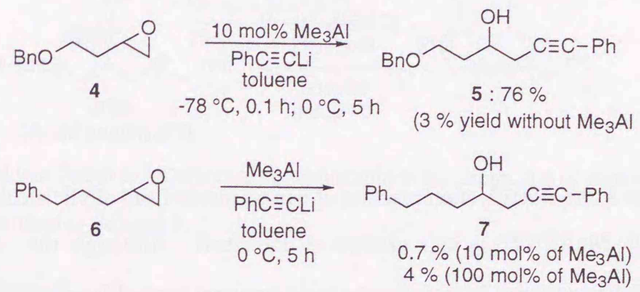
Scheme 3



This possibility has emerged by catalytic use of trialkylaluminum with alkynyllithiums. For instance, reaction of **4** with PhC ≡ CLi in toluene was accelerated by catalytic Me_3Al (10 mol%) at 0 °C for 5 h to furnish 1-(benzyloxy)-6-phenylhex-5-yn-3-ol (**5**) in 76% yield, while alkynylation of **4** with PhC ≡ CLi in toluene in the absence of Me_3Al proceeded quite reluctantly at 0 °C to give only a trace amount of alkynylation product **5** after 5 h (Scheme 4). It should be added that a simple epoxide, 5-phenyl-1-pentene oxide (**6**) was not susceptible to

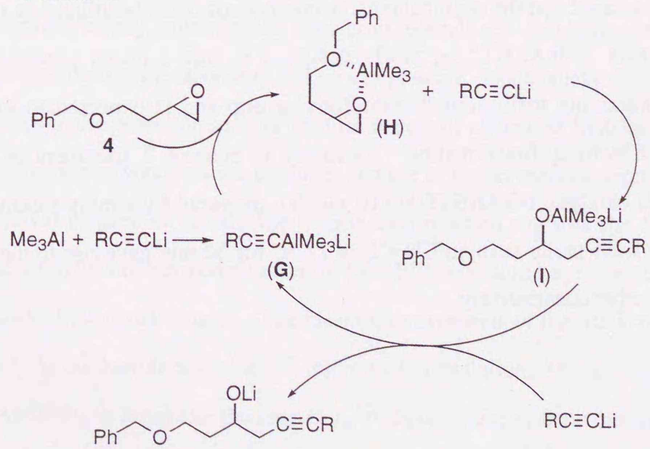
nucleophilic attack of PhC ≡ CLi with Me_3Al (10~100 mol%) under similar reaction conditions as also included in Scheme 4, probably due to the preferable formation of ate complex.

Scheme 4



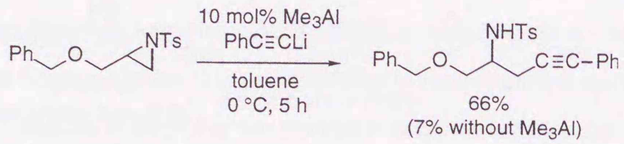
The Me_3Al-catalyzed alkynylation of epoxy ethers can be interpreted by a mechanism as shown in Scheme 5. Thus, the ligand exchange between the initially formed RC ≡ CAlMe_3Li (**G**) and epoxy ether **4** takes place to generate the pentacoordinate Me_3Al complex (**H**). Then, RC ≡ CLi attacks the epoxide moiety of complex (**H**) at the less hindered site to give alkynylation complex (**I**). Further ligand exchange of (**I**) with alkynyllithium produces the end product **5** with regeneration of alkynylaluminate (**G**) for further use in the catalytic cycle of the alkynylation.

Scheme 5



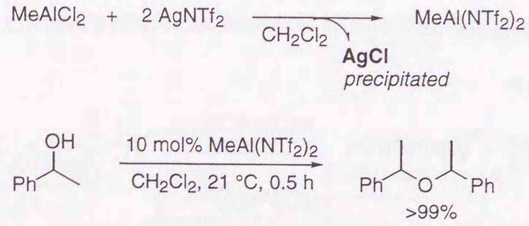
This catalytic system was successfully applicable to the alkynylation of tosyl aziridines with adjacent ether functionality as depicted in Scheme 6, which should provide a promising method for the synthesis of amino alcohols.

Scheme 6



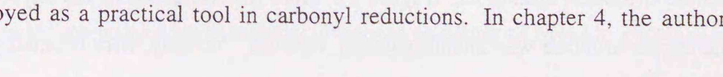
In chapter 3, the etherification reaction of benzyl alcohol and allylic alcohol using highly Lewis acidic $MeAl(NTf_2)_2$ as a catalyst is described. Although the long-established Williamson ether synthesis is probably the most common method for preparation of ethers,[11] the major drawback of this method has been viewed as its unsuitability for base sensitive molecules and the generation of stoichiometric amount of salts.[12,13] Although these problems seem to be overcome by a novel catalytic etherification recently developed by Strauss,[14] direct synthesis of ethers from alcohols through a dehydration process has also emerged as an attractive route for this purpose.[15,16] Kim and co-workers reported $ZnCl_2$-mediated etherification of alcohols, where, unfortunately, stoichiometric amount of Lewis acid ($ZnCl_2$) was necessary for the smooth reaction.[17,18] Taking the high oxygenophilicity into account, the author envisaged that the organoaluminum compounds could be utilized as a catalyst for the ether synthesis. $MeAl(NTf_2)_2$, newly designed in this context, possesses two, highly electronwithdrawing trifluoromethanesulfonyl group and is expected to exert prominent activation of hydroxy functionality. As shown in Scheme 7, treatment of *sec*-phenethyl alcohol with catalytic $MeAl(NTf_2)_2$ (10 mol%), prepared by simply mixing $AgNTf_2$ and $MeAlCl_2$ in a 2:1 molar ratio, in CH_2Cl_2 at 21 °C for 30 min gave rise to the corresponding symmetrical ether quantitatively.

Scheme 7



This method was found to be successfully applicable to the protection of alcohols as benzyl ethers as exemplified in Scheme 8.

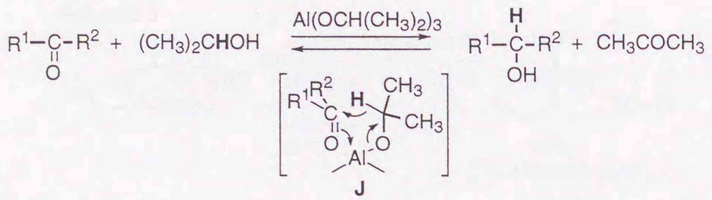
Scheme 8



The Meerwein-Ponndorf-Verley (MPV) reaction is the chemoselective reduction of various carbonyl substrates by using aluminum alkoxides, generally $Al(OPr^i)_3$ as catalyst and *i*-PrOH as hydride source. In this reduction, a hydride transfer from the alcoholate to a carbonyl acceptor reversibly via a six-membered transition state [**J**] is initiated by the activation of the carbonyl upon coordination to Lewis acidic aluminum. The advantage of the MPV reduction includes its chemoselectivity, mild reaction conditions, operational simplicity, safe handling, and ready adaptation both in the laboratory and on a large-scale. Nonetheless, there are several practical problems in the reduction such as need for excess of alcohol as hydride source, low reaction rate, formation of condensation products, and use of higher reaction temperature with concurrent removal of acetone to shift the equilibrated reaction towards the formation of alcohol.[19] Accordingly, various modifications of the MPV reduction have been developed in order to overcome these disadvantages. The recent improvements of the MPV reduction are the use of catalytic lanthanide alkoxides,[20] microwave irradiation,[19b] and the addition of CF_3CO_2H to $Al(OPr^i)_3$ to accelerate the reduction,[19c] though none of them can unfortunately be employed as a practical tool in carbonyl reductions. In chapter 4, the author presents

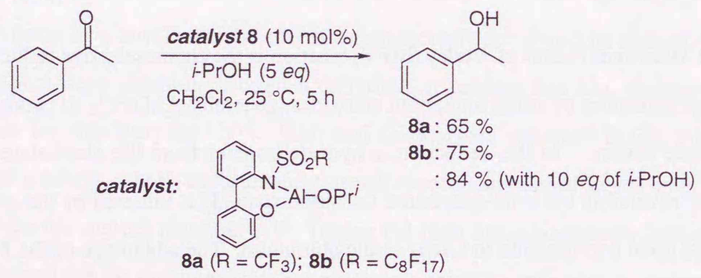
molecular design of new aluminum alkoxides to bring out the inherent potential in the MPV reduction for practical use.

Scheme 9



First, thorough examination of various aluminum ligands was conducted in the reduction of acetophenone as a model system and eventually found that the catalyst **8a** prepared from 2-hydroxy-2'-trifluoromethanesulfonylaminobiphenyl displayed high catalytic efficiency.

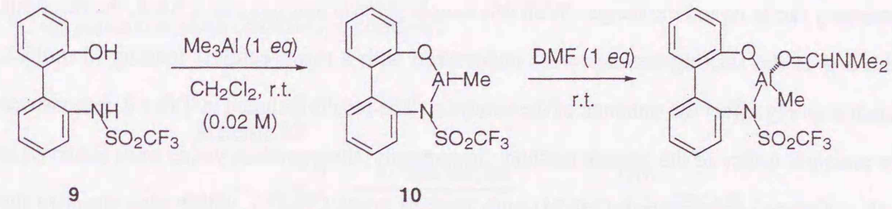
Scheme 10



Further, tuning of the perfluoroalkyl group of sulfonamide moiety afforded a beneficial effect on the catalyst reactivity. Thus, the reaction under the influence of the aluminum isopropoxide **8b** gave rise to *sec*-phenethyl alcohol in 75% yield and, eventually, the chemical yield of the alcohol was improved to 84% using 10 equiv of *i*-PrOH.

To gain information about the actual structure of the new aluminum catalyst, I prepared the complex of the catalyst precursor **9** with DMF as a model example, and the structure was determined by single-crystal X-ray diffraction analysis, revealing the dimeric structure with unique pentacoordinated aluminums (Figure 1). Here the formation of the expected seven-membered cyclic structure was unambiguously verified. Notably, trifluoromethyl moioety

was found to be located away from the aluminum center, suggesting that the introduction of perfluoroalkyl group essentially prvides the electronic effect rather than the steric one.



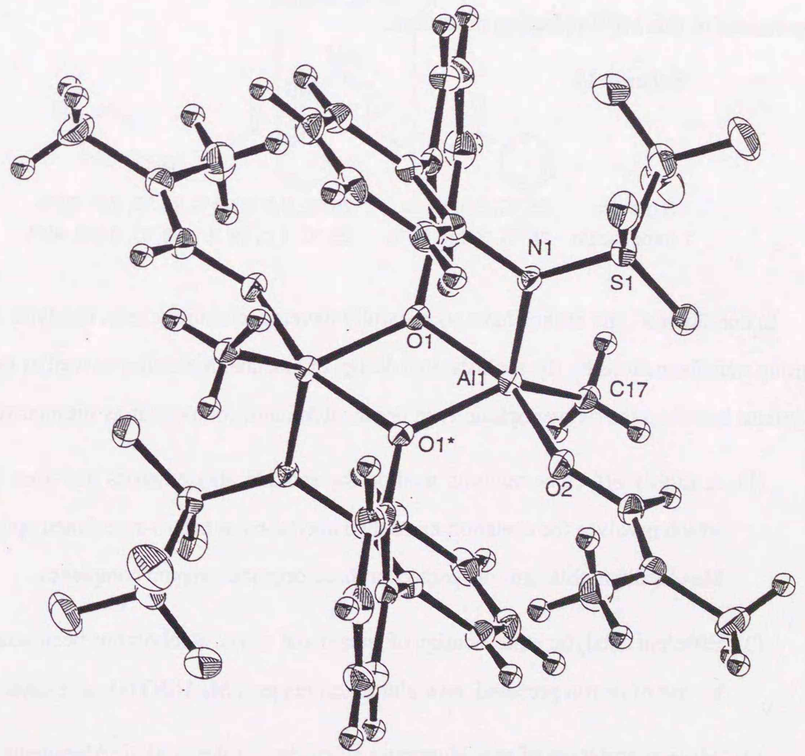
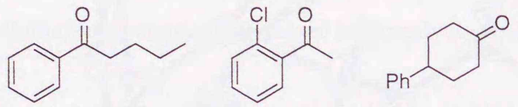


Figure 1. Structure of **4** /DMF complex (ORTEP representation).

Based on the results, we set out to conduct the scale-up experiments to illuminate the practical aspect of our approach, and first examined the possibility of using $Al(OPr^i)_3$ as an aluminum source to avoid the rather troublesome handling of Me_3Al. Fascinatingly, simple

mixing of 10 mol% each of commercially available $Al(OPr^i)_3$ and **2** in CH_2Cl_2 at room temperature and subsequent treatment with *i*-PrOH (10 equiv) and acetophenone at 25 °C for 5 h resulted in formation of *sec*-phenethyl alcohol in 82% yield, indicating the intervention of extremely facile ligand exchange. With this simple yet efficient process in hand, the reactions with 5 g of the starting ketones were undertaken with a lower catalyst loading (5 mol%), which scarcely affect the outcome of the catalysis. The results included in Table 2 demonstrate the potential utility of the present method. Importantly, these product yields were achieved at high substrate concentration (1.0 M) with reagent grade CH_2Cl_2, which also simplify the operations of this MPV reduction procedure.

Scheme 11



5 g scale	25 °C, 5 h: 82 %	25 °C, 3.5 h: 99 %	25 °C, 2 h: 99 %
1 mmol scale	25 °C, 3.5 h: 85 %	25 °C, 1 h: 99 %	25 °C, 0.5 h, 99%

In conclusion , the author have successfully developed entirely new, catalytic functional group transformations by the sophisticated design of essential molecules as well as the reaction systems based on the oxygenophilicity of organoaluminum compounds as summarized below.

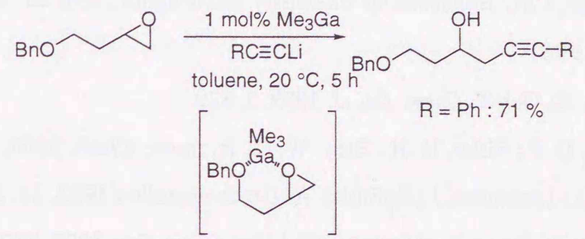
(1) A highly effective catalytic method for epoxide alkynylations has been developed which involves the chelation-controlled alkylation of hetero-substituted epoxides with Me_3Al/alkynyllithiums via pentacoordinate organoaluminum complexes.

(2) Efficient catalytic etherification of benzyl and allylic alcohols has been accomplished by use of *in situ* prepared, new aluminum reagent, $MeAl(NTf_2)_2$ as a catalyst.

