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Methylaluminum Bis(4-substituted-2,6-di-*tert*-butylphenoxide) as an Efficient Nonchelating Lewis Acid: Application to Asymmetric Diels-Alder Reaction and Diastereoselective Alkylation to Alkoxy Carbonyl Substrates

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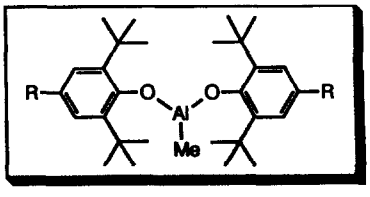
Abstract: The exceptionally bulky methylaluminum bis(4-substituted-2,6-di-*tert*-butylphenoxide) such as MAD or MABR can be successfully utilized as a highly efficient nonchelating Lewis acid for achieving high stereoselectivity in 1,n asymmetric induction in cyclic as well as acyclic systems. Thus, Diels-Alder reaction of the acrylate of D-pantolactone and cyclopentadiene in the presence of such bulky organoaluminum reagents exhibits high diastereoselectivity not observable with ordinary Lewis acids. Furthermore, high levels of nonchelation controlled diastereoselectivity are present in Grignard- and organolithium-types of addition to α- and β-alkoxy cyclic ketones in the presence of MAD or MABR.

Introduction

Control of 1,n asymmetric induction in acyclic and cyclic systems has been a long-standing concern and still remains a formidable challenge in asymmetric organic synthesis.[1] In order to achieve high levels of stereoselectivity, two strategies have been developed: 1) use of Lewis acidic reagents which are capable of bidentate complexation and thence form intermediate chelates, these being attacked by certain nucleophile stereoselectively from the less hindered site (*i.e., chelation control*); and 2) use of reagents incapable of chelation, the stereoselective approach governed by electronic and/or steric factors (*i.e., nonchelation control*).[2] These two approaches generally lead to an opposite sense of diastereoselectivity. Although a variety of chelating Lewis acids have been developed and widely utilized in selective organic synthesis, little is known of how to design efficient nonchelating Lewis acids. Only nonchelating alkylation agents of type $RTi(OPr^i)_3$ are found, for example, in Grignard- and aldol-types of addition to acyclic carbonyl substrates.[3] We now report that exceptionally bulky methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) and methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR) can be successfully utilized as efficient nonchelating Lewis acids for achieving high levels of stereoselectivity in 1,n-asymmetric induction in several reaction systems.

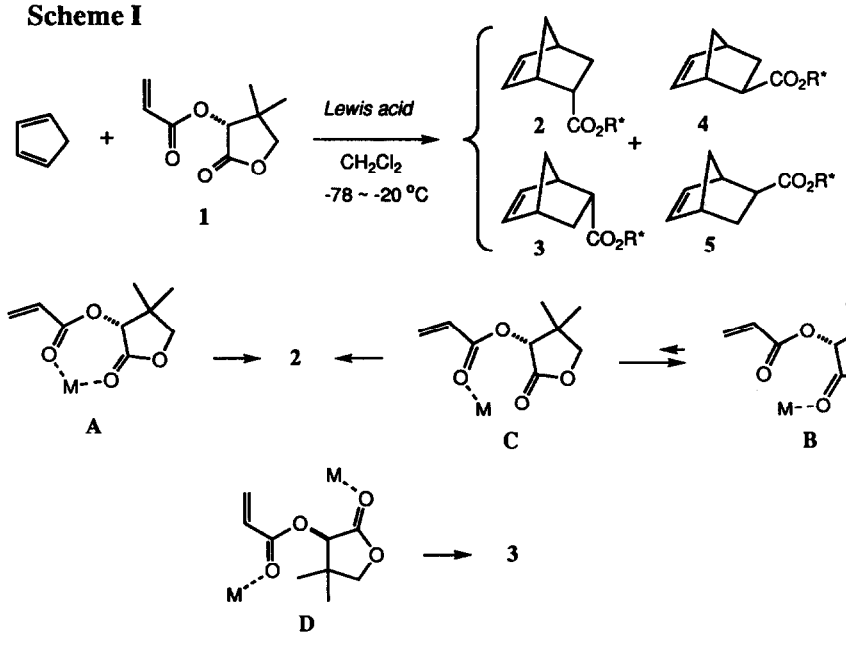


MAD (R = Me)
MABR (R = Br)

Results and Discussion

Asymmetric Diels-Alder Reaction of the Acrylate of D-Pantolactone. Helmchen *et al.* recently reported the highly diastereoselective $TiCl_4$-catalyzed Diels-Alder reaction of the acrylate **1** of commercially available D-pantolactone with cyclopentadiene, where a 1:1 acrylate-$TiCl_4$ chelation complex **A** with the *s-cis* conformation is formed to furnish the chelation-controlled cycloadduct **2** predominantly.[4] According to their procedure, we tested a variety of conventional Lewis acids in this system, always giving the chelation product **2** as a major product as shown in Table 1. Even $EtAlCl_2$, which is reported to be highly effective for obtaining the opposite sense of diastereoselectivity in the Diels-Alder reaction of the acrylate of (*S*)-ethyl lactate with cyclopentadiene [*e.g.*, ratio of (*R,R*)- and (*S,S*)-cycloadducts = 97:3 with $TiCl_4$ and 22:78 with $EtAlCl_2$],[4a,5] afforded the chelation product **2** (entries 10 and 11). In marked contrast, however, use of excess MAD (2 equiv) exhibited a totally opposite sense of stereoselectivity, giving the nonchelation-controlled cycloadduct **3** in 90% de (entry 16).[6] MABR gave a similar result (90% de) (entry 17). It should be added that 1 equiv of MAD afforded the chelation adduct **2** in 50%de (entry 14). Notably, bulky titanium reagent, $TiCl_2(OPr^i)_2$ works here as a chelation agent (entry 4).[3]

