a solution of *p*-toluenesulfonic acid monohydrate in ethanol (0.011 g of $TsOH·H_2O$ in 20 mL of absolute ethanol, pH ~3), and the reaction mixture was stirred at room temperature for 23 h. The mixture was neutralized with saturated aqueous sodium bicarbonate and extracted with methylene chloride. The aqueous layer was extracted with two portions of methylene chloride, and the combined organics were filtered through cotton and concentrated. Separation by HPLC (μ porasil, 1:2 Skelly-B–ethyl acetate) yielded 0.026 g (38%) of **1** as a colorless oil: $[\alpha]_D$ −34.2° (*c* 0.26, $CHCl_3$); ^1H NMR (360 MHz) δ 7.90 (d, 2 H, *J* = 9, C2′-H and C6′-H), 6.85 (d, 2 H, *J* = 9, C3′-H and C5′-H), 5.33 (dd, 1 H, *J* = 8.5, 2, C6-H), 5.12 (d, 1 H, *J* = 5, C1-H), 4.9 (dd, 1 H, *J* = 7, 4, C3-H), 4.05 (d, 1 H, *J* = 13, C10-H), 3.85 (dq, 2 H, *J* = 17, 8, CH_2 on Et), 3.63 (d, 1 H, *J* = 2, C7-H), 3.55 (d, 1 H, *J* = 13, C10-H), 3.52 (m, 2 H, CH_2 on Et), 2.8 (dd, 1 H, *J* = 7, 4, C9-H), 2.35 (m, 1 H, C5-H), 1.95 (ddd, 1 H, *J* = 14, 5, 3, *endo*-C4-H), 1.83 (ddd, 1 H, *J* = 14, 7, 7, *exo*-C4-H), 1,26 (dd, 3 H, *J* = 7, 7, CH_3 on Et), 1.18 (dd, 3 H, *J* = 7, 7, CH_3 on Et); ^{13}C NMR (125 MHz, CD_3OD) δ 168.3 (s, carbonyl C), 163.7 (s, C4′), 133.0 (s, C2′ and C6′), 122.0 (s, C1′), 116.2 (s, C3′ and C5′), 97.8 (d, C1), 94.9 (d, C3), 80.7 (d, C6), 67.3 (s, C8), 64.8 (t, CH_2 of Et), 64.0 (t, CH_2 of Et), 61.4 (t, C10), 61.2 (d, C7), 41.2 (d, C9), 34.2 (d, C5), 30.3 (t, C4), 15.5 (q, CH_3 of Et), 15.5 (q, CH_3 of Et); IR 3580, 3500–3200, 2940, 2880, 1715, 1615, 1520, 1170, 1120, 1030, 980, 860 cm^{-1}; HRMS, *m/e* calcd for $C_{20}H_{26}O_8$ 394.1628, found 394.1636.

Acknowledgment. This research has been supported by the National Institutes of Health (Grant GM-31750) and the Robert A. Welch Foundation (Grant F-626).

Amphiphilic Reactions by Means of Exceptionally Bulky Organoaluminum Reagents. Rational Approach for Obtaining Unusual Equatorial, Anti-Cram, and 1,4 Selectivity in Carbonyl Alkylation

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Abstract: Exceptionally bulky, oxygenophilic organoaluminum reagents, methylaluminum bis(2,6-di-*tert*-butyl-4-alkylphenoxide) (MAD and MAT), have been successfully utilized for stereoselective activation of carbonyl moiety. Combination of MAD or MAT with carbon nucleophiles such as organolithiums or Grignard reagents generates a new amphiphilic reaction system in which the alkylation may be interpreted as the nucleophilic addition of a reactive organometallic compound to an electrophilically activated carbonyl substrate in order to account for the regio- and stereochemical consequences. In contrast to the ordinary alkylations, the amphiphilic alkylation disclosed herein would be categorized into the new, yet unexplored class of alkylation that exhibits high chemoselectivity to carbonyl compounds, and more significantly it allows excellent equatorial and anti-Cram selectivity in carbonyl alkylations, hitherto difficult by the existing methodologies. Further, unusual conjugate addition of organolithium reagents to α,β-unsaturated carbonyl compounds has been accomplished by using the amphiphilic reaction system.