(3) Molecular design of new aluminum alkoxides for the catalytic Meerwein-Ponndorf-Verley (MPV) reduction has been achieved, and various ketone substrates can be reduced efficiently at room temperature to give *secondary* alcohols in high yields. The practical aspect of the new procedure was emphasized by the fact that comparable reactivity was observed in the large-scale experiments with lower catalyst loading.

In appendix, amphiphilic alkylation of the epoxide using the trialkylgallium is described. Regio- and stereoselective ring-opening reaction of hetero-substituted epoxides with alkynyllithiums can be catalyzed by only 1 mol% of Me_3Ga with remarkable efficiency at 0~20 °C via pentacoordinate chelate-type complex.

Scheme 12



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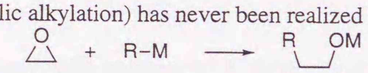
Chapter 2

Pentacoordinate Organoaluminum Chemistry: Catalytic Efficiency of Me_3Al in the Epoxide Cleavage with Alkynyllithiums

Abstract: A new and highly effective catalytic method for epoxide alkynylations has been developed which involves the chelation-controlled alkylation of hetero-substituted epoxides with Me_3Al via pentacoordinate organoaluminum complexes by taking advantage of the exceedingly high affinity of aluminum to oxygen. For example, reaction of epoxy ether, (1-benzyloxy)-3-butene oxide (**1**) in toluene with PhC ≡ CLi under the influence of catalytic Me_3Al (10 mol%) proceeded smoothly at 0 °C for 5 h to furnish the alkynylation product, 1-(benzyloxy)-6-phenylhex-5-yn-3-ol in 76% yield. [*cf.* 3% without Me_3Al catalyst; 78% with stoichiometric Me_3Al under similar conditions] This represents the first catalytic procedure for the amphiphilic alkylation of epoxides. The participation of pentacoordinate Me_3Al complexes of epoxy ethers of type **1** is emphasized by comparing the reactivity with the corresponding simple epoxide, 5-phenyl-1-pentene oxide, which was not susceptible to nucleophilic attack of PhC ≡ CLi with catalytic Me_3Al under similar conditions. The pentacoordinate complex formation of Me_3Al with the epoxy ether **1** is characterized by low-temperature ^{13}C and ^{27}Al NMR spectroscopy. This approach is also applicable to the selective alkynylation of tosyl aziridines with adjacent ether functionality, which provides a promising method for amino alcohol synthesis.

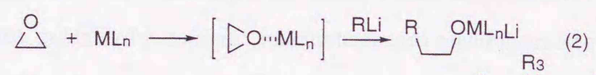
Introduction

The regioselective cleavage of epoxides with carbon nucleophiles is one of the most fundamental and yet important organic transformations, leading to a versatile method for the preparation of a variety of alcohols.[1] Among various organometallic reagents as carbon nucleophiles, organolithium reagents are sometimes curtailed owing to competing β-hydrogen abstractions arising from their Lewis basicity. Accordingly, these reagents are transformed to the corresponding diorganocuprates or organoaluminates to ensure a smooth epoxide opening (eq 1).[1,2] Recently, addition of $BF_3 \bullet OEt_2$ was reported to cause the enhancement of reactivity for the epoxide cleavage with organolithium reagents (eq 2).[3] However, this type of alkylation (*i.e.*, amphiphilic alkylation) has never been realized by combining use of highly oxygenophilic

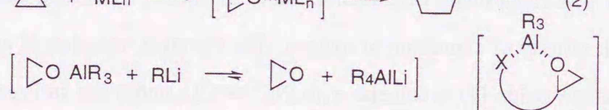


(1)

RM : R_4AlLi, R_2CuLi >> RLi



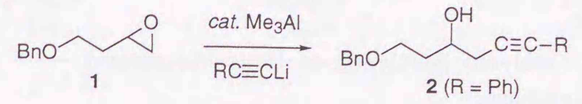
(2)



(**A**)

organoaluminum reagents with organolithiums because of the preferable formation of organoaluminate complexes.[2,4] In this context, we have been interested for some time in the possibility of forming chelation complexes (**A**) of organoaluminums with certain epoxy substrates possessing adjacent hetero-substituents preferentially rather than the ate complex formation with organolithiums. We wish to report that regio- and stereocontrolled alkynylation of such hetero-substituted epoxides with alkynyllithiums can be greatly accelerated under the influence of catalytic Me_3Al (Scheme I). This study offers the new mechanistic elucidation of the epoxide alkylation with tetraalkylaluminate complexes, which is essentially different from those of simple epoxides with aluminate complexes, and is ascribed to the intervention of unfamiliar pentacoordinate trialkylaluminum complexes (**A**) as a key intermediate.[5]

Scheme I



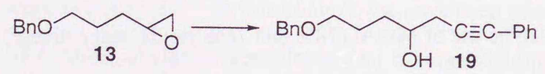
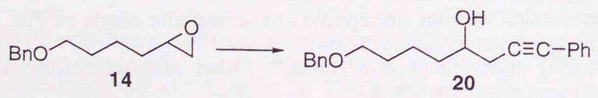
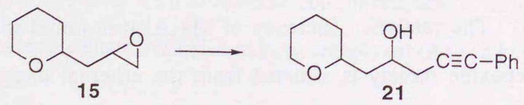
1 **2** (R = Ph)

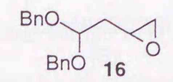
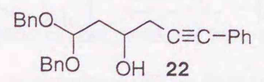
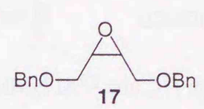
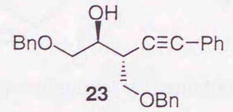
Results and Discussion

First, we chose (1-benzyloxy)-3-butene oxide (**1**) as a representative substrate for our study and examined its alkylation under various reaction conditions. Alkynylation of epoxy ether **1** in toluene with PhC ≡ CLi in ether proceeded quite reluctantly at 0 °C to furnish only a trace amount of alkynylation product, 1-(benzyloxy)-6-phenylhex-5-yn-3-ol (**2** (R = Ph)) after 5 h. Initial ate complex (PhC ≡ $CAlMe_3Li$) formation by mixing with PhC ≡ CLi and Me_3Al in ether/toluene (volume ratio, 1:1), and subsequent treatment with epoxy ether **1** under similar conditions afforded **2** in 19% yield.[4] In contrast, under the influence of catalytic Me_3Al (10 mol%) reaction of **1** with PhC ≡ CLi in ether/toluene was accelerated to furnish **2** in higher yield (51%) at 0 °C for 5 h, indicating that the catalytic use of Me_3Al is indispensable in obtaining satisfactory results under these conditions. Although ether is commonly used for this type of epoxide alkylation with organoaluminates, we assumed that its property as donor solvent retards the alkylation, particularly in the presence of stoichiometric Me_3Al. Indeed, by switching ether/toluene solvents to toluene alone, the yields of **2** were found to be comparable with the stoichiometric or catalytic use of Me_3Al (78% and 76% yields, respectively) as shown in Table I (entry 2); this implies the involvement of the same mechanistic pathway in both the catalytic and stoichiometric systems in non-polar solvents. It should be added that a simple epoxide, 5-phenyl-1-pentene oxide was not susceptible to nucleophilic attack of PhC ≡ CLi with Me_3Al (10~100 mol%) under these conditions.[6] Other alkynyllithiums such as Me_3SiC ≡ CLi work equally well with Me_3Al catalyst (entries 4 and 8).[7] However, the present system did not seem to appreciate the use of aryllithiums and alkyllithiums as nucleophile (entries 5 and 6). The catalytic efficiency of Me_3Al was found to be highly dependent on how far the epoxide moiety is situated from the ethereal oxygen, which consequently manifests the importance of the proposed pentacoordinate chelate formation to attain sufficient level of reactivity (entries 9 and 10). In addition to epoxy ether substrates,

epoxy acetal is also employable and alkynylation of disubstituted epoxide appears feasible (entries 12 and 13).

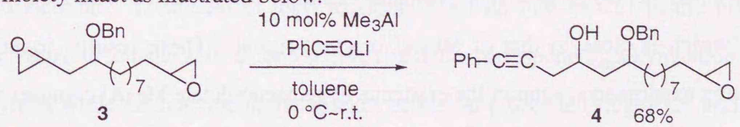
Table I. Me_3Al-Catalyzed Alkylation of Hetero-Substituted Epoxides with Alkyllithiums [a]

entry	alkyllithium (R'Li)	condition (°C, h)	yield, % [b]
	 **1**		
1	PhC ≡ CLi	-78, 0.1; 0, 5	51 [c] (<1) [c d]
2	PhC ≡ CLi	-78, 0.1; 0, 5	76, 78 [e]
3	PhC ≡ CLi	-78, 0.1; 0, 5	70 [f] (3) [d]
4	$Me_3SiC \equiv CLi$	-78, 0.1; 25, 5	73 (7) [d]
5	PhLi	-78, 0.1; 0, 5	59 (37) [d]
6	BuLi	-78, 0.1; 0, 5	30 (6) [d]
	 **12**		
7	PhC ≡ CLi	-78, 0.1; 0, 5	76
8	$Me_3SiC \equiv CLi$	-78, 0.1; 0, 5	71, 45 [e g]
	 **13**		
9	PhC ≡ CLi	-78, 0.1; 0, 5	28
	 **14** **20**		
10	PhC ≡ CLi	-78, 0.1; 0, 5	4
	 **15** **21**		
11	PhC ≡ CLi	-78, 0.1; 0, 5	64

entry	alkyllithium (R'Li)	condition (°C, h)	yield, % [b]
	 **16**  **22**		
12	PhC ≡ CLi	0, 3; 25, 12	57
	 **17**  **23**		
13	PhC ≡ CLi	-78, 0.1; 25, 5	55 [h]

[a] Unless otherwise specified, the reaction was carried out with 1.1 equiv of alkyllithium in distilled toluene under the given reaction conditions in the presence of 10 mol% of Me_3Al. [b] Isolated yield. [c] Use of ether/toluene (vol. ratio, 1:1) as solvent. [d] Isolated yield in parenthesis refers to the reaction without Me_3Al catalyst. [e] Stoichiometric use of Me_3Al. [f] Use of 5 mol% of Me_3Al. [g] Significant amount of methylation product was contaminated. [h] 20 mol% Me_3Al was used.

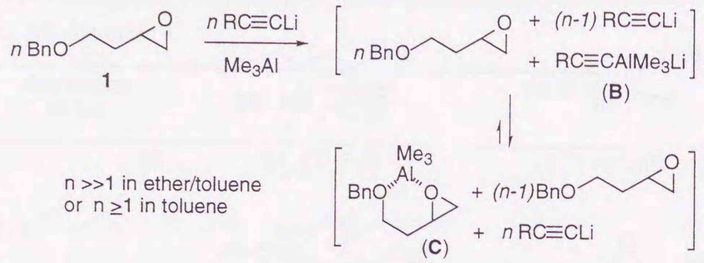
The present approach has been quite useful in the selective functionalization of bisepoxide of type **3**. Indeed, reaction of **3** with PhC ≡ CLi in toluene can be catalyzed by 10 mol% of Me_3Al to afford monoalkynylation product **4** in 68% yield, leaving the remote epoxide moiety intact as illustrated below.



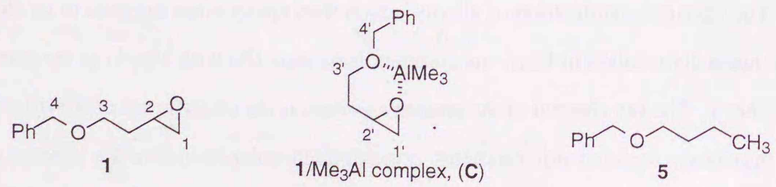
3 **4** 68%

The stronger coordination of alkynyl anion than epoxy ether oxygens to an aluminum reagent normally resulted in facile ate complex formation (**B**) with Me_3Al in the presence of epoxy ether **1**. The key element of the present approach is the catalytic use of Me_3Al compared to the previously reported stoichiometric conditions in order to induce the ligand exchange between alkynyllithium and epoxy ether **1** possessing the chelating ability, thereby allowing the favorable formation of epoxy ether **1**/Me_3Al complex (**C**) in the presence of excess epoxy ether

substrate **1** to Me_3Al (n >> 1). Such chelation complex (**C**) is also conceivable even with the stoichiometric use (n = 1) of PhC ≡ CLi and Me_3Al in the non-polar toluene solvent.



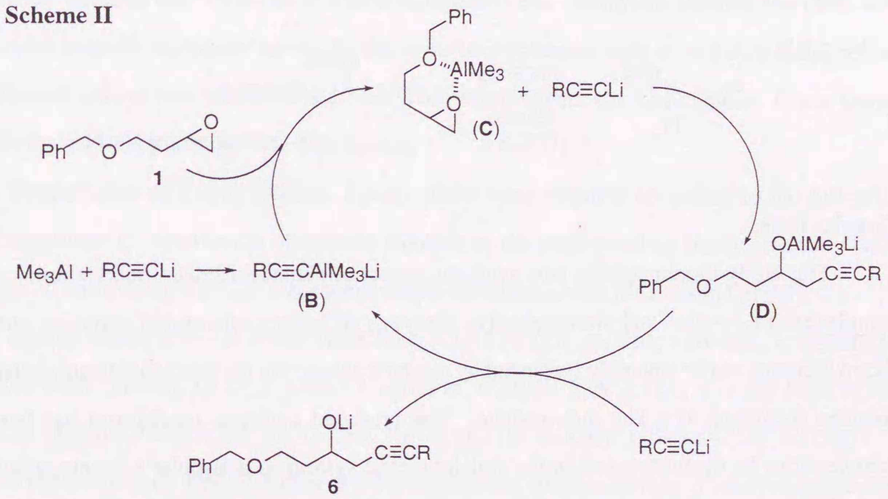
Additional evidence was obtained by taking low-temperature ^{13}C and ^{27}Al NMR studies of these aluminum complexes. The original signals of acyclic carbons C-1~C-4 in epoxy ether **1** occurred at δ 46.50, 49.57, 67.30 and 73.13, respectively. When **1** was complexed with Me_3Al in a 1:1 molar ratio in toluene-d_8 at -50 °C, both a significant downfield shift of epoxide carbons and slight upfield shift of ethereal carbons, C-1'~C-4' in structure (**C**) were observed at δ 53.33, 58.74, and 65.33, 73.04, respectively, by ^{13}C NMR analysis at -50 °C; this suggested the expected chelate formation of aluminum with epoxy ether **1**.[8] In addition to these ^{13}C NMR data, we also carried out the low temperature ^{27}Al NMR analysis of the complex (**C**). The original signal of Me_3Al appeared at δ 153 in CH_2Cl_2 at -50 °C. Addition of epoxy ether **1** to Me_3Al in CH_2Cl_2 showed the Al signal at δ 78, while the coordination of simple epoxide, 5-phenyl-1-pentene oxide to Me_3Al caused a downfield shift to δ 167.[5] It should be noted that the Al peak of the complex of simple benzyl ether **5** with Me_3Al appeared at δ 155 which is close to that of Me_3Al original signal. These results, together with alkynylation experiments, support the existence of pentacoordinate Me_3Al complex as shown in (**C**).[9]