Scheme I



NMR Study of the Acrylate/Lewis Acid Complexes. Although chelation/nonchelation behavior of the acrylate **1**-MAD coordination complex is consistent with the above experimental findings, more direct evidence was obtained by low-temperature ^{13}C NMR spectroscopy. Thus, the 125 MHz ^{13}C NMR measurement of the 1:1 acrylate **1**-$SnCl_4$ chelation complex **A** in $CDCl_3$ at -50 °C showed that the original signals of acrylate carbonyl at δ 164.7 and pantolactone carbonyl at δ 172.7 shifted downfield to δ 165.9 and δ 177.0, respectively. In contrast, the ^{13}C NMR spectrum of 1:1 acrylate **1**-MAD complex under similar conditions showed an upfield shift for acrylate carbonyl (δ 163.8) and a downfield shift for pantolactone carbonyl (δ 182.6), suggesting the intervention of the complex **B**. The possibility of chelation

Table I. Diastereoselective Diels-Alder Reaction of Acrylate **1** and Cyclopentadiene [a]

entry	Lewis acid (equiv)	conditions (°C, h)	yield [b] (%)	*endo*/*exo* [c] (2+3:4+5)	ratio [d] (2:3)
1	$BF_3{\cdot}OEt_2$ (1)	-40, 6; -20, 1	39	94 : 6	74 : 26
2	$TiCl_4$ (0.1)	-20, 2	98	94 : 6	93 : 7
3	$TiCl_4$ (1)	-40, 14	83	97 : 3	97 : 3
4	$TiCl_2(OPr^i)_2$ (1)	-78, 2; -40, 7	91	91 : 9	77 : 23
5	$SnCl_4$ (2)	-40, 2	97	97 : 3	97 : 3
6	Me_3Al (2)	-78, 1	89	96 : 4	91 : 9
7	Et_2AlCl (1)	-78, 2	84	98 : 2	83 : 17
8	Et_2AlCl (2)	-78, 2	78	98 : 2	84 : 16
9	*i*-Bu_2AlCl (2)	-78, 4	87	98 : 2	81 : 19
10	$EtAlCl_2$ (1)	-40, 0.5	98	99 : 1	74 : 26
11	$EtAlCl_2$ (2)	-40, 0.5	97	99 : 1	86 : 14
12	MAPH (4) [e]	-40, 7; -20, 24	90	93 : 7	95 : 5
13	MAIP (4) [e]	-78, 1; -40, 20	87	97 : 3	71 : 29
14	MAD (1)	-20, 28	96	86 : 14	75 : 25
15	MABR (1)	-20, 15	99	83 : 17	71 : 29
16	MAD (2)	-20, 10	96	95 : 5	5 : 95
17	MABR (2)	-20, 2	97	89 : 11	5 : 95

[a] The Diels-Alder reaction of the acrylate **1** and cyclopentadiene was carried out in CH_2Cl_2 under the given reaction conditions. [b] Isolated yield. [c] The *endo*/*exo* ratios were determined by capillary GLC and/or 500 MHz ^1H NMR analysis. [d] The diastereomeric ratios were established by GLC analysis using PEG-HT capillary column. [e] MAPH: methylaluminum bis(2,6-diphenylphenoxide); MAIP: methylaluminum bis(2,6-diisopropylphenoxide).

complex A cannot be absolutely excluded for the 1:1 acrylate 1-MAD complex, but it seems much less likely. Furthermore, signals of acrylate and pantolactone carbonyls in the 1:2 acrylate 1-MAD complex appeared downfield at δ 171.5 and δ 180.0, respectively, implying the existence of the coordination complex D. Hence, the stereoselectivity in the MAD-promoted Diels-Alder reaction of 1 is hypothesized as follows. In the 1:1 acrylate 1-MAD complex, the complex B, though predominant, seems to be in equilibrium with minor complex C with the *s-cis* conformation, which then reacts with cyclopentadiene giving the cycloadduct 2. On the other hand, the diastereomeric adduct 3 would be produced via the complex D with the *s-trans* conformation in the 1:2 acrylate 1-MAD complex.

Chelation/Nonchelation Control in the Alkylation of Alkoxy Cyclic Ketones. The distinct nonchelating ability of MAD and MABR is also seen in Grignard-type of addition to various α- and β-alkoxy cyclic ketones. In spite of the numerous studies seeking to achieve the chelation-controlled selectivity with ordinary α- and β-alkoxy carbonyl substrates,[2,7] the corresponding nonchelation control has been realized *only in acyclic systems* with $RTi(OPr^i)_3$ reagents.[3] Indeed, in cyclic systems, the $RTi(OPr^i)_3$ reagent as a nonchelating agent showed selectivity similar to that of chelation agents by way of the coordination complex F, where R attacks the carbonyl group from the sterically less hindered side opposite to the alkoxy group.[8] For example, addition of α-benzyloxycyclohexanone (6) to MAD (2 equiv) in CH_2Cl_2 at -78 °C yielded a ketone-MAD complex which on subsequent treatment with MeMgBr in ether afforded a mixture of chelation and nonchelation products, 7 and 8 in a ratio of 5:95 (81% yield).[9] In the ketone 6-MAD complex G, MAD shields the less hindered side of the carbonyl (*i.e.*, opposite side to the alkoxy group), and hence MeMgBr appears to attack the carbonyl carbon of the ketone 6-MAD complex G from the sterically less hindered side (*i.e.*, same side to the alkoxy group) leading to the nonchelation product 8 in accord with the experimental finding.[2d,e,9] This amphiphilic alkylation is in sharp contrast to the preferential chelation selectivity in ordinary Grignard alkylation (7/8 = 94:6 with MeMgBr alone) via the chelation intermediate E. $MeTi(OPr^i)_3$ as a non-chelating agent also gave the chelation product 7 (7/8 = 67:33) via F as a nonchelation pathway in a cyclic system.