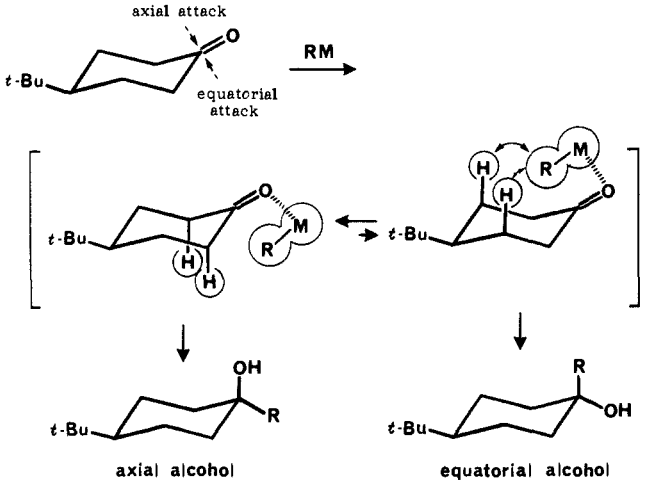
Carbonyl alkylation has long been recognized to be one of the most important C–C bond formation in organic synthesis.[1] Particularly, interest has been focused on the diastereoselective addition of C-nucleophiles (organolithiums and Grignard reagents) to a carbonyl compound possessing at least one chiral center, resulting in what has been termed "1,*n*-asymmetric induction". Among these, the addition of C-nucleophiles to chiral α- or β-alkoxy aldehydes or ketones has been extensively studied in recent years.[2] Accordingly, two strategies (chelation and nonchelation control) have been developed which enabled the achievement of opposite sense of diastereoselectivity by appropriately choosing organometallic reagents. These methods have been successfully applied to a variety of natural product syntheses including ionophores, pheromones, and carbohydrates.[3] In contrast, the alkylation of ordinary chiral aldehydes and ketones having no ability to be chelated is governed only by the electronic and/or steric factors (nonchelation control), and the diastereochemical outcome would be predicted by the Cram rule.[4] Here the numerous studies so far have been pursued for achieving only one side of selectivity, i.e., axial selectivity for cyclic ketones and Cram selectivity for acyclic carbonyl compounds, and the corresponding equatorial and anti-Cram selectivity have not been realized for lack of appropriate methodologies. The objective of our study is the development of a rational approach to this problem which permits a high level of diastereofacial selectivity hitherto quite difficult by the existing methodologies.[5]

According to Ashby and other authors, the stereoselectivity of organometallic compound addition to cyclohexanones is considered to be influenced by two main factors: (1) the steric interaction of the incoming group with the 3,5-axial substituents and (2) the torsional strain of the incoming group with the 2,6-diaxial substituents.[1] For a cyclohexanone with no 3- or 5-axial substituent larger than hydrogen, the axial selectivity is obtainable by the use of bulky organometallics, since steric interaction of the entering, bulky reagent with the axial hydrogens outweighs torsional effects. For example, the axial selectivity is enhanced by changing the reagent from MeMgBr to EtMgBr, *i*-PrMgBr, and *t*-BuMgBr.[1] Similarly, $MeTi(O\text{-}i\text{-}Pr)_3$ possessing bulky ligands is much superior

(1) Review: Ashby, E. C. *Chem. Rev.* **1975**, *75*, 521.
(2) (a) Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31. (b) Eliel, E. L. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Part A, p 125. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.
(3) (a) ApSimon, J. *The Total Synthesis of Natural Products*; Wiley: New York, Vol. 1–5, 1973–1983. (b) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3. (c) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (d) Mulzer, J. *Nachr. Chem. Tech. Lab.* **1984**, *32*, 16.
(4) General review: Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice Hall: New York, 1971.
(5) Preliminary report: Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573.