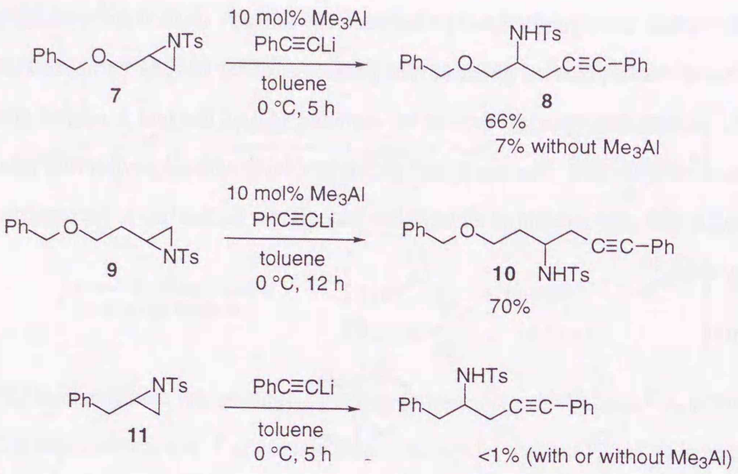
With this experimental and NMR information at hand, the present Me_3Al-catalyzed alkynylation of hetero-substituted epoxides can be interpreted by a mechanism as shown in

Scheme II. Thus, the ligand exchange between the initially formed RC ≡ $CAlMe_3Li$ and epoxy ether **1** takes place to generate the pentacoordinate Me_3Al complex (**C**). Then, RC ≡ CLi attacks the epoxide moiety of complex (**C**) at the less hindered site to give alkynylation complex (**D**). Further ligand exchange of (**D**) with alkynyllithium produces the end product **6** with regeneration of alkynylaluminate (**B**) for further use in the catalytic cycle of the alkynylation.[10]

Scheme II



Our catalytic system was successfully applicable to the alkynylation of tosyl aziridines with adjacent ether functionality,[11] which should provide a promising method for the synthesis of amino alcohols. Treatment of tosyl aziridine **7**[12] with PhC ≡ CLi in the presence of catalytic Me_3Al in toluene at 0 °C for 5 h gave rise to the corresponding alkynylation product **8** in 66% yield, while the reaction in the absence of Me_3Al proceeded sluggishly under similar reaction conditions (7% yield). The reaction of one carbon homologated tosyl aziridine **9**[12] with PhC ≡ CLi worked equally well under the influence of catalytic Me_3Al to furnish the homopropargyl tosylamide **10**. The control experiment with simple aziridine **11**,[12] where the addition of catalytic Me_3Al had almost no influence on the reaction rate, supports the proposed catalytic cycle and its efficacy is based on the formation of the pentacoordinate organoaluminum complex.



Conclusions

This study illuminates the new synthetic aspect of pentacoordinate trialkylaluminum complexes; *i.e.*, regio- and stereoselective cleavage of hetero-substituted epoxides with alkynyllithiums can be smoothly facilitated by catalytic Me_3Al via the pentacoordinate chelate complex formation as a key intermediate. The proposed catalytic mechanism has been considered to be operative even in the stoichiometric system in non-polar solvents, which therefore provides new machanistic elucidation of the epoxide alkylation with tetraalkylaluminate complexes.

Experimental Section

General. Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8100A spectrometer. ^1H, ^{13}C and ^{27}Al NMR spectra were measured on a Varian Gemini-300 (300 MHz) and Bruker MSL-400 (400 MHz) spectrometers. Analytical gas-liquid phase chromatography-mass spectrometer (GC-MS) was performed on Shimadzu GC-17A instruments equipped with a EI-detector and a capillary column of DB-1 (J&W SCIENTIFIC, 0.25 X 30,000 mm) using helium as carrier gas, and GCMS-QP5000. All experiments were carried out under an atmosphere of dry argon. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were

purified by preparative column chromatography on silica gel (E. Merck 9385). Microanalyses were accomplished at the Center for Instrumental Analysis, Hokkaido University. The high-resolution mass spectra (HRMS) were conducted at the School of Agriculture, Hokkaido University.

In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Kanto Chemical Co., Ltd. as "Dehydrated". Toluene was freshly distilled from sodium metal. Benzene and hexane were dried over sodium metal. Methylene chloride and DMF were stored over 4Å molecular sieves. Pyridine and triethylamine were stored over KOH pellets. Trimethylaluminum was obtained from Toso-Akzo Chem. Co. Ltd., Japan. Other simple chemicals were purchased and used as such.

Preparation of Epoxy Ethers. Epoxy ethers were prepared according to the following procedures: (1) conversion of olefinic alcohols to the corresponding benzy ethers by NaH, benzyl bromide in THF; (2) subsequent simple epoxidation with MCPBA in CH_2Cl_2.

Epoxy Ether 1:[13] ^1H NMR ($CDCl_3$) δ 7.27-7.36 (5H, m, Ph), 4.54 (2H, s, $PhCH_2O$), 3.60-3.66 (2H, m, OCH_2), 3.05-3.12 (1H, m, CCHO), 2.79 (1H, t, J = 4.8 Hz, O-CH), 2.53 (1H, dd, J = 2.7, 4.8 Hz, O-CH), 1.87-1.96 (1H, m, CH), 1.75-1.84 (1H, m, CH).

Preparation of Epoxy Ether 3. To an ethereal solution (50 mL) of allylmagnesium bromide (24 mmol) was added 10-undecenal (3.96 mL, 20 mmol) dropwise at -78 °C under argon. The resulting mixture was stirred at -78 °C for 30 min and at 0 °C for additional 30 min. The solution was quenched with saturated NH_4Cl and extracted with ether. The organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (EtOAc/hexane = 1:9 as eluant) gave 1,13-tetradecadien-4-ol (3.54 g, 17 mmol, 84% yield) as a colorless oil: ^1H NMR ($CDCl_3$) δ 5.75-5.90 (2H, m, 2(CH=C)), 4.89-5.17 (4H, m, 2(C=CH_2)), 3.64 (1H, brs, C<u>H</u>OH), 2.30 (1H, ddd, J = 4.8, 6.0, 12.6 Hz, CH), 2.14 (1H, dt, J = 8.1, 13.8 Hz, CH), 2.04 (2H, q, J = 6.9 Hz, CH_2), 1.61 (1H, s, OH), 1.15-1.55 (14H, m, 7CH_2).

After conversion to the benzyl ether with NaH and benzyl bromide in DMF at room temperature, usual epoxidation with MCPBA afforded epoxy ether **3** as a diastereomeric mixture in 28% overall yield: ^1H NMR ($CDCl_3$) δ 7.24-7.40 (5H, m, Ph), 4.46-4.63 (2H, m,

$PhCH_2$), 3.52-3.69 (1H, m, CHOBn), 3.00-3.13 (1H, m, CCH-O), 2.88-2.94 (1H, m, CCH-O), 2.72-2.84 (2H, m, CH-O), 2.42-2.52 (2H, m, CH-O), 1.20-1.88 (18H, m, $9CH_2$); IR (liquid film) 3042, 2930, 2856, 1497, 1456, 1352, 1259, 1094, 1069, 1028, 916, 833, 737, 698 cm^{-1}. MS: *m/z* 332 (M^+), 315, 281, 207, 177, 91 (100%). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.59; H, 9.70.

Epoxy Ether 12:[14] ^1H NMR ($CDCl_3$) δ 7.28-7.37 (5H, m, Ph), 4.63 (1H, d, *J* = 12.0 Hz, PhCHO), 4.56 (1H, d, *J* = 12.0 Hz, PhCHO), 3.78 (1H, dd, *J* = 3.0, 11.4 Hz, O-CH), 3.44 (1H, dd, *J* = 5.7, 11.4 Hz, O-CH), 3.17-3.22 (1H, m, CCHO), 2.81 (1H, dd, *J* = 3.9, 4.8 Hz, O-CH), 2.63 (1H, dd, *J* = 2.4, 4.8 Hz, O-CH).

Epoxy Ether 13:[15] ^1H NMR ($CDCl_3$) δ 7.19-7.41 (5H, m, Ph), 4.51 (2H, s, $PhCH_2$), 3.44-3.58 (2H, m, CH_2), 2.89-2.97 (1H, m, CH-O), 2.74 (1H, dd, *J* = 3.9, 5.1 Hz, O-CH), 2.47 (1H, dd, *J* = 2.7, 5.1 Hz, O-CH), 1.52-1.86 (4H, m, $2CH_2$).

Epoxy Ether 14:[16] ^1H NMR ($CDCl_3$) δ 7.23-7.42 (5H, m, Ph), 4.50 (2H, s, $PhCH_2$), 3.49 (2H, t, *J* = 6.3 Hz, CH_2), 2.86-2.94 (1H, m, CH-O), 2.74 (1H, dd, *J* = 4.2, 5.1 Hz, O-CH), 2.46 (1H, dd, *J* = 2.7, 5.1 Hz, O-CH), 1.45-1.75 (6H, m, $3CH_2$).

Preparation of Epoxy Ether 15.[17] To a mixture of Me_3SiOTf (159 μL, 0.8 mmol) and allyltrimethylsilane (1.41 mL, 8.8 mmol) in dry CH_2Cl_2 (25 mL) was added dropwise 2-methoxytetrahydropyrane (985 μL, 8 mmol) at -40 °C under argon. The resulting mixture was kept at -40 °C for 4 h and 0 °C for 2.5 h with stirring, and then poured into saturated $NaHCO_3$. The extractive workup was performed with ether. The ethereal extracts were washed with brine, dried over Na_2SO_4 and concentrated. Purification of the residual oil by column chromatography on silica gel (ether/hexane = 1:20 as eluant) gave 2-(2-propenyl)tetrahydropyrane (541 mg, 4.3 mmol, 54% yield). Subsequent exposure to usual epoxidation conditions afforded epoxide **15** in 54% yield. ^1H NMR ($CDCl_3$) δ 3.96-4.01 (1H, m, O-CH), 3.40-3.56 (2H, m, O-CH_2), 3.03-3.12 (1H, m, CCH-O), 2.75-2.82 (1H, m, O-CH), 2.48-2.51 (1H, m, O-CH), 1.74-1.87 (2H, m, CH_2), 1.26-1.67 (6H, m, $3CH_2$).

Preparation of Epoxy Acetal 16. A mixture of 3-butenal diethylacetal (175 μL, 1 mmol), benzyl alcohol (310 μL, 3 mmol) and pyridinium *p*-toluenesulfonate (catalytic amount) in benzene was refluxed for 4.5 h with azeotropic removal of ethanol. The resulting solution

was cooled down to room temperature and solvents were evaporated. Purification of the rediual products by column chromatography on silica gel (EtOAc/hexane = 1:20 as eluant) gave 3-butenal dibenzylacetal (187 mg, 0.698 mmol, 70% yield). Simple epoxidation of the acetal with MCPBA afforded epoxy acetal **16** in 55% yield. ^1H NMR ($CDCl_3$) δ 7.26-7.37 (10H, m, 2Ph), 4.97 (1H, dd, *J* = 4.8, 6.6 Hz, $CH(OBn)_2$), 4.57-4.75 (4H, m, $2PhCH_2$), 3.04-3.10 (1H, m, CCH-O), 2.78 (1H, t, *J* = 4.5 Hz, O-CH), 2.51 (1H, dd, *J* = 2.7, 4.8 Hz, O-CH), 2.06 (1H, ddd, *J* = 4.5, 6.6, 14.1 Hz, CH), 1.91 (1H, ddd, *J* = 4.8, 6.6, 14.1 Hz, CH); IR (liquid film) 3063, 3032, 2926, 2834, 1497, 1454, 1350, 1223, 1080, 1049, 1026, 850, 737, 698 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.83; H, 7.10.

Epoxy Ether 17:[18] ^1H NMR ($CDCl_3$) δ 7.25-7.35 (10H, m, 2Ph), 4.62 (2H, d, *J* = 12.0 Hz, PhCHO), 4.51 (2H, d, *J* = 12.0 Hz, PhCHO), 3.69 (2H, dd, *J* = 3.6, 11.4 Hz, BnO-CH), 3.53 (2H, dd, *J* = 6.3, 11.4 Hz, BnO-CH), 3.24-3.29 (2H, m, 2(CH-O)).

Tosyl Aziridine 7:[12] ^1H NMR ($CDCl_3$) δ 7.85 (2H, d, *J* = 8 Hz, Ph), 7.27-7.34 (5H, m, Ph), 7.19-7.22 (2H, m, Ph), 4.43 (2H, s, $PhCH_2O$), 3.62 (1H, dd, *J* = 4.2, 11.4 Hz, OCH), 3.42 (1H, dd, *J* = 6.3, 11.4 Hz, OCH), 2.99-3.07 (1H, m, CH-N), 2.68 (1H, d, *J* = 7.2 Hz, N-CH), 2.43 (3H, s, $ArCH_3$), 2.20 (1H, d, *J* = 4.5 Hz, N-CH); IR (liquid film) 3011, 2926, 2866, 1599, 1497, 1454, 1326, 1160, 1097, 924, 870, 816 cm^{-1}. MS: *m/z* 317 (M^+), 212, 211, 162, 155, 147, 120, 91 (100%), 65, 56. HRMS Calcd for $C_{17}H_{19}NO_3S$: 317.1087 (M^+). Found: 317.1106 (M^+).

Preparation of Tosyl Aziridine 9:[12] To a solution of epoxide **1** (1.41 g, 7.9 mmol) in 10% H_2O-EtOH (30 mL) was added NH_4Cl (854 g, 15.8 mmol) and NaN_3 (2.62 g, 39.5 mmol) at room temperature. The reaction mixture was heated and refluxed for 1 h. The resulting solution was poured into saturated NH_4Cl and extracted with ether. The ethereal extracts were dried over Na_2SO_4 and concentrated. Purification of the residual oil by column chromatography on silica gel (EtOAc/hexane = 1:4 as eluant) gave the corresponding azide (1.61 g, 7.9 mmol) quantitatively as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.27-7.39 (5H, m, Ph), 4.52 (2H, s, $PhCH_2$), 3.94-4.07 (1H, m, C<u>H</u>OH), 3.59-3.77 (2H, m, CH_2OBn), 3.22-3.35 (2H, m, CH_2N_3), 3.16 (1H, s, OH), 1.67-1.91 (2H, m, CH_2).