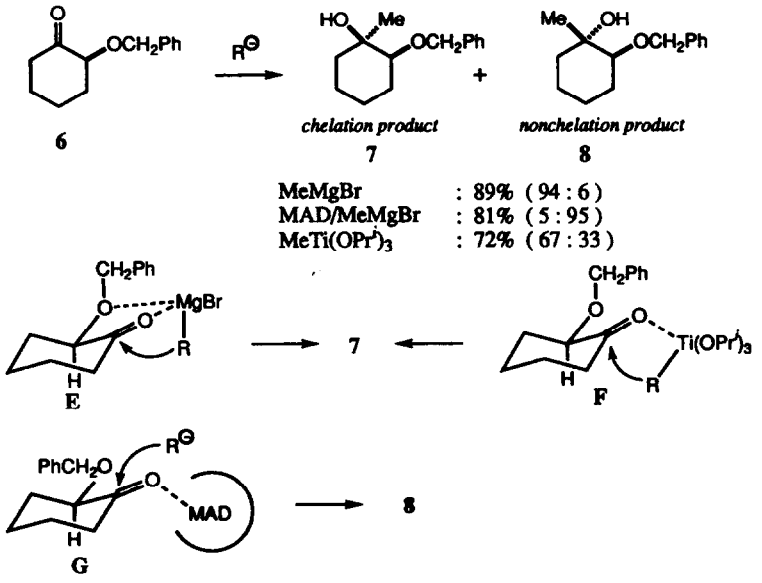
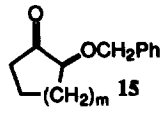
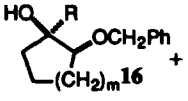
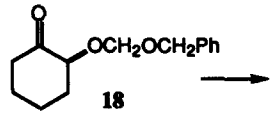
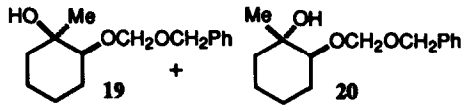
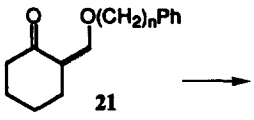
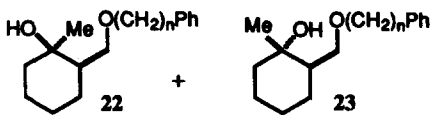


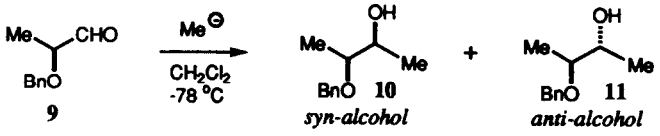
Table II. Chelation/Nonchelation Selectivity in the Alkylation of Cyclic α- and β-Alkoxycarbonyl Compounds [a]

entry	ketone	nucleophile	Lewis acid	% yield [b,c]	ratio [d]
					
1	(m = 1)	MeMgBr	none	69	70 : 30
2			MAD	72	0 : 100
3		$MeTi(OPr^i)_3$	none	89	52 : 48
4	(m = 2)	MeMgBr	none	89	94 : 6
5			MAD	81	5 : 95
6			MABR	89	10 : 90
7		MeLi	MAD	82	9 : 91
8		$MeTi(OPr^i)_3$	none	72	67 : 33
9		EtMgBr	none	91	98 : 2
10			MAD	42	24 : 76
11		BuC≡CLi	none	99	75 : 25
12			MAD	97	19 : 81
13	(m = 3)	MeMgBr	none	74	99 : 1
14			MAD	35	4 : 96
					
15		MeMgBr	none	64	92 : 8 [e]
16			MAD	52	13 : 87 [e]
					
17	(n = 1)	MeMgBr	none	93	76 : 24
18			MAD	62	21 : 79
19		$MeTi(OPr^i)_3$	none	93	100 : 0
20	(n = 0)	MeMgBr	none	85	91 : 9
21			MAD	71	10 : 90

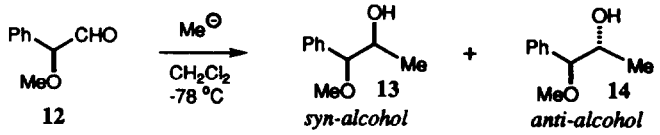
[a] The alkylation was carried out in ether/CH_2Cl_2 solvents at -78 °C for 0.5-1 h. [b] Isolated yield. [c] R = Me, Et, and 1-hexynyl. [d] Unless otherwise stated, the isomeric ratio was determined by capillary GLC analysis. [e] Determined by HPLC analysis.

Other examples are listed in Table II. In addition to various Grignard reagents, organolithiums are equally employable (entries 4-12). The nonchelation selectivity tends to be lower in β-alkoxy cyclic ketones (entry 18), and this tendency is ascribable to stronger coordination of the ethereal oxygen to MAD than that in α-alkoxy cyclic systems, where the coordination ability of an ethereal oxygen is lowered by the participation of neighboring carbonyl moiety. In fact, switching of benzyl to more electron-withdrawing phenyl groups enhanced the nonchelation selectivity (entry 21). The similar tendency is observed in the case of α-(benzyloxymethoxy)cyclohexanone (**18**), where the benzyloxy moiety coordinates to MAD more strongly than the other ethereal oxygen (entries 15 and 16 *vs* 4 and 5).

Chelation/Nonchelation Control in the Alkylation of α-Alkoxy Aldehydes. In the case of α-alkoxy aldehydes, the amphiphilic alkylation with MAD/MeMgBr or MABR/MeMgBr exhibited the diastereoselectivity similar to that with MeMgBr itself as exemplified by the methylation of α-(benzyloxy)propionaldehyde (**9**) and α-methoxyphenylacetaldehyde (**12**).

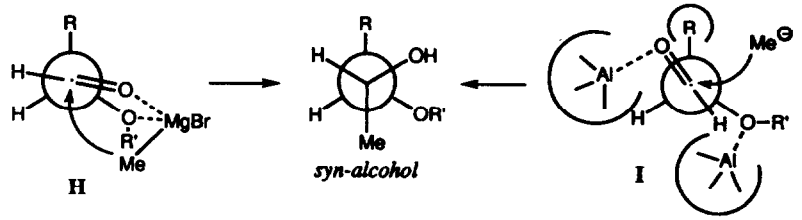


MeMgBr : 85% (89 : 11)
MAD/MeMgBr : 78% (98 : 2)
MABR/MeMgBr : 72% (95 : 5)



MeMgBr : 49% (91 : 9)
MAD/MeMgBr : 59% (80 : 20)
MABR/MeMgBr : 50% (72 : 28)

The stereochemistry of ordinary nucleophilic addition to the α-alkoxy aldehydes **9** and **12**, has been postulated to occur from conformations that form intermediate chelates and place the nucleophile (MeMgBr) in an antiperiplanar arrangement with the R group at the adjacent chiral center, leading to the *syn* products **10** and **13**, respectively, as depicted in the model **H**.[2,10] In contrast, with the amphiphilic reaction system the alkylation should be expected to proceed by the initial formation of the sterically least hindered complex **I** preferentially on treatment of **9** and **12** with MAD or MABR and subsequent attack of the nucleophile (Me^-) from the site opposite to the bulky aluminum reagent, affording the *syn* products **10** and **13**, respectively.[9]



The *syn* selectivity tends to be lowered by changing the R group of α-alkoxy aldehydes from methyl to phenyl. This trend is predictable from the mechanistic viewpoint of the amphiphilic alkylation, since the nucleophile is forced to attack the carbonyl carbon from the sterically crowded site, *i.e.*, between the R and alkoxy groups in the model I.