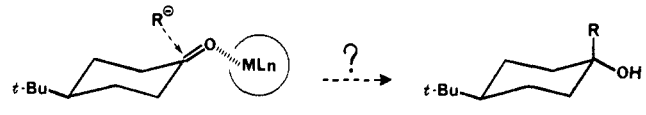
0002-7863/88/1510-3588$01.50/0

as a methylation agent to MeLi for obtaining the axial selectivity.[6]

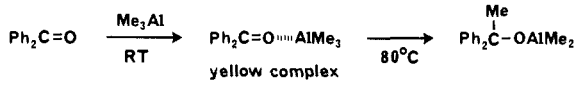


RM =	MeMgBr	69:31
	EtMgBr	71:29
	i-PrMgBr	82:18
	t-BuMgBr	100:0
RM =	MeLi	65:35
	MeTi(O-*i*-Pr)$_3$	94:6

In contrast, the equatorial selectivity is expected to obtain by using a small nucleophile. However, even methyllithium as the smallest methylation agent gave only 35% equatorial alcohol. Clearly, the strategy of modifying the nucleophile is not effective for obtaining the desired equatorial selectivity.[7] In this context, we have been intrigued for some time in the possibility that the addition of C-nucleophiles to the ketone–Lewis acid complex would occur from the axial site preferentially resulting in formation of equatorial alcohol, since the steric interaction of the Lewis acid with the 3,5-axial hydrogens would become a dominant factor and the torsional strain is out of consideration in the ketone–Lewis acid



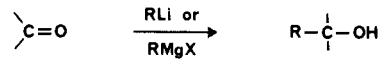
complex. The choice of organoaluminum reagents as Lewis acid would be suitable for our purpose in view of their high oxygenophilicity as well as the ease of modification in organoaluminum reagents.[8] Actually, reaction of benzophenone with trimethylaluminum in a 1:1 ratio is reported to give a long-lived monomeric 1:1 complex at room temperature which decomposes to dimethylaluminum 1,1-diphenylethoxide only during some minutes at 80 °C.[9]



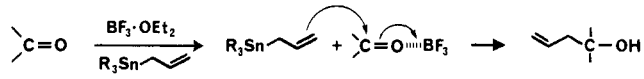
The known carbonyl alkylations can be divided into two classes depending on the mode of activation of either alkyl group or carbonyl substrate.[1,2] The nucleophilic addition of a highly

Classification of Carbonyl Alkylations

(1) Nucleophilic Alkylation



(2) Electrophilically Activated Alkylation

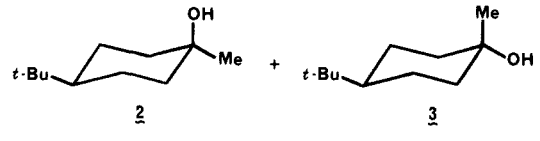


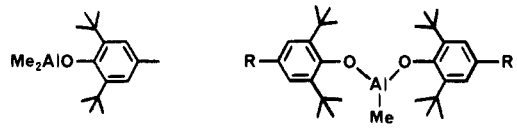
(3) Amphiphilic Alkylation

reactive organometallic compound (alkyllithium, Grignard reagent, etc.) to a carbonyl group is most widely utilized. The other, less general type of alkylation is effected by the combination of an electrophilically activated carbonyl substrate with an unactivated alkylation agent.[10] In contrast, the present new alkylation is interpretable as the nucleophilic addition of a reactive organometallic compound to an electrophilically activated carbonyl substrate. Such an amphiphilically activated alkylation, if successful, should be categorized into the third, yet unexplored class of alkylation that is expected to exhibit some unique selectivity not observable in ordinary alkylations.