$LiAlH_4$ (293 mg, 7.1 mmol) was added portionwise to a solution of the azide (1.61 g, 7.3 mmol) in ether (15 mL) at 0 °C under argon and the mixture was stirred there for 1 h. After the addition of H_2O (430 μL, 23.7 mmol) and NaF (1.33 g, 31.6 mmol), vigorous stirring was maintained at 0 °C for 30 min. The resulting mixture was filtered through celite pad and the filtrate was concentrated to give crude amino alcohol as a colorless oil (984 mg, 5.0 mmol) in 69% yield: ^{1}H NMR ($CDCl_3$) δ 7.25-7.40 (5H, m, Ph), 4.52 (2H, s, $PhCH_2$), 3.67 (2H, q, J = 6.0 Hz, CH_2OBn), 3.60-3.77 (1H, m, C<u>H</u>OH), 2.77 (1H, dd, J = 3.6, 12.6 Hz, CH-N), 2.60 (1H, dd, J = 7.8, 12.6 Hz, CH-N), 2.45 (3H, brs, OH and NH_2), 1.70-1.78 (2H, m, CH_2).

The crude amino alcohol (983 mg, 5.0 mmol) obtained above was dissolved into pyridine (10 mL) and tosyl chloride (1.43 g, 7.5 mmol) was added at 0 °C under argon. The reaction mixture was stirred at room temperature for 7 h. This was then poured into saturated $NaHCO_3$ and extracted with ether. The organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification by column chromatography on silica gel (EtOAc/hexane = 1:1 as eluant) afforded hydroxy tosylamide as an orange crystal (1.26 g, 3.6 mmol) in 72% yield: ^{1}H NMR ($CDCl_3$) δ 7.72 (2H, d, J = 8.4 Hz, Ts), 7.26-7.37 (9H, m, Ts and Ph), 5.14 (1H, t, J = 6.6 Hz, NH), 4.48 (2H, s, $PhCH_2$), 3.85-3.96 (1H, m, C<u>H</u>OH), 3.55-3.72 (2H, m, CH_2OBn), 3.34 (1H, s, OH), 2.98-3.11 (1H, m, CH-N), 2.80-2.91 (1H, m, CH-N), 2.41 (3H, s, $ArCH_3$), 1.63-1.87 (2H, m, CH_2).

To a solution of the tosylamide (990 mg, 2.8 mmol) in THF (14 mL) was added a 1.59 M hexane solution of BuLi (3.56 mL, 5.66 mmol) at 0 °C followed by the addition of tosyl chloride (648 mg, 3.40 mmol). The mixture was then allowed to warm to room temperature and stirred there for 1 h. The solution was poured into water and extracted with ether. The ethereal extracts were dried over Na_2SO_4 and concentrated. The residual oil was purified by column chromatography on silica gel (ether/hexane/dichloromethane = 1:8:8 as eluant) to give the desired tosyl aziridine **9** as a colorless oil (728 mg, 2.2 mmol) in 78% yield: ^{1}H NMR ($CDCl_3$) δ 7.82 (2H, d, J = 8.7 Hz, Ts), 7.19-7.41 (7H, m, Ts and Ph), 4.37 (2H, s, $PhCH_2$), 3.41-3.48 (1H, m, CHOBn), 3.29-3.66 (1H, m, CHOBn), 2.87-2.95 (1H, m, CH-N), 2.68 (1H, d, J = 6.9 Hz, N-CH), 2.44 (3H, s, $ArCH_3$), 2.13 (1H, d, J = 4.5 Hz, N-CH),

1.87-1.98 (1H, m, CH), 1.51-1.62 (1H, m, CH). IR (liquid film) 3030, 2924, 2864, 1597, 1454, 1325, 1163, 1096, 930, 818, 716, 698 cm^{-1}. MS: *m/z* 331 (M^+), 305, 281, 184, 44 (100%). Anal. Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.05; H, 6.43; N, 4.16.

General Method for Me_3Al-Catalyzed Cleavage of Epoxide with Alkynyllithiums. To a solution of phenylacetylene (54 μL, 0.48 mmol) in toluene (4 mL) was added a 1.56 M hexane solution of BuLi (282 μL, 0.44 mmol) dropwise at 0 °C under argon. The suspension was stirred for 30 min and then cooled to -78 °C. Epoxy ether (0.4 mmol) was added dropwise followed by the addition of a 0.5 M hexane solution of Me_3Al (80 μL, 0.04 mmol) at the same temperature. The resulting mixture was allowed to warm to 0 °C and stirred there for 5 h. The solution was then poured into 1 *N* HCl and extractive workup was performed with ether. The combined organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane as eluant) gave the corresponding homopropargyl alcohol.

Homopropargyl Alcohol 2 (R = Ph): ^{1}H NMR ($CDCl_3$) δ 7.25-7.41 (10H, m, 2Ph), 4.54 (2H, s, $PhCH_2O$), 4.01-4.11 (1H, m, C<u>H</u>OH), 3.66-3.81 (2H, m, OCH_2), 3.10 (1H, d, J = 3.6 Hz, OH), 2.67 (1H, dd, J = 6.0, 16.8 Hz, CHC ≡ C), 2.60 (1H, dd, J = 6.3, 16.8 Hz, CHC ≡ C), 1.85-2.05 (2H, m, CH_2); IR (liquid film) 3451, 3032, 2920, 2884, 1491, 1454, 1364, 1099, 1028, 756, 692 cm^{-1}. Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.41; H, 7.25.

Homopropargyl Alcohol 2 (R = $SiMe_3$): ^{1}H NMR ($CDCl_3$) δ 7.29-7.38 (5H, m, Ph), 4.53 (2H, s, $PhCH_2O$), 3.92-4.02 (1H, m, C<u>H</u>OH), 3.63-3.78 (2H, m, OCH_2), 3.01 (1H, d, J = 3.6 Hz, OH), 2.48 (1H, dd, J = 6.0, 16.8 Hz, CHC ≡ C), 2.41 (1H, dd, J = 6.3, 16.8 Hz, CHC ≡ C), 1.77-1.97 (2H, m, CH_2), 0.15 (9H, s, $3CH_3$); IR (liquid film) 3443, 3032, 2959, 2862, 2176, 1454, 1420, 1364, 1250, 1099, 1030, 843, 760, 698, 648 cm^{-1}. Anal. Calcd for $C_{16}H_{24}O_2Si$: C, 69.51; H, 8.75. Found: C, 69.71; H, 8.85.

Homopropargyl Alcohol 4: ^{1}H NMR ($CDCl_3$) δ 7.26-7.42 (10H, m, 2Ph), 4.44-4.67 (2H, m, $PhCH_2$), 4.05-4.09 (0.2H, m, C<u>H</u>OH), 3.90-4.03 (0.8H, m, C<u>H</u>OH), 3.64-3.81

(1H, m, CHOBn), 3.71 (1H, s, OH), 3.08-3.11 (0.2H, m, CCHO), 2.87-2.92 (0.8H, m, CCHO), 2.72-2.76 (0.8H, m, CH-O), 2.63-2.68 (0.2H, m, CH-O), 2.44-2.63 (3H, m, $CH_2C \equiv C$ and CH-O), 2.46 (1H, dd, J = 2.4, 2.7 Hz, CH-O), 1.20-1.95 (18H, m, $9CH_2$); IR (liquid film) 3489, 3034, 2930, 2856, 1491, 1456, 1094, 1074, 1028, 758, 694 cm^{-1}. MS: *m/z* 434 (M^+), 391, 369, 301, 43 (100%). Anal. Calcd for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81. Found: C, 79.88; H, 8.92. After debenzylation, the diol can be converted to its acetonide, which confirms the regiochemistry of the selective alkynylation.

Homopropargyl Alcohol 18 (R' = C ≡ CPh): ^1H NMR ($CDCl_3$) δ 7.26-7.40 (10H, m, 2Ph), 4.60 (2H, s, $PhCH_2O$), 4.01-4.10 (1H, m, C<u>H</u>OH), 3.69 (1H, dd, J = 3.9, 9.6 Hz, OCH), 3.58 (1H, dd, J = 6.6, 9.6 Hz, OCH), 2.72 (1H, dd, J = 6.3, 16.8 Hz, CHC ≡ C), 2.66 (1H, dd, J = 6.6, 16.8 Hz, CHC ≡ C), 2.48 (1H, d, J = 4.8 Hz, OH); IR (liquid film) 3433, 3063, 3032, 2910, 2804, 1599, 1491, 1454, 1117, 1028, 756, 692 cm^{-1}. Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.21; H, 6.91.

Homopropargyl Alcohol 18 (R' = C ≡ CSiMe$_3$): ^1H NMR ($CDCl_3$) δ 7.27-7.42 (5H, m, Ph), 4.58 (2H, s, $PhCH_2O$), 3.92-4.00 (1H, m, C<u>H</u>OH), 3.61 (1H, dd, J = 3.9, 9.6 Hz, OCH), 3.50 (1H, dd, J = 6.6, 9.6 Hz, OCH), 2.53 (1H, dd, J = 6.0, 16.8 Hz, CHC ≡ C), 2.46 (1H, dd, J = 6.6, 16.8 Hz, CHC ≡ C), 2.39 (1H, d, J = 4.8 Hz, OH), 0.14 (9H, s, $3CH_3$); IR (liquid film) 3443, 2959, 2901, 2864, 2176, 1454, 1250, 1117, 1030, 843, 760, 698 cm^{-1}. Anal. Calcd for $C_{15}H_{22}OSi$: C, 68.65; H, 8.45. Found: C, 68.62; H, 8.40.

Homopropargyl Alcohol 19: ^1H NMR ($CDCl_3$) δ 7.24-7.44 (5H, m, Ph), 4.53 (2H, s, $PhCH_2$), 3.80-3.90 (1H, m, C<u>H</u>OH), 3.52-3.56 (2H, m, CH_2OBn), 2.76 (1H, brs, OH), 2.61 (2H, dd, J = 1.2, 3.0 Hz, $CH_2C \equiv C$), 1.74-1.86 (2H, m, CH_2), 1.60-1.70 (2H, m, CH_2); IR (liquid film) 3416, 3063, 3030, 2922, 2860, 2363, 1599, 1491, 1454, 1364, 1097, 1072, 1028, 758, 737, 694 cm^{-1}. MS: *m/z* 294 (M^+), 276, 257, 247, 233, 220, 91 (100%). Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.41; H, 7.69.

Homopropargyl Alcohol 20: ^1H NMR ($CDCl_3$) δ 7.24-7.45 (5H, m, Ph), 4.51 (2H, s, $PhCH_2$), 3.80-3.86 (1H, m, C<u>H</u>OH), 3.50 (2H, t, J = 6.3 Hz, OCH_2), 2.65 (1H, dd, J = 5.0, 16.8 Hz, CHC ≡ C), 2.55 (1H, dd, J = 6.8, 16.8 Hz, CHC ≡ C), 2.02 (1H, brs, OH),

1.55-1.70 (4H, m, $2CH_2$); IR (liquid film) 3417, 3063, 3030, 2937, 2862, 1599, 1491, 1454, 1362, 1101, 1028, 758, 737, 694 cm^{-1}. MS: *m/z* 308 (M^+), 290, 261, 247, 231, 205, 91 (100%). Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.77; H, 7.94.

Homopropargyl Alcohol 21: The complete structural assignment has been performed after conversion to the corresponding acetate. ^1H NMR ($CDCl_3$) δ 7.38-7.42 (2H, m, Ph), 7.27-7.30 (3H, m, Ph), 5.16-5.25 (1H, m, CH-OAc), 3.92-3.98 (1H, m, CH-O), 3.32-3.43 (2H, m, $O\text{-}CH_2$), 2.63-2.83 (2H, m, $CH_2\text{-}C \equiv C$), 2.08 and 2.09 (3H, s, $COCH_3$), 1.78-2.00 (3H, m, CH_2 and CH), 1.46-1.67 (4H, m, $2CH_2$), 1.26-1.35 (1H, m, CH); IR (liquid film) 2936, 2847, 1732, 1491, 1441, 1373, 1244, 1092, 1047, 1030, 758, 692 cm^{-1}. Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.04; H, 7.77.

Homopropargyl Alcohol 22: ^1H NMR ($CDCl_3$) δ 7.26-7.41 (15H, m, 3Ph), 5.02 (1H, t, J = 5.4 Hz, $CH(OBn)_2$), 4.74 (1H, d, J = 11.7 Hz, PhCH), 4.72 (1H, d, J = 11.7 Hz, PhCH), 4.62 (1H, d, J = 11.7 Hz, PhCH), 4.60 (1H, d, J = 11.7 Hz, PhCH), 4.04-4.13 (1H, m, C<u>H</u>OH), 3.00 (1H, d, J = 3.3 Hz, OH), 2.65 (1H, dd, J = 5.4, 16.5 Hz, CHC ≡ C), 2.58 (1H, dd, J = 6.6, 16.5 Hz, CHC ≡ C), 2.16 (1H, ddd, J = 2.7, 5.4, 14.1 Hz, CH), 2.03 (1H, ddd, J = 5.4, 9.3, 14.1 Hz, CH); IR (liquid film) 3446, 3032, 2929, 1491, 1456, 1207, 1126, 1057, 1026, 756, 737, 695 cm^{-1}. Anal. Calcd for $C_{26}H_{26}O_3$: C, 80.80; H, 6.78. Found: C, 80.75; H, 6.92.

Homopropargyl Alcohol 23: ^1H NMR ($CDCl_3$) δ 7.29-7.39 (15H, m, 3Ph), 4.54-4.64 (4H, m, $2PhCH_2O$), 4.16 (1H, dq, J = 3.0, 6.0 Hz, C<u>H</u>-OH), 3.83 (1H, dd, J = 7.8, 9.3 Hz, OCH), 3.75 (1H, dd, J = 5.4, 9.3 Hz, OCH), 3.69 (1H, dd, J = 6.3, 9.3 Hz, OCH), 3.65 (1H, dd, J = 5.7, 9.3 Hz, OCH), 3.17 (1H, ddd, J = 3.0, 5.4, 7.8 Hz, CH-C ≡ C), 2.60 (1H, d, J = 6.0 Hz, OH); IR (liquid film) 3452, 3063, 3030, 2914, 2864, 2361, 2341, 1599, 1491, 1454, 1364, 1207; 1101, 1028, 912, 758, 739, 696 cm^{-1}. MS: *m/z* 386 (M^+), 311, 236, 128, 105, 91 (100%). HRMS Calcd for $C_{26}H_{26}O_3$: 386.1883 (M^+). Found: 386.1900 (M^+).