In summary, our study reveals that the exceptionally bulky methylaluminum bis(4-substituted-2,6-di-*tert*-butylphenoxide) can be utilized as a highly efficient nonchelating Lewis acid for achieving high stereoselectivity in 1,n asymmetric induction in cyclic as well as acyclic systems, and various data presented in this article imply the high synthetic potential of our new methodology in stereochemical control.

Experimental Section

General. Infrared (IR) spectra were recorded on a SHIMADZU FTIR-8100 spectrometer. ^1H NMR spectra were measured on a Varian Gemini-200 spectrometer. Analytical gas-liquid phase chromatography (GLC) was performed on Shimadzu GC-8A instruments equipped with a flame ionization detector and a capillary column of PEG-HT (0.25 X 25,000 mm) using nitrogen as carrier gas. High-performance liquid chromatography (HPLC) analyses were measured on a JASCO TRI ROTAR-V and JASCO UVIDEC-100-II instruments using Jasco Finepak Sil column (4.6 X 250 mm). 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 Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University.

In experiments requiring dry solvents, ether was freshly distilled from sodium metal using benzophenone ketyl as indicator. Benzene and hexane were dried over sodium metal. Methylene chloride was stored over 4A molecular sieves. In the catalytic process, methylene chloride as solvent was freshly distilled before use. Triethylamine was 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 Acrylate 1. The acrylate **1** of D-pantolactone was prepared from acryloyl chloride, D-pantolactone, and triethylamine in CH_2Cl_2 according to a literature procedure.[4a]

Preparation of α- and β-Alkoxy Cyclic Ketones. α-Benzyloxycyclohexanone (**6**) was prepared from 1,2-cyclohexanediol in 57% overall yield via the three-step sequences: (1) protection of this diol as benzaldehyde acetal with benzaldehyde dimethylacetal and catalytic *p*-TsOH; (2) reductive cleavage of the acetal with DIBAH in CH_2Cl_2; (3) Swern oxidation of the benzyloxy alcohol. Other α-benzyloxycycloalkanones were prepared in a similar manner as described above.

α-Benzyloxycyclohexanone (6): ^1H NMR ($CDCl_3$) δ 7.27-7.38 (5H, m, Ph-H), 4.77 (1H, d, J = 12.0 Hz, CH-Ph), 4.48 (1H, d, J = 12.0 Hz, CH-Ph), 3.89 (1H, dd, J = 5.6, 9.8 Hz, CH-O), 2.50-2.59 (1H, m, CH-C=O), 2.15-2.34 (2H, m, CH-C=O and CH), 1.90-2.01 (2H, m, CH_2), 1.59-1.90 (3H, m, CH and CH_2); IR (liquid film) 2942, 2867, 1721, 1497, 1453, 1211, 1072, 837, 739, 698 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.40; H, 8.05.

α-Benzyloxycyclopentanone 15 (m = 1): ^1H NMR ($CDCl_3$) δ 7.29-7.39 (5H, m, Ph-H), 4.84 (1H, d, J = 12.0 Hz, CH-Ph), 4.69 (1H, d, J = 12.0 Hz, CH-Ph), 3.81 (1H, dd, J = 9.6, 10.2 Hz, CH-O), 2.16-2.34 (3H, m, CH_2-C=O and CH), 1.93-2.09 (1H, m, CH), 1.60-1.90 (2H, m, CH_2); IR (liquid film) 2967, 2880, 1748, 1497, 1455, 1121, 1049, 818, 741, 698 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.69; H, 7.67.

α-Benzyloxycycloheptanone 15 (m = 3): ^1H NMR ($CDCl_3$) δ 7.30-7.36 (5H, m, Ph-H), 4.68 (1H, d, J = 11.7 Hz, CH-Ph), 4.44 (1H, d, J = 11.7 Hz, CH-Ph), 4.06 (1H, m, CH-O), 2.59 (1H, ddd, J = 5.1, 8.4, 15.6 Hz, CH-C=O), 2.42 (1H, ddd, J = 4.8, 7.5, 15.6 Hz, CH-C=O), 1.74-1.97 (4H, m, $2CH_2$), 1.48-1.72 (4H, m, $2CH_2$); IR (liquid film) 2932, 2861, 1713, 1455, 1327, 1208, 1113, 1028, 737, 698 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.00; H, 8.27.

α-(Benzyloxymethoxy)cyclohexanone (**18**),[7e] α-(benzyloxymethyl)cyclohexanone **21** (n = 1),[11] and α-(phenoxymethyl)cyclohexanone **21** (n = 0)[12] were prepared by literature methods.

Preparation of MAD. To a solution of 2,6-di-*tert*-butyl-4-methylphenol (2 equiv) in CH_2Cl_2 was added at room temperature a 2 *M* hexane solution of Me_3Al (1 equiv). The methane gas (~2 equiv) evolved

immediately. The resulting colorless solution was stirred at room temperature for 1 h and used as a solution of MAD in CH_2Cl_2 without any purification. Other modified organoaluminum reagents such as MABR, MAPH, and MAIP were prepared *in situ* from Me_3Al and the corresponding phenols in CH_2Cl_2 at room temperature for 1 h.