Results and Discussions

Amphiphilic Alkylation of Cyclohexanones. The concept of an amphiphilic reaction system was first examined by the addition of a primary organolithium or a Grignard reagent (as nucleophile) to an unhindered cyclohexanone in the presence of an organoaluminum reagent (as Lewis acid). 4-*tert*-Butylcyclohexanone (**1**) is reported to react with MeLi at low temperature producing





Lewis acid:none	79:21
Me_3Al	76:24
i-Bu_3Al	64:36
Me_2AlOPh	72:28
Me_2AlO(2-mesityl)	69:31
DAD	5:95
MAD	1:99
MAT	0.5:99.5

a mixture of axial and equatorial alcohols, **2** and **3**, in a ratio of 79:21.[7a] Initial complexation of the ketone **1** with Me_3Al or *i*-Bu_3Al followed by treatment with MeLi at −78 °C gave a slight improvement in equatorial selectivity.[11] These disappointingly poor results might be due to the decomplexation by the undesired nucleophilic attack of MeLi to the Lewis acidic aluminum center.

(6) Recent stereoselective synthesis of axial alcohols from cyclohexanones: (a) MacDonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280. (b) Ashby, E. C.; Lin, J. J.; Watkins, J. J. *Tetrahedron Lett.* **1977**, 1709. (c) Ashby, E. C.; Willard, G. F. *J. Org. Chem.* **1978**, *43*, 4094. (d) Ashby, E. C.; Noding, S. A. *Ibid.* **1979**, *44*, 4371. (e) Weidmann, B.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 2451. (f) Weidmann, B.; Maycock, C. D.; Seebach, D. *Ibid.* **1981**, *64*, 1552. (g) Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1 and references cited therein.

(7) Previous attempt for equatorial alkylation with alkylaluminums: (a) Laemmle, J. T.; Ashby, E. C.; Roling, P. V. *J. Org. Chem.* **1973**, *38*, 2526. (b) Ashby, E. C.; Laemmle, J. T. *Ibid.* **1975**, *40*, 1469. Unfortunately, all organoaluminums except Me_3Al and Ph_3Al gave large amounts of reduction product.

(8) Recent review: Maruoka, K.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 668.

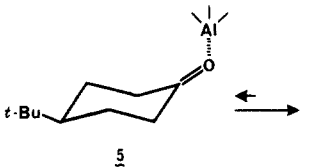
(9) Mole, T.; Surtees, J. R. *Aust. J. Chem.* **1964**, *17*, 961.

(10) This type of alkylation is exemplified by the Lewis acid promoted addition of allylic silanes and stannanes to carbonyl compounds. See: (a) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths: London, 1981; p 97. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (c) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: New York, 1983; p 173.

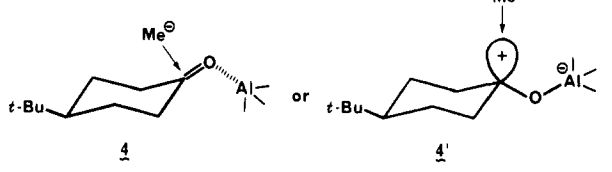
(11) For similar attempt, see: Ashby, E. C.; Laemmle, J. T. *J. Org. Chem.* **1975**, *40*, 1469.

Accordingly, some variation in the aluminum reagent was studied in detail under similar alkylation conditions. Among various aluminum modifiers, organoaluminum aryloxide seems to be most satisfactory in order to introduce the bulkiness and not to reduce the Lewis acidity too much. Attempted use of dimethylaluminum phenoxide and 2,4,6-trimethylphenoxide gave comparable results to those with trialkylaluminums (Me_3Al and i-Bu_3Al). Surprisingly, however, by switching the aluminum ligands to the more bulky 2,6-di-*tert*-butyl-4-methylphenoxy group the exceedingly high stereochemical control (95% equatorial selectivity) was attained. Further introduction of the bulky aryloxy moiety enabled the use of methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)[12] and methylaluminum bis(2,4,6-tri-*tert*-butylphenoxide) (abbreviated to MAD or MAT, respectively), both of which exhibited the virtually complete equatorial selectivity in carbonyl alkylation.[13] The effect of stoichiometry in the reagent has also been examined, and 3 equiv of MeLi and MAD each was found to be satisfactory as revealed in Table I. The need of excess MAD/MeLi would be interpreted as follows. When a small quantity of MeLi was added to the MAD–ketone complex at the initial stage of the reaction, decomplexation of the MAD–ketone by the attack of MeLi to the aluminum center also takes place in competition with the desired carbonyl alkylation. The free ketone, thus generated, again forms a 1:1 complex with excess MAD, thereby allowing the reuse for amphiphilic alkylation by adding the remaining MeLi.