Tosylamide 8 : ^1H NMR ($CDCl_3$) δ 7.75 (2H, d, J = 8.4 Hz, Ts), 7.21-7.34 (12H, m, Ts and Ph), 5.01 (1H, d, J = 7.8 Hz, NH), 4.45 (2H, s, $PhCH_2$), 3.56-3.66 (2H, m, OCH and CH-N), 3.41-3.45 (1H, m, OCH), 2.72 (1H, dd, J = 5.1, 16.8 Hz, CH-C ≡ C), 2.62

(1H, dd, J = 7.2, 16.8 Hz, CH-C ≡ C), 2.39 (3H, s, $ArCH_3$); IR (liquid film) 3375, 3033, 2924, 2868, 1599, 1491, 1414, 1339, 1161, 1090, 814 cm^{-1}. MS: *m/z* 419 (M^+), 344, 304, 155, 115, 91 (100%), 65. HRMS Calcd for $C_{25}H_{25}NO_3S$: 419.1557 (M^+). Found: 419.1570 (M^+).

Tosylamide 10 : ^1H NMR ($CDCl_3$) δ 7.76 (2H, d, J = 8.4 Hz, Ts), 7.26-7.39 (12H, m, Ts and Ph), 5.36 (1H, d, J = 7.8 Hz, NH), 4.40 (2H, s, $PhCH_2$), 3.51-3.68 (2H, m, CHOBn and CHNTs), 3.41-3.49 (1H, m, CHOBn), 2.67 (1H, dd, J = 3.9, 17.1 Hz, CH-C ≡ C), 2.53 (1H, dd, J = 7.1, 17.1 Hz, CH-C ≡ C), 2.40 (3H, s, $ArCH_3$), 1.89 (2H, q, J = 6.0 Hz, CH_2); IR (liquid film) 3281, 2922, 2872, 2247, 1599, 1491, 1454, 1329, 1168, 1094, 912, 816, 758, 735, 694, 667 cm^{-1}. MS: *m/z* 433 (M^+), 363, 322, 279, 212, 43 (100%). Anal. Calcd for $C_{26}H_{27}NO_3S$: C, 72.03; H, 6.28; N, 3.23. Found: C, 71.49; H, 6.43; N, 3.13.

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(6) The yields of the reactions were 0.7% (10 mol% of Me_3Al) and 4% (100 mol%), respectively.

(7) The catalytic use of Me_3Al is crucial for obtaining satisfactory yield of the alkynylation product in the case of $Me_3SiC \equiv CLi$, since significant amount of methylation product arises from using stoichiometric Me_3Al (See also entry 8 of Table I).

(8) Although the upfield shift of ethereal carbons suggests the interaction of aluminum with ether oxygen, we have not yet been able to identify the origin of this behavior. We did, however, confirm the formation of the expected chelate-type complex (**C**) by ^{27}Al NMR analysis.

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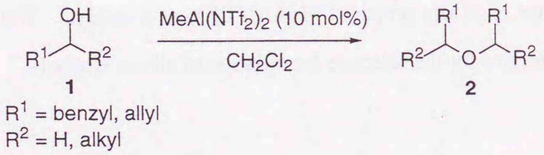
Chapter 3

Efficient Catalytic Procedure for Etherification of Alcohols with $MeAl(NTf_2)_2$

Abstract: Efficient catalytic etherification of benzyl and allylic alcohols has been accomplished by use of *in situ* prepared $MeAl(NTf_2)_2$ as a catalyst. The new method was also found to be effective for the selective benzylation of allylic alcohols.

The long-established Williamson ether synthesis is probably the most common method for preparation of ethers, which requires initial transformation of alcohols into the corresponding halides or tosylates and their displacement with strongly basic alkoxides or phenoxides.[1,2] The major drawback of this method has been viewed as its unsuitability for base sensitive molecules and the generation of stoichiometric amount of salts.[3,4] Although these problems seem to be overcome by a novel catalytic etherification recently developed by Strauss,[5] direct synthesis of ethers from alcohols through a dehydration process has also emerged as an attractive route for this purpose.[6,7] Kim and co-workers reported $ZnCl_2$-mediated etherification of alcohols, where, unfortunately, stoichiometric amount of Lewis acid ($ZnCl_2$) was necessary for the smooth reaction.[8,9] Here we wish to disclose a new, efficient catalytic procedure for the direct etherification of alcohols utilizing highly Lewis acidic $MeAl(NTf_2)_2$ as a catalyst (Scheme 1).

Scheme 1

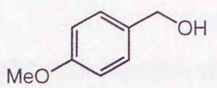
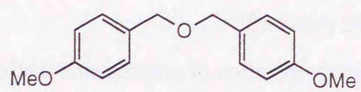
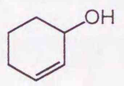
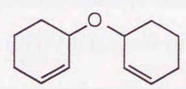
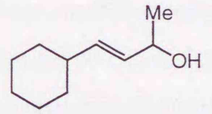
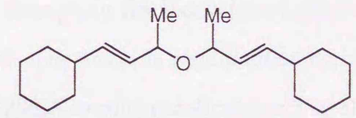
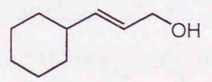
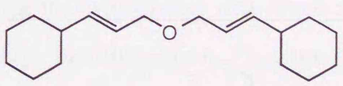
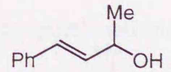
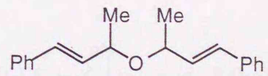
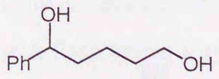
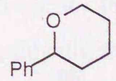


1 **2**

R^1 = benzyl, allyl
R^2 = H, alkyl

Treatment of *sec*-phenethyl alcohol (**1**; R^1 = Ph, R^2 = Me) with catalytic $MeAl(NTf_2)_2$ (10 mol%) [prepared by simply mixing $AgNTf_2$[10] and $MeAlCl_2$ in a 2:1 molar ratio] in CH_2Cl_2 at 21 °C for 30 min gave rise to the corresponding symmetrical ether (**2**; R^1 = Ph, R^2 = Me) quantitatively (Table 1, entry 1). Neither deoxygenation (reduction) nor elimination product was detected. Notably, use of 1 mol% of the catalyst can still facilitate the etherification to afford **2** (R^1 = Ph, R^2 = Me) in reasonable chemical yield (62%) (entry 3). Other selected examples are summarized in Table 1.

Table 1. Catalytic, Direct Etherification of Alcohols with $MeAl(NTf_2)_2$ [a]

entry	alcohol	condition (°C, h)	product	yield % [b]
1	PhCH(Me)OH	21, 0.5	Ph(Me)CHOCH(Me)Ph	>99
2		21, 2		79 [c]
3		21, 24		62 [d]
4	$PhCH_2OH$	40, 48	$PhCH_2OCH_2Ph$	83
5		-25, 3		53
6		0, 2		81
7		-10, 4		82
8		21, 5		20
9		-25, 3		84
10		21, 2		73 [e]

[a] Unless otherwise specified, the etherification was carried out in freshly distilled CH_2Cl_2 (0.2 M) with 10 mol% of $MeAl(NTf_2)_2$ under the indicated reaction conditions. [b] Isolated yield. [c] Use of 5 mol% of $MeAl(NTf_2)_2$. [d] Use of 1 mol% of $MeAl(NTf_2)_2$. [e] The reaction was performed in a concentration of 0.05 M to prevent intermolecular ether formation.

Various benzylic and allylic alcohols can be transformed into their symmetrical ethers with high efficiency by choosing appropriate reaction conditions which probably correspond to the stability of each intermediary carbocation. Dibenzyl ether can be prepared in high yield in spite of the prolonged reaction time, whereas the yield was significantly diminished in the etherification of *primary* allylic alcohols (entries 4 and 8). This system was also found to be effective for the synthesis of cyclic ethers. For instance, 1-phenyl-1,5-pentanediol, on reaction with 10 mol% of $MeAl(NTf_2)_2$ in CH_2Cl_2 at 21 °C for 2 h, furnished 2-phenyltetrahydropyran in 73% yield (entry 10).

The selective preparation of unsymmetrical ethers appears feasible in the presence of catalytic $MeAl(NTf_2)_2$ (10 mol%) under mild conditions as illustrated below.

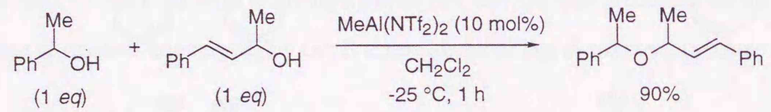
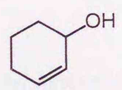
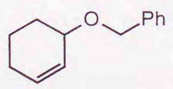
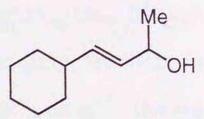
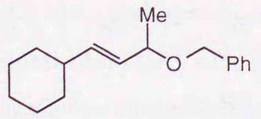
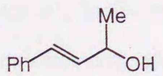
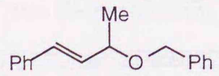


Table 2. Catalytic Benzylation of Allylic Alcohols with $MeAl(NTf_2)_2$ [a]

entry	alcohol	condition (°C, h)	product	yield % [b]
1		0, 4		65
2		0, 2		65
3		0, 2		89

[a] The reaction was carried out in freshly distilled CH_2Cl_2 with excess benzyl alcohol (5 equiv) in the presence of catalytic $MeAl(NTf_2)_2$ (10 mol%) under the given reaction conditions. [b] Isolated yield.

These results obtained so far prompted us to examine the possibility of applying the present method to the protection of alcohols as benzyl ethers. As listed in Table 2, allylic alcohols were indeed converted into their benzyl ethers by treatment with excess benzyl alcohol (5 equiv) under the influence of $MeAl(NTf_2)_2$ (10 mol%) in CH_2Cl_2 at 0 °C for several hours, which certainly offers a new, yet selective protection technique of hydroxy functionality on the allylic position.[11]

Experimental Section

General. Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8100A spectrometer. ^1H NMR spectra were measured on a Varian Gemini-200 (200 MHz) and JEOL JNM-FX 400 (400 MHz) spectrometers. All experiments were carried out under an atmosphere of dry argon. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel (E. Merck 9385).

In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Kanto Chemical Co., Ltd. as "Dehydrated". Pyridine and triethylamine were stored over KOH pellets. Methylene dichloride was freshly distilled from Calcium hydride. Methylaluminumdichloride was obtained from Toso-Akzo Chem. Co. Ltd., Japan. Other simple chemicals were purchased and used as such.

A typical experimental procedure $MeAl(NTf_2)_2$-Catalyzed Etherification of Alcohols. Silver bis(trifluoromethanesulfonyl)amide (76.6 mg, 0.2 mmol)[10] was placed in a dry two-neck flask with a stirring bar under argon, and freshly distilled CH_2Cl_2 (5 mL) was introduced. The suspension was carefully degassed and a 1 M hexane solution of $MeAlCl_2$ (100 μL, 0.1 mmol) was added dropwise at 21 °C. After the mixture was stirred for 30 min, *sec*-phenethyl alcohol (**1**; R^1 = Ph, R^2 = Me) (132 μL, 1.1 mmol) was added and stirring was continued at 21 °C for an additional 30 min. The resulting reaction mixture was then poured into 1 *N* HCl and extracted with ether. The combined organic extracts were dried over Na_2SO_4.

Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (hexane/EtOAc = 20:1 as eluant) gave symmetrical ether (**2**; R^1 = Ph, R^2 = Me) (124.2 mg, 0.55 mmol, >99% yield) as a colorless oil.

Bis-3-cyclohexenyl ether: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.70-5.84 (4H, m, CH=CH), 3.95-4.02 (2H, m, CH), 1.51-2.06 (12H, m, CH_2). IR (liquid film) 3026, 2934, 2862, 2837, 2359, 1649, 1437, 1398, 1078, 1014, 941, 752, 660 cm^{-1}.

Bis-4-cyclohexyl-2-but-3-ene ether: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.49 (0.8H, dd, J = 6.6, 15.6 Hz, CH=CH), 5.44 (1.2H, dd, J = 7.4, 15.6 Hz, CH=CH), 5.33 (0.8H, ddd, J = 1.2, 6.6, 15.6 Hz, CH=CH), 5.20 (1.2H, ddd, J = 1.2, 7.4, 15.6 Hz, CH=CH), 3.79-3.94 (2H, m, CH), 1.92-1.95 (2H, m, CH), 1.05-1.72 (26H, m, CH_2 and CH_3). IR (liquid film) 2972, 2924, 2853, 1666, 1448, 1367, 1308, 1163, 1134, 1067, 966, 893cm^{-1}.

Bis-4-phenyl-2-but-3-ene ether: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.52 (0.6H, d, J = 16.0 Hz, Ph-C*H*=CH), 6.49 (1.4H, d, J = 16.2 Hz, Ph-C*H*=CH), 6.18 (0.6H, dd, J = 8.0, 16.2 Hz, Ph-CH=C*H*), 6.11 (1.4H, dd, J = 8.0, 16.2 Hz, Ph-CH=C*H*), 4.22 (0.6H, qd, J = 6.4, 6.4 Hz, CH), 4.17 (1.4H qd, J = 6.4, 6.4 Hz, CH), 1.35 (1.8H, d, J = 6.4 Hz, CH_3), 1.32 (4.2H, d, J = 6.4 Hz, CH_3). IR (liquid film) 3082, 3059, 3026, 2974, 2866, 2357, 1597, 1493, 1448, 1367, 1309, 1140, 1067, 966, 748, 692 cm^{-1}.

Bis-3-Cyclohexyl-2-propene ether: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.65 (0.6H, d, J = 6.4 Hz, CH=CH), 5.61 (1.4H, d, J = 6.4 Hz, CH=CH), 5.52 (1.4H, td, J = 1.2, 6.0 Hz, CH=CH), 5.49 (0.6H, td, J = 1.2, 6.0 Hz, CH=CH), 3.90 (4H, dd, J = 1.2, 6.4 Hz, CH_2), 1.93-2.00 (2H, m, CH), 1.02-1.31 (20H, m, CH_2). IR (liquid film) 2926, 2850, 2361, 2341, 1448, 1117, 968 cm^{-1}.

General Procedure of MeAl(NTf_2)$_2$-Catalyzed Benzyl Protection of Allylic Alcohols. To a solution of Silver bis(trifluoromethanesulfonyl)amide (0.0776 g, 0.2 mmol) in methylene dichloride (5 mL) was added a 1.0 M hexane solution of $MeAlCl_2$ (100 μL, 0.1 mmol) under argon at room temperature and the reaction mixture was stirred for 0.5 hour and then added benzyl alcohol (0.264 mL, 2.55 mmol) at room temperature. The reaction mixture was added allylic alcohol (0.55 mmol) at 0 °C and then stirred for 5 hour. The mixture was

poured into 1*N* HCl and extracted with ether. The ethereal layer was dried over Na_2SO_4. Evaporation of solvent and purification by colum chromatography on silica gel (hexane/EtOAc as eluent) gave the corresponding benzyl ether.