Asymmetric Diels-Alder Reaction of the Acrylate 1 with MAD. To a solution of MAD (1 mmol) in CH_2Cl_2 were added acrylate **1** (83 μL, 0.5 mmol) and cyclopentadiene (81 μL, 1 mmol) at -20 °C. The solution was stirred at -20 °C for 10 h. The reaction mixture was poured into 1*N* HCl, extracted with CH_2Cl_2, and dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography (ether/hexane = 1:1 as eluant) gave Diels-Alder adducts **2** ~ **5** (R* =D-pantolactonyl) in 96% yield. The used 2,6-di-*tert*-butyl-4-methylphenol can be readily removed chromatographically from the crude products, since this nonpolar phenol comes off the column before the desired Diels-Alder adducts. The isomeric ratio of the adducts was determined by capillary GLC analysis based on separated 4 peaks: t_R (**5** (R* =D-pantolactonyl)) = 16.9 min, t_R (**4** (R* =D-pantolactonyl)) = 17.7 min, t_R (**3** (R* =D-pantolactonyl)) = 18.9 min, t_R (**2** (R* =D-pantolactonyl)) = 21.8 min at the column temperature of 180°C. Diels-Alder adduct **3**:[4] ^{1}H NMR ($CDCl_3$) δ 6.22 (1H, dd, *J* = 3.1, 5.4 Hz, CH=), 6.10 (1H, dd, *J* = 2.5, 5.4 Hz, CH=), 5.32 (1H, s, CH-O), 3.95-4.10 (2H, m, CH_2-O), 3.31 (1H, br s, CH), 3.05-3.15 (1H, m, CHC=O), 2.95 (1H, br s, CH), 1.91-2.03 (1H, m, CH), 1.32-1.50 (3H, m, CH and CH_2), 1.17 (3H, s, CH_3), 1.11 (3H, s, CH_3).

Asymmetric Diels-Alder reactions with other modified organoaluminum reagents, MABR, MAPH, and MAIP were carried out in a similar manner as described above.

Asymmetric Diels-Alder Reaction of the Acrylate 1 with Ordinary Lewis Acids. A solution of Lewis acids in CH_2Cl_2 was added to a mixture of the acrylate **1** and cyclopentadiene in CH_2Cl_2 at -78 °C and the resulting mixture was stirred under the conditions indicated in Table I. The solution was then poured into dil HCl and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel (ether/hexane as eluants) to furnish Diels-Alder adducts. Diels-Alder adduct **2**:[4] ^{1}H NMR ($CDCl_3$) δ 6.27 (1H, dd, *J* = 3.1, 5.8 Hz, CH=), 5.91 (1H, dd, *J* = 2.8, 5.8 Hz, CH=), 5.34 (1H, s, CH-O), 3.97-4.11 (2H, m, CH_2-O), 3.28 (1H, br s, CH), 3.16 (1H, dt, *J* = 3.8, 4.0, 9.0 Hz, CHC=O), 2.96 (1H, br s, CH), 1.89-2.02 (1H, m, CH), 1.31-1.52 (3H, m, CH and CH_2), 1.19 (3H, s, CH_3), 1.15 (3H, s, CH_3).

Low-Temperature ^{13}C NMR Spectroscopy of the Acrylate 1/MAD Complex. MAD was prepared and purified by crystallization for the NMR study. Thus, a solution of Me_3Al (15 mL, 30 mmol) was added to a solution of 2,6-di-*tert*-butyl-4-methylphenol (13.22 g, 60 mmol) in degassed hexane (40 mL) at room temperature. The white precipitate appeared immediately. After 1 h, this mixture was heated until the precipitate redissolved in hexane. The resulting solution was stood for 3 h, yielding colorless crystal which was filtered in an argon box. Since the crystal includes some impurities such as 2,6-di-*tert*-butyl-4-methylphenol and inorganic aluminum salts, this was further recrystallized from hexane (45 mL) at -20 °C to give essentially pure MAD (7.83 g, 54% yield): ^{1}H NMR ($CDCl_3$) δ 7.04 (4H, s, C_6H_2), 2.28 (6H, s, CH_3), 1.53 (36H, s, $C(CH_3)_3$), -0.35 (3H, s, Al-CH_3); ^{13}C NMR ($CDCl_3$) δ 152.0, 138.2, 127.7, 125.9, 34.94, 31.56, 21.40, -9.09 (Al-$\underline{C}H_3$).

MAD (0.3 mmol) was transferred to the dry flask in an argon box, and $CDCl_3$ (0.2 mL) was added at room temperature. Then this solution was cooled to -78 °C and the acrylate **1** (0.15 or 0.3 mmol) was added at this temperature. The mixture was transferred by cannula to a 5-mm NMR tube at -78 °C and the 125 MHz ^{13}C

NMR spectra were taken at -50 °C. The coordination pattern of the acrylate **1**/MAD complex was measured by low-temperature ^{13}C NMR analysis of carbonyl carbons of the acrylate **1**.

Acrylate **1**: ^{13}C NMR ($CDCl_3$) δ 172.7 (pantolactone C=O), 164.7 (acrylate C=O), 133.6 (CH_2=), 126.3 (CH=), 75.84 (C-O), 74.73 (C-O), 40.37 (CMe_2), 22.59 (CH_3), 19.77 (CH_3).

Acrylate **1**-MAD (1:1) complex: ^{13}C NMR ($CDCl_3$) δ 182.6 (pantolactone C=O··Al), 163.8 (acrylate C=O).

Acrylate **1**-MAD (1:2) complex: ^{13}C NMR ($CDCl_3$) δ 180.0 (pantolactone C=O··Al), 171.5 (acrylate C=O··Al).

The ^{13}C NMR measurement of the 1:1 acrylate **1**-MAD complex at -20 °C showed a similar result.

Low-Temperature ^{13}C NMR Spectroscopy of the Acrylate 1/$SnCl_4$ Complex. To a solution of the acrylate **1** (0.3 mmol) in $CDCl_3$ (0.2 mL) in a 5-mm NMR tube was added $SnCl_4$ (0.3 mmol) at -78 °C and the 125 MHz ^{13}C NMR spectra were taken at -50 °C. The coordination pattern of the acrylate **1**/$SnCl_4$ complex was measured by low-temperature ^{13}C NMR analysis of carbonyl carbons of the acrylate **1**.

Acrylate **1**-$SnCl_4$ (1:1) complex: ^{13}C NMR ($CDCl_3$) δ 177.0 (pantolactone C=O··Sn), 165.9 (acrylate C=O··Sn), 135.9 (CH_2=), 125.6 (CH=), 79.21 (C-O), 76.11 (C-O), 41.18 (CMe_2), 22.36 (CH_3), 19.78 (CH_3).