The association of organoaluminum reagents through electron deficient bonds is a common phenomenon. However, in view of the bulky phenoxy group, MAD and MAT exist as monomeric aluminum species in nature, which could exhibit their high oxygenophilicity.[12] Hence, the unusually high equatorial selectivity observed herein may be ascribed to the eminent affinity of the oxygenophilic MAD and MAT for carbonyl oxygen. Treatment of the ketone **1** with MAD or MAT would produce the stable 1:1 complex. When MeLi was added as a nucleophile, the bulky aluminum reagent resulted in the preferential formation of the sterically favored isomer **4** or **4'** rather than the alternative **5**.



5



4 **4'**

Then MeLi appears to attack the carbonyl carbon of the complex **4** or **4'** from the sterically less hindered side leading to the equatorial alcohol **3** in accord with the experimental findings. The initial ate complex formation by the attack of MeLi to the aluminum reagent followed by reaction with the ketone seems to be unlikely, since treatment of **1** with a mixture of MeLi and MAD at −78 °C gave a result (axial/equatorial = 84:16) similar to that in the sole addition of MeLi.

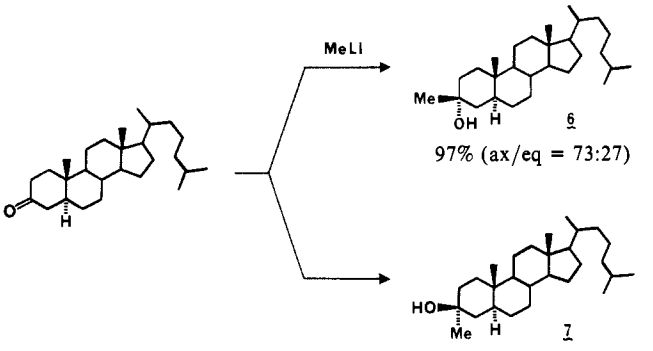
Some other examples are listed in Table II, which also includes the results in the absence of modified organoaluminum reagents for comparison. Clearly, MAD and MAT have played a crucial role for stereoselective activation of a carbonyl moiety leading to the stereoselective synthesis of hitherto unaccessible equatorial alcohols from cyclic ketones. The use of simple Grignard reagents as nucleophiles is also highly effective and in certain cases the stereoselection is complete. Introduction of large alkyl groups into the more hindered position of a ketone seems to be sluggish. Alkylation of 2-methylcyclohexanone with Et- or BuMgBr in the presence of MAD resulted in total recovery of the starting ketone. A similar tendency was observed in the methylation of the 2-phenylcyclopentanone–MAD complex. The radical pathway of the reaction was excluded by the simple alkylation of 2-(3-butenyl)cyclohexanone in the presence of MAD or MAT (entries 27 and 28).

Table I. Effect of Stoichiometry in the Methylation of the Ketone **1**–MAD Complex[a]

MAD (equiv)	MeLi[b] (equiv)	yield (%)	ratio[c] (ax/eq)
1	1	31	2:98
2	2	59	1:99
3	3	84	1:99
3	1	15	1:99

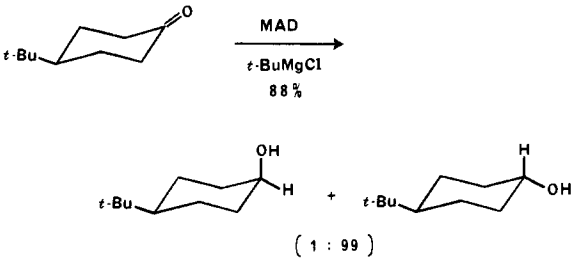
[a] Reaction was carried out in toluene at −78 °C for 2 h. [b] An ethereal solution. [c] Determined by GLC analysis.