4-Phenyl-2-but-3-ene benzyl ether: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25-7.42 (10H, m, ArH), 6.55 (1H, d, J = 12.0 Hz, Ph-C*H*=CH), 4.62 (1H, ABq, J = 9.0 Hz, CH_2Ph), 4.44 (1H, ABq, J = 9.0 Hz, CH_2Ph), 4.09-4.12 (1H, m, CH), 1.38 (3H, d, J = 4.8 Hz, CH_3). IR (liquid film) 3082, 3028, 2974, 2862, 2359, 1454, 1088, 1070, 968, 760, 694 cm^{-1}.

2-Cyclohexene benzyl ether: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23-7.37 (5H, m, ArH), 5.89 (2H, m, CH=CH), 4.61 (1H, ABq, J = 9.0 Hz, CH_2), 4.55 (1H, ABq, J = 9.0 Hz, CH_2), 3.93-3.98 (1H, m, CH), 1.50-2.09 (6H, m, CH_2). IR (liquid film) 3065, 3028, 2936, 2862, 1497, 1454, 1323, 1086, 1072, 948, 735, 698 cm^{-1}.

4-Cycohexyl-2-propen benzyl ehter: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24-7.33 (5H, M, ArH), 5.45-5.59 (1H, m, CH=CH), 5.30-5.36 (1H, m, CH=CH), 4.27-4.58 (2H, m, CH_2Ph), 3.17-3.87 (1H, m, CH), 1.90-2.15 (1H, m, CH), 1.16-1.78 (13H, m, CH_2 and CH_3). IR (liquid film) 2926, 2852, 2359, 2338, 1452, 1094, 968, 735, 698 cm^{-1}.

Reference and Notes

(1) A. W. Williamson, *J. Chem. Soc.*, 1852, **4**, 229.

(2) N. Baggett, *Comprehensive Organic Synthesis*, series ed. by D. Barton and W. D. Ollis, vol. ed. by J. F. Stoddart, Pergamon, Oxford, 1979, Vol. 1, p. 799.

(3) H, Normant and T. Cuvigny, *Bull. Soc. Chim. Fr.*, 1965, 1866.

(4) S. D. Burke, F. J. Schoenen, and M. S. Nair, *Tetrahedron Lett.*, 1987, **28**, 4143.

(5) L. Bagnell, T. Cablewski, and C. R. Strauss, *Chem. Commun.*, 1999, 283.

(6) J. Emert, M. Goldenberg, G. L. Chiu, and A. Valeri, *J. Org. Chem.*, 1977, **42**, 2012.

(7) I. Noda, K. Horita, Y. Oikawa, and O. Yonemitsu, *Tetrahedron Lett.,* 1986, **27**, 1917.

(8) S. Kim, K. N. Chung, and S. Yang, *J. Org. Chem.*, 1987, **52**, 3917.

(9) Only few catalytic procedures for the synthesis of ethers were described in the literature as summarized by Lemaire and co-workers, who reported hydrogenolysis of hemiacetals as an alternative to the Williamson's ether synthesis: V. Bethmont, F. Fache, and M. Lemaire, *Tetrahedron Lett.,* 1995, **36**, 4235.

(10) $AgNTf_2$ was kindly supplied by Central Glass Co. Ltd.

(11) For usual protection of alcohols as ethers, see: T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Second ed. John Wiley & Sons, New York, 1991, p. 14.

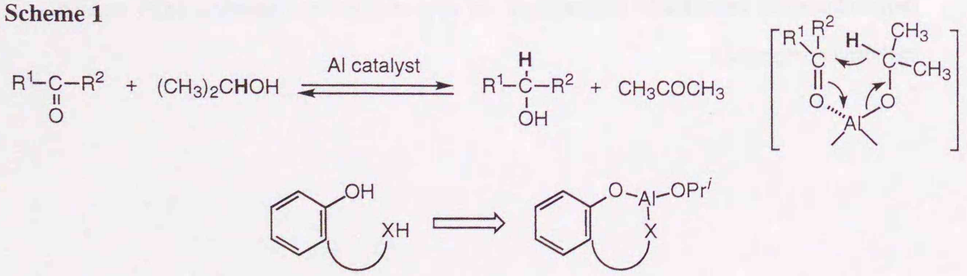
Chapter 4

Practical Approach for Meerwein-Ponndorf-Verley Reduction of Carbonyl Substrates with Newly Designed Aluminum Catalysts

Abstract: Powerful aluminum catalyst **2** has been developed for the highly efficient, catalytic Meerwein-Ponndorf-Verley (MPV) reduction of various ketone substrates under mild conditions. For example, reduction of 1-acetonaphthone in CH_2Cl_2 with *i*-PrOH (10 equiv) and a catalytic amount of **2** (10 mol%), prepared *in situ* from **1**, Me_3Al and *i*-PrOH, proceeds quite smoothly at 25 °C to furnish the corresponding *secondary* alcohol in 97% yield after 5 h. This is the most reactive aluminum-based catalyst system and enables facile hydride transfer from *i*-PrOH to cyclic and acyclic aliphatic ketones as well as aromatic ketones. The actual structure of the new aluminum catalyst was elucidated by using single-crystal X-ray diffraction analysis. Furthermore, the scale-up experiments with 5 g of substrates and 5 mol% of the catalyst **2**, generated by simply mixing $Al(OPr^i)_3$ and **1**, at 1.0 M substrate concentration demonstrate the remarkable potential of our approach for the practical MPV reduction of carbonyl compounds.

The Meerwein-Ponndorf-Verley (MPV) reaction, involving a reversible hydride transfer *via* six-membered transition state, has long been recognized as a particularly mild reduction method that has several attractive features.[1-3] The reaction is operationally very simple using cheap, nontoxic and nonhazardous reagents such as $Al(OPr^i)_3$ and *i*-PrOH, and is compatible with a broad range of functional groups present in the substrate. However, these advantages seemed to be canceled by the usual need for the relatively drastic reaction conditions because of the poor reactivity of the traditional $Al(OPr^i)_3$/*i*-PrOH catalyst system, where continuous removal of acetone is necessary to shift the equilibrium and hence undesirable side reactions seem inevitable. Accordingly, a number of modern variants of metal alkoxide-hydride source combinations have been elaborated to allow the classical methodology to regain an appropriate place in organic synthesis.[4-7] Although our recently introduced unique catalytic procedure with bidentate aluminum alkoxides certainly contributed to such an endeavor, it unfortunately requires *sec*-phenethyl alcohol as a hydride donor for smooth reduction of simple acyclic aliphatic ketones.[8] This constitutes a major difficulty, especially in the reduction of aromatic ketones, which prompted us to make further effort to bring out the inherent potential in the MPV reduction for practical use. Herein we wish to report our preliminary results on the development of new aluminum alkoxides for efficient catalytic MPV reduction of various ketone substrates including aromatic ketones with *i*-PrOH as a convenient hydride source under mild reaction conditions, providing a simple yet practical method for carbonyl reduction.

Scheme 1



Our strategy for the development of an aluminum catalyst featuring high activity as well as ease of preparation was based on the modification of simple aluminum phenoxide through introduction of an additional heteroatom-containing functionality on the *ortho* position of the parent phenol aromatic ring as schematically illustrated in Scheme 1. Attempted reduction of acetophenone as a representative substrate in the presence of diisopropoxyaluminum phenoxide (10 mol%) (prepared *in situ* from phenol, Me_3Al and *i*-PrOH) and *i*-PrOH as a hydride source (5 equiv) in CH_2Cl_2 at 25 °C for 5 h resulted in total recovery of the starting ketone as shown in Table 1 (entry 1), and use of salicylic acid as an aluminum ligand gave none of the desired *sec*-phenethyl alcohol (entry 2). Although the reactivity was slightly enhanced by aluminum isopropoxides derived from catechol and *o*-(methanesulfonylamino)phenol, it was far from a synthetically satisfactory level (entries 3 and 4). However, use of the phenol possessing trifluoromethanesulfonamide functionality improved the yield of *sec*-phenethyl alcohol (30%) and a similar result was obtained with the 2,2'-biphenol based catalyst (46%) (entries 5 and 6),[9] which led us to consider the possibility of combining the two structural characteristics. The synthesis of 2-hydroxy-2'-(trifluoromethanesulfonylamino)biphenyl (**1**) was thus pursued starting from phenol. Interestingly, the treatment of acetophenone with 10 mol% of catalyst, prepared from **1**, Me_3Al and *i*-PrOH, in CH_2Cl_2 at 25 °C for 5 h produced the corresponding *sec*-alcohol in 65% yield (entry 7). Here, tuning of the perfluoroalkyl group of sulfonamide moiety afforded a beneficial effect on the catalyst activity. Thus, the reaction under the influence of the aluminum isopropoxide **3** derived from 2-hydroxy-2'-(perfluorooctanesulfonylamino)biphenyl (**2**) gave rise to *sec*-phenethyl alcohol in 76% yield and, eventually, the isolated yield of the alcohol was improved to 85% using 10 equiv of *i*-PrOH (entries 8 and 9) (Scheme 2).[10]

Scheme 2

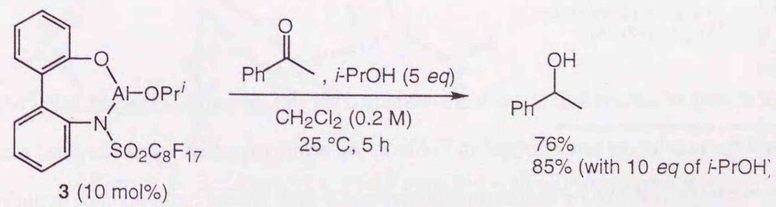
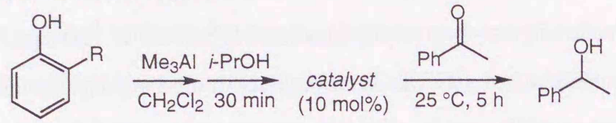
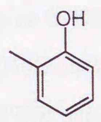
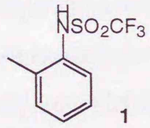
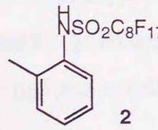


Table 1. Catalytic MPV Reduction of Acetophenone with Various Aluminum Catalysts. [a]



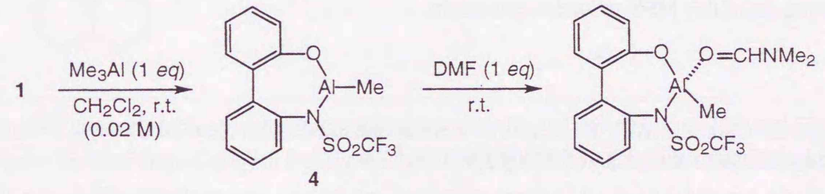
entry	R	*i*-PrOH (equiv)	yield, % [b]
1	H	5	n.r. [c]
2	COOH	5	n.r. [c]
3	OH	5	8
4	$NHSO_2CH_3$	5	9
5	$NHSO_2CF_3$	5	30
6		5	46
7	 **1**	5	65
8	 **2**	5	76
9		10	85

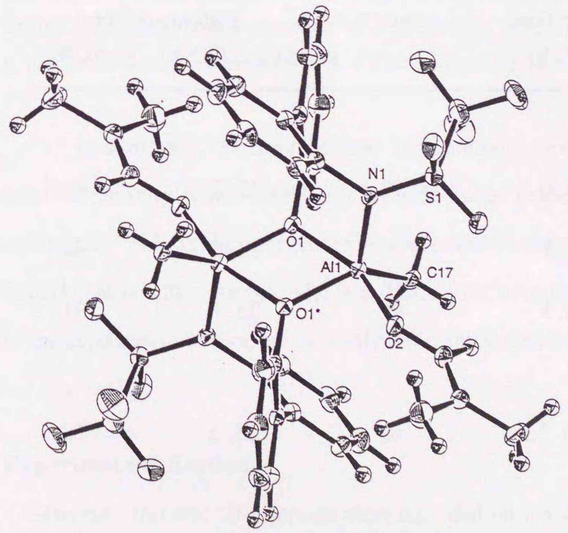
[a] The MPV reduction of acetophenone was conducted with several aluminum catalysts (10 mol%) and *i*-PrOH (distilled from CaH_2) in freshly distilled CH_2Cl_2 at 25 °C for 5 h. [b] Isolated yield.
[c] n.r. = no reaction.

A variety of ketone substrates were examined for this optimized catalytic MPV reduction with **3** and the results are summarized in Table 2. As easily expected, cyclic ketones such as 4-phenylcyclohexanone can be reduced instantaneously to 4-phenylcyclohexanol quantitatively

(*cis*/*trans* = 17:83) (entry 1). Simple aliphatic ketones were also found to be efficiently converted to the corresponding *sec*-alcohols in excellent yields (entries 2 and 3). Moreover, the present catalytic system based on the newly developed aluminum catalyst allows smooth hydride transfer from *i*-PrOH to various aromatic ketones (entries 4-7).

To gain information about the actual structure of the new aluminum catalyst, we prepared the complex of the catalyst precursor **4** with DMF as a model example, and the structure was determined by single-crystal X-ray diffraction analysis, revealing the dimeric structure with unique pentacoordinated aluminums (Figure 1).[11,12] Here, the formation of the expected seven-membered cyclic structure was unambiguously verified. Notably, trifluoromethyl moiety was found to be located away from the aluminum center, suggesting that the introduction of perfluoroalkyl group essentially provides the electronic effect rather than the steric one.



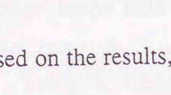
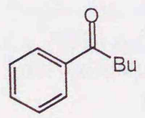


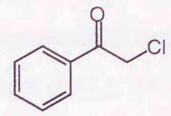
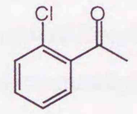
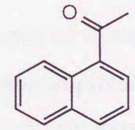
Crystal Data	
Crystal System	monoclinic
Space Group	$P2_1/c$
a / Å	9.4834(7)
b / Å	9.4378(7)
c / Å	21.375(1)
β / °	97.856(3)
V / $Å^3$	1895.2(2)
Z	2
D_{calc} / gcm^{-3}	1.508
μ(MoKα) / cm^{-1}	2.72
R	0.063
R_w	0.129

Figure 1. Structure of **4** /DMF complex (ORTEP representation).

Based on the results, we set out to conduct the scale-up experiments to illuminate the practical aspect of our approach, and first examined the possibility of using $Al(OPr^i)_3$ as an aluminum source to avoid the rather troublesome handling of Me_3Al. Fascinatingly, simple mixing of 10 mol% each of commercially available $Al(OPr^i)_3$[13] and **2** in CH_2Cl_2 at room temperature and subsequent treatment with *i*-PrOH (10 equiv) and acetophenone at 25 °C for 5 h resulted in formation of *sec*-phenethyl alcohol in 82% yield,[14] indicating the intervention of extremely facile ligand exchange.[15] With this simple yet efficient process in hand, the reactions with 5 g of the starting ketones were undertaken with a lower catalyst loading (5 mol%), which scarcely affect the outcome of the catalysis. The results included in Table 2 demonstrate the potential utility of the present method.[16] Importantly, these product yields were achieved at high substrate concentration (1.0 M) with reagent grade CH_2Cl_2, which also simplify the operations of this MPV reduction procedure.