General Procedure for Amphiphilic Alkylation of α- and β-Alkoxy Cyclic Ketones. To a solution of MAD (1.5 mmol) in CH_2Cl_2 (5 mL) was added at -78 °C carbonyl compound (0.5 mmol) followed by an ethereal solution of RLi or RMgX (1.5 mmol). The solution was maintained at -78 °C for 2 h. The reaction mixture was poured into 1 N HCl, and extracted with CH_2Cl_2. The combined extracts were, after drying over Na_2SO_4 and concentration, purified by column chromatography on silica gel (ether/hexane as eluant) to furnish a mixture of diastereomeric alcohols as listed in Table II. The isomeric ratio was determined by capillary GLC by comparison with authentic samples, which were prepared by the alkylation of the carbonyl compound with RLi or RMgX (3 equiv) at -78 °C for 1 h.

The physical properties and analytical data of diastereomeric alcohols are as follows.

***erythro*-2-Benzyloxy-1-methyl-1-cyclopentanol 16 (m = 1; R = Me):** ^1H NMR ($CDCl_3$) δ 7.29–7.39 (5H, m, Ph-H), 4.67 (1H, d, *J* = 11.8 Hz, CH-Ph), 4.52 (1H, d, *J* = 11.8 Hz, CH-Ph), 3.50 (1H, dd, *J* = 5.8, 6.4 Hz, CH-O), 2.73 (1H, br s, OH), 1.69-1.99 (4H, m, $2CH_2$), 1.46–1.68 (2H, m, CH_2), 1.27 (3H, s, CH_3); IR (liquid film) 3559, 2967, 1497, 1455, 1372, 1206, 1103, 941, 737, 698 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.79; H, 8.85.

***threo*-2-Benzyloxy-1-methyl-1-cyclopentanol 17 (m = 1; R = Me):** ^1H NMR ($CDCl_3$) δ 7.29–7.38 (5H, m, Ph-H), 4.63 (1H, d, *J* = 12.1 Hz, CH-Ph), 4.51 (1H, d, *J* = 12.1 Hz, CH-Ph), 3.59-3.65 (1H, m, CH-O), 2.19 (1H, br s, OH), 1.96-2.10 (1H, m, CH), 1.60–1.82 (5H, m, CH and $2CH_2$), 1.37 (3H, s, CH_3); IR (liquid film) 3389, 2965, 1497, 1455, 1372, 1204, 1109, 922, 735, 698 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.54; H, 8.82.

***erythro*-2-Benzyloxy-1-methyl-1-cyclohexanol (7):** ^1H NMR ($CDCl_3$) δ 7.28–7.39 (5H, m, Ph-H), 4.68 (1H, d, *J* = 11.6 Hz, CH-Ph), 4.46 (1H, d, *J* = 11.6 Hz, CH-Ph), 3.22 (1H, dd, *J* = 4.8, 7.0 Hz, CH-O), 2.41 (1H, br s, OH), 1.14-1.84 (8H, m, $4CH_2$), 1.24 (3H, s, CH_3); IR (liquid film) 3495, 2936, 2863, 1467, 1455, 1372, 1094, 1028, 735, 698 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.40; H, 9.27.

***threo*-2-Benzyloxy-1-methyl-1-cyclohexanol (8):** ^1H NMR ($CDCl_3$) δ 7.29–7.38 (5H, m, Ph-H), 4.70 (1H, d, *J* = 11.8 Hz, CH-Ph), 4.48 (1H, d, *J* = 11.8 Hz, CH-Ph), 3.28 (1H, dd, *J* = 4.2, 9.8 Hz,

CH-O), 2.20 (1H, br s, OH), 1.91-2.04 (1H, m, CH), 1.52–1.80 (3H, m, CH and CH_2), 1.24 (3H, s, CH_3), 1.20-1.50 (4H, m, $2CH_2$); IR (liquid film) 3427, 2936, 2863, 1497, 1455, 1372, 1098, 1030, 735, 698 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.29; H, 9.12.

***erythro*-2-Benzyloxy-1-ethyl-1-cyclohexanol 16 (m = 2; R = Et):** ^1H NMR ($CDCl_3$) δ 7.26–7.37 (5H, m, Ph-H), 4.67 (1H, d, J = 11.6 Hz, CH-Ph), 4.44 (1H, d, J = 11.6 Hz, CH-Ph), 3.26 (1H, dd, J = 4.2, 8.7 Hz, CH-O), 2.18 (1H, br s, OH), 1.48-1.86 (7H, m, CH and $3CH_2$), 1.15–1.44 (3H, m, CH and CH_2), 0.87 (3H, t, J = 7.5 Hz, CH_3); IR (liquid film) 3569, 2938, 2863, 1455, 1389, 1165, 963, 868, 735, 698 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.69; H, 9.31.

***threo*-2-Benzyloxy-1-ethyl-1-cyclohexanol 17 (m = 2; R = Et):** ^1H NMR ($CDCl_3$) δ 7.26–7.36 (5H, m, Ph-H), 4.67 (1H, d, J = 11.8 Hz, CH-Ph), 4.43 (1H, d, J = 11.8 Hz, CH-Ph), 3.34 (1H, dd, J = 3.6, 8.8 Hz, CH-O), 2.28 (1H, br s, OH), 1.46-2.00 (7H, m, CH and $3CH_2$), 1.24–1.35 (3H, m, CH and CH_2), 0.88 (3H, t, J = 7.5 Hz, CH_3); IR (liquid film) 3561, 2940, 1497, 1455, 1356, 1208, 1073, 974, 884, 737, 698 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.64; H, 9.23.

***erythro*-2-Benzyloxy-1-(1-hexynyl)-1-cyclohexanol 16 (m = 2, R = 1-Hexynyl):** ^1H NMR ($CDCl_3$) δ 7.27–7.38 (5H, m, Ph-H), 4.73 (1H, d, J = 11.6 Hz, CH-Ph), 4.64 (1H, d, J = 11.6 Hz, CH-Ph), 3.54 (1H, t, J = 5.4 Hz, CH-O), 2.83 (1H, br s, OH), 2.24 (2H, t, J = 6.6 Hz, CH_2), 1.88-2.05 (1H, m, CH), 1.25-1.83 (11H, m, CH and $5CH_2$), 0.91 (3H, t, J = 7.2 Hz, CH_3); IR (liquid film) 3450, 2936, 2863, 1456, 1354, 1175, 1073, 976, 866, 737, 698 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.63; H, 9.15.