The present approach has been quite useful in the stereoselective alkylation of steroidal ketone. Reaction of 3-cholestanone with MeLi gave predominantly 3β-methylcholestan-3α-ol (axial alcohol) (**6**), whereas amphiphilic alkylation of the ketone with the MAD/MeLi or MAT/MeLi system afforded 3α-methylcholestan-3β-ol (equatorial alcohol) (**7**) exclusively.



MAD/MeLi: 98% (ax/eq = 2:98)
MAT/MeLi: 99% (ax/eq = 1:99)

Amphiphilic Reduction of Cyclohexanones. In contrast to the facile MAD- or MAT-mediated alkylation of cyclic ketones with primary organolithiums or Grignard reagents, both alkylation and reduction occurred concurrently by the use of *sec*- or *tert*-alkylmagnesium halide as nucleophile. Treatment of the ketone **1** with MAD followed by the addition of i-PrMgBr gave rise to reduction products predominantly in 44% yield. GLC analysis indicated the ratio of the reduced axial/equatorial alcohol to be 2:98. This observation has prompted us to search for the amphiphilic reduction of cyclic ketones leading to the stereocontrolled synthesis of equatorial alcohols.[14,15] A series of reducing agents were surveyed by combination of **1** with MAD. Among these, t-BuMgCl and related analogues have proved to be most satisfactory (axial/equatorial = 1:99). Phenethylmagnesium chloride



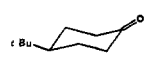
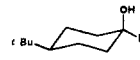
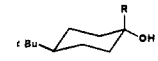
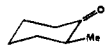
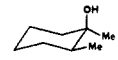
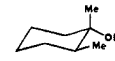
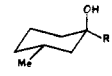
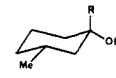
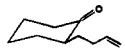
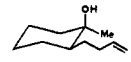
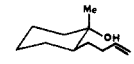
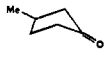
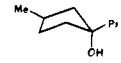
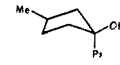
(12) Strarowieyski, K. B.; Pasynkiewicz, S.; Skowrońska-Ptasińska, M. *J. Organomet. Chem.* **1975**, *90*, C43.

(13) Other strong Lewis acids such as $TiCl_4$ and BF_3·OEt_2 were not effective.

(14) Preliminary report: Maruoka, K.; Sakurai, M.; Yamamoto, H. *Tetrahedron Lett.* **1985**, *26*, 3853.

(15) Reviews of carbonyl reductions: (a) Hajős, A. C. Se. *Complex Hydrides and Related Reducing Agents in Organic Synthesis*; Elsevier: New York, 1979. (b) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567. (c) Brown, H. C.; Krishnamurthy, S. *Aldrich. Acta* **1979**, *12*, 3. (d) Hudlický, M. *Reductions in Organic Chemistry*; Ellis Horwood: Chichester, 1984.

Table II. Stereoselective Alkylation of Cyclic Ketones[a]

entry	ketone	nucleophile[b]	Lewis acid[c]	yield[d] (%)	ratio[e] (ax/eq)
					
1		MeLi	none		79:21[g]
2			DAD	81	5:95
3			MAD	84	1:99
4			MAT	92	0.5:99.5
5		MeLi + MAD[f]		78	84:16
6		EtMgBr	none	95	48:52
7			MAD	91	0:100
8		BuMgBr	none	58	56:44
9			MAD	67	0:100
10		allylMgBr	none	86	48:52
11			MAD	90	9:91
					
12		MeLi	none		92:8[g]
13			DAD	80	58:42
14			MAD	84	14:86
15			MAD	90	7:93[h]
16			MAT	80	10:90[h]
17		MeLi + MAD[f]		81	91:9
					