Table 2. Catalytic MPV Reduction of Ketone Substrates with New Al Catalyst **3**[a] and Scale-Up Experiments with 5 g of Starting Ketones. [b]

entry	substrate ($R^1C{=}OR^2$)	conditions (°C, h)	yield, % [c]	scale-up reaction conditions (°C, h)	scale-up reaction yield, % [c]
1		25, 0.5	99	25, 2	99 [d]
2	$CH_3(CH_2)_6COCH_3$	25, 5	97	25, 5	94
3	$[CH_3(CH_2)_3]_2C{=}O$	25, 5	92	25, 5	91
4		25, 3.5	85	25, 5	82

entry	substrate ($R^1C{=}OR^2$)	conditions (°C, h)	yield, % [c]	scale-up reaction conditions (°C, h)	scale-up reaction yield, % [c]
5		25, 5	99	25, 5	98
6		25, 1	99	25, 3.5	99
7		25, 5	97	25, 9	95

[a] The MPV reduction of various ketone substrates was effected with **3** (10 mol%) and *i*-PrOH (10 equiv, distilled from CaH_2) in freshly distilled CH_2Cl_2 (0.2 M) under the indicated reaction conditions. [b] The reaction was carried out in reagent grade CH_2Cl_2 (1.0 M) and distilled *i*-PrOH (10 equiv) in the presence of **3** (5 mol%), prepared from $Al(OPr^i)_3$ and **2**, under the given conditions. [c] Isolated yield. [d] The *cis*/*trans* ratio was 17:83.

In summary, we have devised an essentially new aluminum alkoxide exerting high catalytic activity with *i*-PrOH as a hydride donor in the MPV reduction of various ketone carbonyls. This is the most reactive aluminum-based catalyst reported so far and has the remarkable potential for practical use. Further improvement of the reactivity and development of the asymmetric version are currently under intensive investigation in our laboratory.

Experimental Section

General. Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8100A spectrometer. ^1H NMR spectra were measured on a Varian Gemini-200 (200 MHz), 300 (300 MHz) and

JEOL JNM-FX 400 (400 MHz) spectrometers. All experiments were carried out under an atmosphere of dry argon. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel (E. Merck 9385). Microanalyses were accomplished at the Center for Instrumental Analysis, Kyoto University. The high-resolution mass spectra (HRMS) were conducted at the School of Engineering, Kyoto University.

In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Kanto Chemical Co., Ltd. as "Dehydrated". Methylene dichloride was freshly distilled from Calcium hydride. DMF was stored over 4Å molecular sieves. Triethylamine and pyridine were stored over KOH pellets. Trimethylaluminum was obtained from Toso-Akzo Chem. Co. Ltd.; Japan. Other simple chemicals were purchased and used as such.

A typical experimental procedure Scale-up reaction with acetophenone. 2-Hydroxy-2'-(perfluorooctanesulfonylamino)biphenyl (1.39 g, 2.1 mmol) and $Al(OPr^i)_3$ (0.43 g, 2.1 mmol)[13] were placed in a dry, two-neck flask with a Teflon-coated stirring bar under argon and CH_2Cl_2 (42 mL, reagent grade purchased from Wako Chemical Co., Ltd.) was introduced. The resulting mixture was stirred for 15 min at room temperature and then 2-propanol (31.3 mL, 412 mmol) distilled from CaH_2 was introduced at the same temperature and stirring was continued for an additional 15 min. Freshly distilled acetophenone (5 g, 41.6 mmol) was added at 25 °C and the reaction solution was stirred for 5 h. This solution was poured into 1 *N* HCl and extracted three times with ether. The ethereal extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (H = 12 cm, ϕ = 7 cm, acetone/hexane = 1:9 as eluant) gave *sec*-phenethyl alcohol (4.15 g, 34.0 mmol; 82% yield). The ligand, 2-hydroxy-2'-(perfluorooctanesulfonylamino)biphenyl, can be recovered by the following elution with ethyl acetate. In addition, purification of the reduction product by vacum distillation is also recommended.

***N*-methanesulfonyl-*o*-aminophenol:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (1H, dd, J = 1.6, 7.6 Hz, ArH), 7.17 (1H, ddd, J = 1.6, 6.8, 8.4 Hz, ArH), 6.97 (1H, dd, J = 0.9, 8.4

Hz, ArH), 6.95 (1H, ddd, J = 1.6, 7.6 7.6 Hz, ArH), 6.38 (1H, brs, NH), 6.18 (1H, brs, OH), 3.01 (3H, s, CH_3). IR (KBr) 3495, 3213, 3205, 1595, 1501, 1419, 1400, 1337, 1308, 1149, 986, 762cm^{-1}. HRMS Calcd for $C_7H_9NO_3S$: 187.0303 (M^+). Found: 187.0311 (M^+). Anal. Calcd for $C_7H_9NO_3S$: C, 44.91; H, 4.85; N, 7.48;. Found: C, 44.92; H, 4.73; N, 7.49.

Preparation of *N*-trifluoromethanesulfonyl-*o*-aminophenol. A solution of *o*-aminophenol (0.57 g, 5.0 mmol) in CH_2Cl_2 (5 mL) was added pyridine (445 µL. 5.5 mmol) and catalytic amount of DMAP at room temperature. After stirred for 15 min, the mixture was added dropwise Boc_2O (1.13 g, 5.0 mmol) under argon at room temperature. The reaction mixture was stirred for over night at the same temperature and then quenched with water and extracted with ether. The ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of solvent and purification by column chromatography on silica gel (EtOAc / hexane = 1/4 ~ 1/1 as eluent) gave 2-*t*-butoxycarbonyloxyaniline (1.05 g, 5.0 mmol 99 % yield).^{1}H NMR ($CDCl_3$, 400MHz) δ 6.97-7.08 (2H, m, ArH), 6.73-6.85 (2H, m, ArH), 3.71 (2H, br s, NH_2), 1.56 (9H, s, Bu^t).

A solution of 2-*t*-Butoxycarbonyloxyaniline (0.491 g, 2.35 mmol) in CH_2Cl_2 (9 mL) was added triethylamine (393 mL, 2.82 mmol) at room temperature, and then cooled down to -78 °C. To the mixture was added dropwise trifluoromethanesulfonic anhydride (432 µL, 2.58 mmol) under argon. After stirred for 0.5 h at -78 °C, the reaction mixture was quenched with water and extracted with ether. The ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of solvent and purification by column choromatography on silica gel (EtOAc / hexane = 1/9 ~ 1/1 as eluent) gave *N*-trifluoromethanesulfonyl-2-*t*-butoxy carbonyloxyaniline (0.688 g, 2.0 mmol, 85 % yield).

A solution of *N*-trifluoromethanesulfonyl-2-*t*-butoxycarbonyloxyaniline (0.143 g, 0.5 mmol) in ethylacetate was added 3*N* HCl (4 mL) and then stirred for 10 h at room temperature. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of solvent and purification by column chromatography on silica gel (CH_2Cl_2 / hexane = 1/1 to CH_2Cl_2 as eluent) gave *N*-trifluoromethanesulfonyl-*o*-aminophenol (0.088 g, 0.44 mmol, 88 % yield). ^{1}H NMR ($CDCl_3$,

400 MHz) δ 7.45 (1H, dd, J = 1.6, 8.0 Hz, ArH), 7.16 (1H, td, J = 1.6, 8.0 Hz, ArH), 6.97 (1H, td, J = 1.6, 8.0 Hz, ArH), 6.94 (1H, br s, NH), 6.81 (1H, dd, J = 1.6, 8.0 Hz, ArH), 5.36 (1H, br s, OH). IR (KBr) 3499, 3269, 1603, 1514, 1468, 1410, 1229, 1202, 1138, 752, 642 cm^{-1}. HRMS Calcd for $C_7H_6F_3NO_3S$: 241.0020 (M^+). Found: 241.0022 (M^+).

Preparation of 2-Hydroxy-2'-*N*-trifluoromethanesulfonylaminobiphenyl. To a solution of sodium hydride (2.4 g, 60 mmol) in THF (90 mL) and DMF (10 mL) was added phenol (4.75 g, 60 mmol) under argon at 0°C and the reaction mixture was stirred at 0°C for 30 min and then added chloromethylmethylether (4.75 mL, 60 mmol) at 0°C and the reaction mixture was stirred for 3.5 h at 0°C to room temperature. This mixture was poured into water and extracted with ether and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatgraphy on silica gel (fexane / EtOAc = 1/0 ~20/1 as eluant) gave methoxymethoxybenzene (6.90 g, 50 mmol, 99% yield) as a colerless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25-7.33 (3H, m, ArH), 7.00-7.06 (2H, m, ArH), 5.10 (2H, s, CH_2), 3.48 (3H, s, CH_3). To a 1.56 M hexane solution of BuLi (31.2 mL, 48.7 mmol) in ether (50 mL) was added *N*,*N*,*N*',*N*'-tetramethylethylenediamine (7.30 mL, 48.7 mmol) under argon at 0 °C and the reaction mixture was stirred at room temperature for 30 min and then transfered to methoxymethoxybenzene (5.60 g, 40.6 mmol) in ether (50mL) at 0 °C and the reaction mixture was stirred at room temperature for 6 h and then transfered to trimethylborate (6.02 mL, 52.8 mmol) in THF (100 mL) at -78°C and the reaction mixture was stirred at -78°C to room temperature for 12 h . This mixture was poured into 1*N* HCl and extracted with ether. Ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatgraphy on silica gel (hexane/EtOAc = 5/1~1/1 as eluant) gave 2-methoxymethoxyphenylboric acid (5.50 g, 32.0 mmol, 79% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, dd, J = 2.0, 7.6 Hz, ArH), 7.43 (1H, dd, J = 2.0, 7.6 Hz, ArH), 7.06-7.14 (2H, m, ArH), 5.86 (2H, s, $B(OH)_2$), 5,30 (2H, s, CH_2), 3.52 (3H, s, CH_3). A solution of 2-methoxymethoxyphenylboric acid (2.43 g, 13.3 mmol) and 2-bromoaniline(1.94 g, 11.3 mmol), palladium(II)acetate (126.8 mg, 0.565 mmol) and triphenylphosphine (650.4 mg, 2.48 mmol and Potassium carbonate(1.83 g, 13.3mmol) in DME (113 mL) was stirred at reflux for 19 h. This mixture was poured into water and extracted

with ether and dried with Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatgraphy on silica gel (hexane/EtOAc = 5/1 as eluant) gave 2-(2'-methoxymethoxyphenyl)aniline (1.82 g, 6.78 mmol, 60% yield) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.07-7.40 (6H, m, ArH), 6.74-6.88 (2H, m, ArH), 5.09 (2H, s, CH_2), 3.69 (2H, br s, NH_2), 3.35 (3H, s, CH_3). To a solution of 2-(2'-methoxymethoxyphenyl)aniline (208.6 mg, 0.91 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (0.152 mL, 1.1 mmol) under argon at -78°C and the reaction mixture was stirred at -78°C for 30 min and then added trifluoromethanesulfonic anhydride (0.183 mL, 1.0 mmol) at -78°C and the reaction mixture was stirred at -78°C for 1 h. This mixture was poured into water and extracted with ether and dried with Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatgraphy on silica gel (hexane/EtOAc=20/1 as eluant) gave 2-methoxymethoxy-2'-*N*-trifluoromethanesulfonylaminobiphenyl (263 mg, 0.728 mmol, 80% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (1H, br s, NH), 7.57-7.60 (1H, m, ArH), 7.40-7.47 (3H, m, ArH), 7.34-7.38 (1H, m, ArH), 7.26-7.31 (2H, m, ArH), 7.17-7.22 (1H, m, ArH), 5.16 (2H, s, CH_2), 3.34 (3H, s, CH_3). To a solution of 2-methoxymethoxy-2'-*N*-trifluoromethanesulfonylaminobiphenyl (263 mg, 0.728 mmol) in methanol (7.3 mL) was added 1*N* HCl (0.73 mL) at room temperature and the reaction mixture was stirred at reflux for 11.5 h. This mixture was poured into sat. $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4. Evaporation of solvent and purification of the residual oil by column chromatography on silica gel (hexane/CH_2Cl_2= 1/1 ~ CH_2Cl_2) gave 2-hydroxy-2'-*N*-trifluoromethanesulfonylaminobiphenyl (196 mg, 0.619 mmol, 85 % yield) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (1H, br s, NH), 7.58 (1H, dd, J = 1.6, 7.6 Hz, ArH), 7.31-7.46 (4H, m, ArH), 7.26 (1H, dd, J = 1.2, 7.6 Hz, ArH), 7.09 (1H, td, J = 0.8, 7.6 Hz, ArH), 6.91 (1H, d, J = 8.0 Hz, ArH), 5.73 (1H, br s, OH). IR (KBr) 3526, 3294, 1487, 1445, 1394, 1354, 1329, 1234, 1194, 1167, 1148, 966, 762 cm^{-1}. HRMS Calcd for $C_{13}H_{10}F_3NO_3S$: 317.0333 (M^+). Found: 317.0320 (M^+). Anal. Calcd for $C_{13}H_{10}F_3NO_3S$: C, 49.21; H, 3.18; F, 17.96; N, 4.41. Found: C, 49.21; H, 3.18; F, 18.00; N, 4.41.