***threo*-2-Benzyloxy-1-(1-hexynyl)-1-cyclohexanol 17 (m = 2, R = 1-Hexynyl):** ^1H NMR ($CDCl_3$) δ 7.30–7.38 (5H, m, Ph-H), 4.76 (1H, d, J = 12.3 Hz, CH-Ph), 4.57 (1H, d, J = 12.3 Hz, CH-Ph), 3.23 (1H, dd, J = 4.0, 11.2 Hz, CH-O), 2.93 (1H, br s, OH), 2.26 (2H, t, J = 6.6 Hz, CH_2), 1.85-2.03 (2H, m, CH_2), 1.14-1.84 (10H, m, $5CH_2$), 0.91 (3H, t, J = 7.2 Hz, CH_3); IR (liquid film) 3456, 2936, 2863, 1497, 1455, 1362, 1102, 1073, 911, 735, 698 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.61; H, 9.24.

***erythro*-2-Benzyloxy-1-methyl-1-cycloheptanol 16 (m = 3; R = Me):** ^1H NMR ($CDCl_3$) δ 7.33–7.37 (5H, m, Ph-H), 4.69 (1H, d, J = 11.3 Hz, CH-Ph), 4.43 (1H, d, J = 11.3 Hz, CH-Ph), 3.21 (1H, dd, J = 1.7, 8.7 Hz, CH-O), 1.28-1.96 (11H, m, $5CH_2$ and OH), 1.24 (3H, s, CH_3); IR (liquid film) 3567, 2930, 2863, 1497, 1455, 1368, 1069, 1028, 930, 733, 698 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.94; H, 9.04.

***threo*-2-Benzyloxy-1-methyl-1-cycloheptanol 17 (m = 3; R = Me):** ^1H NMR ($CDCl_3$) δ 7.28–7.35 (5H, m, Ph-H), 4.79 (1H, d, J = 11.7 Hz, CH-Ph), 4.44 (1H, d, J = 11.7 Hz, CH-Ph), 3.33 (1H, dd, J = 2.4, 9.6 Hz, CH-O), 2.43 (1H, s, OH), 1.90-2.02 (1H, m, CH), 1.34–1.81 (9H, m, CH and $4CH_2$), 1.22 (3H, s, CH_3); IR (liquid film) 3651, 2932, 2863, 1497, 1455, 1372, 1067, 1028, 947, 735, 696 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.98; H, 9.25.

***erythro*-2-(Benzyloxymethoxy)-1-methyl-1-cyclohexanol (19):**[7e] ^1H NMR ($CDCl_3$) δ 7.28-7.39 (5H, m, Ph-H), 4.90 (1H, d, J = 6.9 Hz, CH-Ph), 4.79 (1H, d, J = 6.9 Hz, CH-Ph), 4.65 (2H, s, O-CH_2-O), 3.44 (1H, dd, J = 4.2, 8.7 Hz, CH-O), 2.21 (1H, br s, OH), 1.51-1.86 (5H, m, CH and $2CH_2$), 1.26 (3H, s, CH_3), 1.21-1.47 (3H, m, CH and CH_2); IR (liquid film) 3495, 2936, 2863, 1455, 1375, 1159, 1103, 1042, 941, 737, 698 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.95; H, 8.65.

***threo*-2-(Benzyloxymethoxy)-1-methyl-1-cyclohexanol (20):** ^{1}H NMR ($CDCl_3$) δ 7.26-7.36 (5H, m, Ph-H), 4.89 (1H, d, *J* = 6.9 Hz, O-CH-O), 4.84 (1H, d, *J* = 6.9 Hz, O-CH-O), 4.74 (1H, d, *J* = 11.7 Hz, CH-Ph), 4.62 (1H, d, *J* = 11.7 Hz, CH-Ph), 3.40 (1H, dd, *J* = 4.5, 10.5 Hz, CH-O), 3.10 (1H, br s, OH), 1.86-1.96 (1H, m, CH), 1.65-1.80 (2H, m, CH_2), 1.54-1.64 (1H, m, CH), 1.24-1.47 (4H, m, $2CH_2$), 1.22 (3H, s, CH_3); IR (liquid film) 3493, 2865, 1455, 1379, 1103, 1044, 982, 853, 737, 698 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.00; H, 8.77.

***erythro*-2-(Benzyloxymethyl)-1-methyl-1-cyclohexanol 22 (n = 1):** ^{1}H NMR ($CDCl_3$) δ 7.28–7.35 (5H, m, Ph-H), 4.50 (2H, s, CH_2Ph), 3.89 (1H, dd, *J* = 3.6, 9.3 Hz, CH-O), 3.49 (1H, dd, *J* = 2.7, 9.3 Hz, CH-O), 3.27 (1H, s, OH), 1.87 (1H, ddd, *J* = 3.6, 11.4, 12 Hz, CH), 1.60-1.79 (3H, m, CH and CH_2), 1.36-1.51 (3H, m, CH and CH_2), 1.23 (3H, s, CH_3), 1.21-1.31 (2H, m, CH_2); IR (liquid film) 3509, 2930, 1455, 1370, 1163, 1098, 1001, 943, 735, 698 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.97; H, 9.40.

***threo*-2-(Benzyloxymethyl)-1-methyl-1-cyclohexanol 23 (n = 1):** ^{1}H NMR ($CDCl_3$) δ 7.29–7.38 (5H, m, Ph-H), 4.52 (2H, s, CH_2Ph), 3.93 (1H, s, OH), 3.52 (1H, t, *J* = 9.3 Hz, CH-O), 3.43 (1H, dd, *J* = 5.1, 9.3 Hz, CH-O), 1.84-1.94 (1H, m, CH), 1.59-1.74 (3H, m, CH and CH_2), 1.37-1.53 (2H, m, CH_2), 1.18-1.32 (2H, m, CH_2), 1.14 (3H, s, CH_3), 0.82-0.96 (1H, m, CH); IR (liquid film) 3454, 2930, 1497, 1455, 1366, 1140, 1075, 984, 735, 698 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.80; H, 9.03.