Preparation of 2-Hydroxy-2'-N-perfluorooctanesulfonylaminobiphenyl. To a 1.61 M hexane solution of BuLi (2.48 mL, 4.0 mmol) in ether (2 mL) was added *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (0.60 mL, 4.0 mmol) under argon at 0 °C and then added a solution of 2-(2'-methoxymethoxyphenyl) aniline (208.6 mg, 0.91 mmol) in ether (1 mL). After the mixture was stirred for 1 h at 0 °C adn added THF (1 mL) to dissolve the lithium salt, perfluoro-1-octanesulfonyl fluoride (0.562 mL, 2.0 mmol) was added under argon and then stirred for 1 h at 0 °C and 3.5 h at room temperature. The reaction mixture was poured into water and extracted with ether and dried with Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatgraphy on silica gel (hexane/EtOAc = 4/1 as eluant) gave 2-methoxymethoxy-2'-*N*-perfluorooctanesulfonylaminobiphenyl (674 mg, 0.95 mmol, 47% yield). To a solution of 2-methoxymethoxy-2'-*N*-perfluorooctanesulfonylamino biphenyl (622 mg, 0.87 mmol) in methanol (6 mL) was added 1*N* HCl (4 mL) at room temperature and the reaction mixture was stirred at reflux for 3.5 h. This mixture was poured into sat. $NaHCO_3$, and extracted with CH_2Cl_2. The ethereal layer was dried over Na_2SO_4. Evaporation of solvent and purification of the residual oil by column chromatography on silica gel (hexane/CH_2Cl_2= 1/1 ~ CH_2Cl_2) gave 2-hydroxy-2'-*N*-perfluorooctanesulfonylamino biphenyl (386 mg, 0.58 mmol, 67 % yield) as a white powder. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.92 (1H, br s, NH), 7.65 (1H, dd, J = 1.6, 8.0 Hz, ArH), 7.32-7.47 (4H, m, ArH), 7.26 (1H, dd, J = 1,6, 8.0 Hz, ArH), 7.09 (1H, td, J =1.2, 7.6 Hz, ArH), 6.95 (1H, dd, J = 1.0, 8.2 Hz, ArH), 5.44 (1H, s, OH). IR (KBr) 3476, 3194, 1408, 1356, 1269, 1232, 1213, 1205, 1182, 1155, 752cm^{-1}. MS: m/z 667 (M^+), 184 (100%). 156, 154. HRMS Calcd for $C_{20}H_{10}F_{17}NO_3S$: 667.0109 (M^+). Found: 667.0106 (M^+). Anal. Calcd for $C_{20}H_{10}F_{17}NO_3S$: C, 36.00; H, 1.51; F, 48.40; N, 2.10. Found: C, 35.71; H, 1.35; F, 48.32; N, 2.40.

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(9) Attempted reduction of acetophenone with previously reported (2,7-dimethyl-1,8-biphenylenedioxy)bis(diisopropoxyaluminum)[8] (10 mol%) as a catalyst under otherwise identical conditions produced *sec*-phenethyl alcohol in 35% yield.

(10) The requisite aluminum ligand **2** can be readily prepared from phenol in 5 steps: (i) NaH, MOMCl, THF (99%); (ii) BuLi, ether, then $B(OMe)_3$, H_3O^+ (85%); (iii) 2-bromoaniline, $Pd(OAc)_2$, PPh_3, K_2CO_3, DME (70%); (iv) BuLi, TMEDA, $C_8F_{17}SO_2F$, ether (50% with recovery of the starting material); (v) HCl, MeOH (99%). Spectroscopic characterization of **2**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.92 (1H, s, NH), 7.65 (1H, dd, J = 1.6, 8.0 Hz, ArH), 7.32-7.47 (4H, m, ArH), 7.26 (1H, dd, J = 1.6, 8.0 Hz, ArH), 7.09 (1H, dt, J = 1.2, 7.6 Hz, ArH), 6.95 (1H, dd, J = 1.0, 8.2 Hz, ArH), 5.44 (1H, s, OH). IR (KBr) 3476, 3194, 1489, 1440, 1408, 1356, 1269, 1232, 1213, 1205, 1182, 1155, 1065, 935, 835, 752 cm^{-1}. MS: *m/z* 667 (M^+), 184 (100%), 156, 154. HRMS Calcd for $C_{20}H_{10}F_{17}NO_3S$: 667.0109 (M^+). Found: 667.0106 (M^+). Anal. Calcd for $C_{20}H_{10}F_{17}NO_3S$: C, 36.00; H, 1.51; F, 48.40; N, 2.10. Found: C, 35.71; H, 1.35; F, 48.32; N, 2.40.

(11) Crystal structure data for the complex of **4** with DMF collected at 123 K: $C_{34}H_{36}Al_2F_6N_4S_2O_8$, M_w = 860.75, monoclinic, space group $P2_1/c$, a = 9.4834(7) Å, b = 9.4378(7) Å, c = 21.375(1) Å, β = 97.856(3)°, V = 1895.2(2) $Å^3$, Z = 2, D_{calcd} = 1.508 g/cm^3, R_1 = 0.063.

(12) Shibasaki, Sasai and co-workers have reported the pentacoordinated aluminum structure of $(CH_3)_2Al_2$(binaphthoxide)$_2$(thf)$_2$. T. Arai, H. Sasai, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **1998**, *120*, 441.

(13) Purchased from Aldrich Chemical Co., Ltd. as 99.99% purity.

(14) This simple method resulted in the slight decrease of the chemical yield probably due to the incomplete catalyst formation, which is technically inevitable at present.

(15) As expected, attempted reduction of acetophenone with $Al(OPr^i)_3$ (10 mol%) and *i*-PrOH (10 equiv) at 25 °C for more than 5 h showed no evidence of the product formation.

(16) For the result of the scale-up reaction with acetophenone, see experimental section.

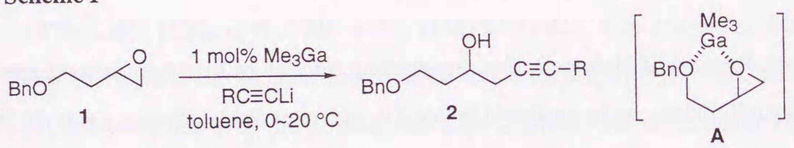
Appendix

Remarkable Catalytic Activity of Me3Ga in the Alkylation of Hetero-Substituted Epoxides with Alkynyllithiums

Abstract: Regio- and stereoselective ring-opening reaction of hetero-substituted epoxides with alkynyllithiums can be catalyzed by Me_3Ga with remarkable efficiency at 0~20 °C via pentacoordinate chelate-type complex.

Recently, we disclosed the trimethylaluminum-catalyzed regio- and stereoselective ring opening of hetero-substituted epoxides with alkyllithiums, and demonstrated that the catalytic efficiency is ascribable to the intervention of unfamiliar pentacoordinate trialkylaluminum complexes.[1] Continuing of our interest in the reactivity and selectivity profile of pentacoordinate chelate-type complexes of other main group metals, trialkylgallium proved to be a greatly superior catalyst for this type of epoxide cleavage reaction, thereby further enhancing its synthetic potential.[2] We here wish to report that the reaction of alkynyllithiums with hetero-substituted epoxides can be effected by *1 mol%* of Me_3Ga catalyst in toluene at 0~20 °C via pentacoordinate chelate-type complex as a key intermediate (Scheme I).[3]

Scheme I

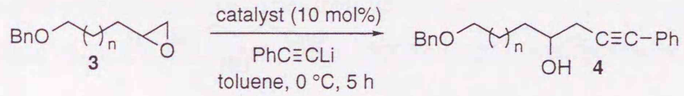


Initial treatment of epoxy ether, 1-(benzyloxy)-3-butene oxide (**1**) in freshly distilled toluene with PhC ≡ CLi in the presence of catalytic Me_3Ga (10 mol%) at -78 °C and subsequent stirring at 0 °C for 5 h gave rise to the alkynylation product, 1-(benzyloxy)-6-phenylhex-5-yn-3-ol (**2**; R = Ph) in 90% yield (entry 1, Table I). Notably, reaction of a carbon analogue of **1**, 6-phenyl-1-hexene oxide with PhC ≡ CLi under similar reaction conditions afforded only a trace amount of the alkynylation product, 1,8-diphenyl-1-octyn-4-ol (10% yield even after stirring at 20 °C for 5 h), indicating that the possible formation of chelate type complex **A** was responsible for obtaining sufficient reactivity. It should be emphasized that the catalytic amount of Me_3Ga can be reduced to 1 mol% without losing a synthetically satisfactory level of efficiency.[4] In the absence of Me_3Ga catalyst, the alkynylation of **1** proceeded quite reluctantly (3% with PhC ≡ CLi at 0 °C for 5 h) .[1] Other selected examples are listed in Table I. The alkynylation also proceeded smoothly with Me_3SiC ≡ CLi (entries 4 and 8) but, unfortunately, not with C_4H_9C ≡ CLi (entry 5). The present catalytic method seemed to be

applicable to the regio- and stereoselective cleavage of epoxy acetals and 1,2-disubstituted epoxy ethers (entries 11 and 12), though a certain decrease of the reactivity was observed.

Interestingly, one carbon elongated epoxy ether, 1-(benzyloxy)-4-pentene oxide (**3**, n = 1), also underwent smooth alkynylation with PhC ≡ CLi and catalytic Me_3Ga (10 mol%) at 0 °C giving the corresponding homopropargyl alcohol **4** (n = 1) in 71% yield, whereas the yield was significantly lowered by use of Me_3Al under otherwise similar reaction conditions (16%), indicating the advantage of Me_3Ga in this type of epoxide cleavage assisted by chelate formation (Scheme II). In addition, subsequent examination of the alkynylation of **3** (n = 2) revealed the limitation of our approach as also shown in Scheme II.

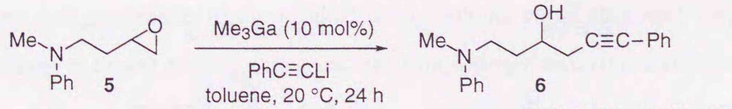
Scheme II



Me_3Ga : 71% (n = 1), 19% (n = 2)
Me_3Al : 28% (n = 1), 4% (n = 2)

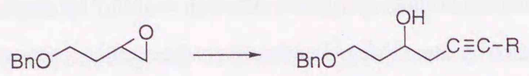
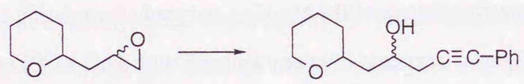
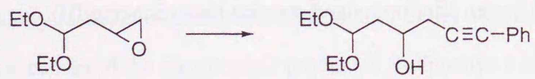
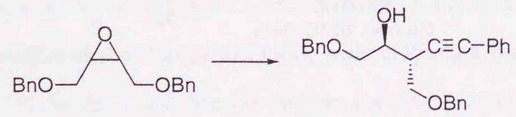
Another characteristic feature of the Me_3Ga-catalyzed alkynylation is its applicability to epoxy amines. For instance, treatment of epoxy amine **5** with PhC ≡ CLi under the influence of Me_3Ga (10 mol%) in toluene at 20 °C for 24 h produced the alkynylation product **6** in 38% yield.[5] In contrast, however, the use of Me_3Al in place of Me_3Ga as a catalyst gave none of the desired amino alcohol **6** even after prolonged reaction time (Scheme III).

Scheme III



38% [~0% with Me_3Al]

Table I. Me_3Ga-Catalyzed Alkylation of Hetero-Substituted Epoxides with Alkynyllithiums [a]

entry	alkynyllithium (RC ≡ CLi)	condition (°C, h)	yield, % [b]
	 **1**	**2**	
1	R = Ph	-78, 0.1; 0, 5	90 [c]
2	R = Ph	-78, 0.1; 0, 5	47
3	R = Ph	-78, 0.1; 20, 5	71
4	R = Me_3Si	-78, 0.1; 20, 10	71
5	R = C_4H_9	-78, 0.1; 20, 13	21
			
6	R = Ph	-78, 0.1; 0, 5	69
7	R = Ph	-78, 0.1; 20, 3	80
8	R = Me_3Si	-78, 0.1; 20, 10	80
			
9	R = Ph	-78, 0.1; 0, 5	66
10	R = Ph	-78, 0.1; 20, 5	77
			
11	R = Ph	-78, 0.1; 20, 5	47
			
12	R = Ph	-78, 0.1; 20, 5	46 [c]

[a] Unless otherwise specified, the reaction was carried out with 1.1 equiv of alkynyllithium in distilled toluene under the given reaction conditions in the presence of 1 mol% of Me_3Ga. [b] Isolated yield. [c] Use of 10 mol% of Me_3Ga.

Experimental Section

General. Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8100A spectrometer. ^1H NMR spectra were measured on a Varian Gemini-300 (300 MHz) spectrometer. All experiments were carried out under an atmosphere of dry argon. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel (E. Merck 9385).

In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Kanto Chemical Co., Ltd. as "Dehydrated". Toluene was freshly distilled from sodium metal. Hexane was dried over sodium metal. Trimethylaluminum and trimethylgallium were obtained from Toso-Akzo Chem. Co. Ltd., Japan. Other simple chemicals were purchased and used as such.

General Method for Me_3Ga-Catalyzed Cleavage of Epoxide with Alkynyllithiums. To a solution of phenylacetylene (543 μL, 4.8 mmol) in freshly distilled toluene was added 1.56 M hexane solution of BuLi (2.82 mL, 4.4 mmol) at 0 °C under argon and the mixture was stirred for 30 min. After cooling to -78 °C, epoxy ether (713 mg, 4 mmol) was added dropwise followed by the addition of 0.5 M hexane solution of Me_3Ga (80 μL, 0.04 mmol). The resulting mixture was then allowed to warm to 21 °C and stirred there for 5 h. The solution was poured into 1 *N* HCl and extractive workup was performed with ether. The combined organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (EtOAc/hexane as eluant) gave the corresponding homopropargyl alcohol as a colorless oil.

References and Notes

(1) Ooi T, Kagoshima N, Ichikawa H, Maruoka K. *J. Am. Chem. Soc.* 1999;*121*:3328. See also: Ooi T, Kagoshima N, Maruoka K. *J. Am. Chem. Soc.* 1997;*119*:5754.

(2) For a review of epoxide chemistry including ring opening, see: Gorzynski SJ. *Synthesis* 1984:629.

(3) Utimoto K, Lambert C, Fukuda Y, Shiragami H, Nozaki H. *Tetrahedron Lett.* 1984;*25*:5423.

(4) Attempted reaction of **1** with PhC ≡ CLi under the influence of Me_3Ga (1 mol%) in THF at 20 °C for 5 h gave only a trace amount of **2**, probably because of interference with the crucial chelate formation by the coordination of THF solvent to the gallium center. This result could also exclude the possibility that the ate complex might be an active species for the present alkynylation. See ref. 3.

(5) The reaction conditions were not optimized.

Publication list

Chapter 2 — Pentacoordinate Organoaluminum Chemistry: Catalytic Efficiency of Me_3Al in the Epoxide Cleavage with Alkynyllithium
T. Ooi, N. Kagoshima, H.Ichikawa, K. Maruoka
J. Am. Chem. Soc., **1999**, *119*, 3328.

Chapter 3 — Efficient Catalytic Procedure for Etherification of Alcohols with $MeAl(NTf_2)_2$
T. Ooi, H. Ichikawa, Y. Itagaki, K. Maruoka
Heterocycles, **2000**, *52*, 575.

Chapter 4 — Practical Approach for Meerwein-Ponndorf-Verley Reduction of Carbonyl Substrates with Newly Designed Aluminum Catalysts
T. Ooi, H. Ichikawa, K. Maruoka
Manuscript submitted for publication.

Appendix — Remarkable Catalytic Activity of Me_3Ga in the Alkylation of Hetero-Substituted Epoxides with Alkynyllithiums
T. Ooi, J. Morikawa, H. Ichikawa, K. Maruoka
Tetrahedron Lett., **1999**, *40*, 5881.

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