***erythro*-2-(Phenoxymethyl)-1-methyl-1-cyclohexanol 22 (n = 0):** ^{1}H NMR ($CDCl_3$) δ 7.26–7.32 (2H, m, Ph-H), 6.90–6.99 (3H, m, Ph-H), 4.17 (1H, dd, *J* = 3.9, 9.3 Hz, CH-OPh), 4.09 (1H, dd, *J* = 3.0, 9.3 Hz, CH-OPh), 2.37 (1H, s, OH), 1.49-1.84 (7H, m, CH and $3CH_2$), 1.32 (3H, s, CH_3), 1.21-1.43 (2H, m, CH_2); IR (liquid film) 3567, 2932, 1601, 1499, 1375, 1244, 1171, 1032, 941, 754, 691 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.22; H, 8.94.

***threo*-2-(Phenoxymethyl)-1-methyl-1-cyclohexanol 23 (n = 0):** ^{1}H NMR ($CDCl_3$) δ 7.26–7.32 (2H, m, Ph-H), 6.91–6.99 (3H, m, Ph-H), 4.10 (1H, dd, *J* = 8.3, 9.3 Hz, CH-OPh), 3.88 (1H, dd, *J* = 6.0, 9.3 Hz, CH-OPh), 2.98 (1H, s, OH), 1.97-2.07 (1H, m, CH), 1.67-1.82 (4H, m, $2CH_2$), 1.42-1.54 (1H, m, CH), 1.25-1.34 (2H, m, CH_2), 1.20 (3H, s, CH_3), 1.06-1.16 (1H, m, CH); IR (liquid film) 3285, 2940, 1603, 1499, 1372, 1246, 1163, 1036, 922, 752, 691 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.33; H, 9.00.

The GLC retention times of each isomer using a capillary column of PEG-HT at the indicated column temperature are as follows.

Methylation of α-benzyloxycyclopentanone **15** (m = 1): 14.8 min (**16** (m = 1; R = Me)), 29.8 min (**17** (m = 1; R = Me)) at 150 °C.

Alkylation of α-benzyloxycyclohexanone **15** (m = 2): methylation: 34.9 min (**16** (m = 2; R = Me)), 55.8 min (**17** (m = 2; R = Me)) at 140 °C; ethylation: 29.7 min (**16** (m = 2; R = Et)), 43.3 min (**17** (m = 2; R = Et)) at 150 °C; hexynylation: 116.5 min (**16** (m = 2; R = 1-hexynyl)), 120.2 min (**17** (m = 2; R = 1-hexynyl)) at 160 °C.

Methylation of α-benzyloxycycloheptanone **15** (m = 3): 53.8 min (**16** (m = 3; R = Me)), 77.4 min (**17** (m = 3; R = Me)) at 140 °C.

Methylation of (α-benzyloxymethyl)cyclohexanone **21** (n = 1): 34.9 min (**22** (n = 1)), 45.7 min (**23** (n = 1)) at 160 °C.

Methylation of (α-phenoxymethyl)cyclohexanone **21** (n = 0): 41.1 min (**22** (n = 0)), 54.7 min (**23** (n = 0)) at 170 °C.

In the case of α-(benzyloxymethoxy)cyclohexanone (**18**), the isomeric ratio of **19/20** was determined by HPLC analysis based on separated 2 peaks: t_R (**19**) = 10.3 min, t_R (**20**) = 13.9 min (EtOAc-hexane = 1:4, flow rate 1 mL/min).

Stereochemical Assignment of Hexynylation Products. The stereochemical structures of hexynylation products **16** and **17** (R = 1-hexynyl, m = 2) were, after catalytic hydrogenation over Pd/C and H_2 in THF, correlated to the hexylation products **16** and **17** (R = hexyl, m = 2), which were prepared by treatment of **15** (m = 2) with hexylmagnesium bromide in ether at -78 °C.

General Procedure for Amphiphilic Alkylation of α-Alkoxy Aldehydes. Amphiphilic alkylation of α-alkoxy aldehydes was carried out in a similar manner as described for the general procedure for amphiphilic alkylation of α- and β-alkoxy cyclic ketones. The isomeric ratio was determined by capillary GLC by comparison with authentic samples, which were prepared by the alkylation of the carbonyl compound with MeMgBr (3 equiv) in ether/CH_2Cl_2 at -78 °C for 1 h.

The physical properties and analytical data of diastereomeric alcohols are as follows.

***syn*-3-Benzyloxy-2-butanol (10):**[13] ^{1}H NMR ($CDCl_3$) δ 7.28–7.36 (5H, m, Ph-H), 4.67 (1H, d, *J* = 11.4 Hz, CH-Ph), 4.44 (1H, d, *J* = 11.4 Hz, CH-Ph), 3.61 (1H, ddq, *J* = 2.4, 6.3, 7.2 Hz, C<u>H</u>-OH), 3.31 (1H, dq, *J* = 6.3, 7.2 Hz, CH-O), 2.76 (1H, d, *J* = 2.4 Hz, OH), 1.17 (3H, d, *J* = 6.3 Hz, CH_3), 1.16 (3H, d, *J* = 6.3 Hz, CH_3).

***syn*-1-Methoxy-1-phenyl-2-propanol (13):**[14] ^{1}H NMR ($CDCl_3$) δ 7.29–7.38 (5H, m, Ph-H), 3.78-3.88 (2H, m, 2CH-O), 3.24 (3H, s, CH_3-O), 1.59 (1H, br s, OH), 0.97 (3H, d, *J* = 6 Hz, CH_3).

The GLC retention times of each isomer using a capillary column of PEG-HT at the indicated column temperature are as follows.

Methylation of α-benzyloxypropanal (**9**): t_R (**10**) = 71.6 min, t_R (**11**) = 90.9 min at 100 °C.

Methylation of α-methoxyphenylacetaldehyde (**12**): t_R (**13**) = 10.0 min, t_R (**14**) = 13.7 min at 120 °C.

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