18		MeLi	none	80	83:17
19			DAD	77	48:52
20			MAD	69	9:91[h]
21			MAT	95	3:97[h]
22		BuMgBr	none	86	79:21
23			MAD	75	1:99
24		AllylMgBr	none	95	56:44
25			MAD	72	24:76
					
26		MeLi	none	88	94:6
27			MAD	90	6:94
28		MeMgI	MAT	35	3:97
					
29		MeLi	none	77	75:25
30			MAD	82	1:99
					
31		PrMgBr	none	54	55:45
32			MAD	79	50:50

[a] Unless otherwise noted, alkylation was carried out by using a ketone, nucleophile, and Lewis acid (1:3:3 molar ratio) at −78 °C for 2–3 h. [b] Used as an ethereal solution. [c] Dimethylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide, methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide), and methylaluminum bis(2,4,6-tri-*tert*-butylphenoxide) are abbreviated to DAD, MAD, and MAT, respectively. [d] Isolated yield. [e] Determined by GLC analysis. [f] The ketone was added to an equimolar mixture of MeLi and MAD in ether–toluene at −78 °C. [g] See ref 6a. [h] The reaction was conducted at −95 °C for 3 h.

afforded a number of byproducts. Use of complex metal hydride reagents such as $LiAlH_4$, $LiBH_4$, lithium triethylborohydride (Super-Hydride), lithium tri-*sec*-butylborohydride (L-Selectride) exhibited little effect of MAD.

As revealed in Table III, the reaction is applicable to a variety of cyclohexanones. This amphiphilic reduction appears to be complementary to the existing methodologies using L-Selectride for obtaining axial selectivity.[16] As an oxygenophilic aluminum reagent, MAD is superior to DAD (entries 3 and 13). Notably, in the absence of MAD reaction of **1** with *t*-BuMgCl afforded a complex reaction mixture. It should be added that initial treatment of MAD with *t*-BuMgCl at 0 °C for 30 min followed by addition of **1** gave the similar stereoselectivity (axial/equatorial = 2:98) (entry 2). This implies that the interaction of MAD (as Lewis acid for the ketone) with *t*-BuMgCl (as nucleophile) is negligible under the conditions described above, and hence these two reagents constitute an amphiphilic system in the reduction of cyclohexanones. In contrast to the conventional methodology for the synthesis of equatorial alcohols using Cl_2AlH under thermodynamic conditions,[17] this reaction is irreversible, and the products are kinetically controlled.[18]

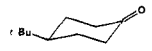
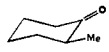
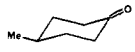
Chemoselectivity in the MAD- or MAT-Mediated Alkylations. In addition to the eminent equatorial selectivity, the present amphiphilic reaction has proved to possess the high chemoselectivity toward carbonyl moieties. Aldehydes and cyclic ketones are readily susceptible toward the nucleophilic attack of organometallic compounds in the presence of MAD, while certain acyclic ketones and esters are reluctant to the MAD-mediated alkylations under the standard conditions.[19] Among acyclic ketones, sterically less

(16) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

(17) (a) Eliel, E. L.; Rerick, M. N. *J. Am. Chem. Soc.* **1960**, *82*, 1367. (b) Eliel, E. L.; Martin, R. J. L.; Nasipuri, D. *Organic Syntheses*: Wiley: New York, 1973; Collect. Vol. 5, p 175.

(18) For equatorial selectivity with silyl hydride, see: Semmelhack, M. F.; Misra, R. N. *J. Org. Chem.* **1982**, *47*, 2469.

Table III. Stereoselective Reduction of Cyclohexanones[a]

entry	ketone	Lewis acid	reducing agent[b]	condn (°C, h)	yield[c] (%)	ratio[d] (ax/eq)
1		MAD	*t*-BuMgCl	0, 2.5	88	1:99
2		MAD + *t*-BuMgCl[e]		0, 3	93	2:98
3		DAD	*t*-BuMgCl	0, 2	81	3:97
4		MAD	*i*-PrMgBr	−78, 15	44	2:98
5		MAD	*i*-Bu_3Al	0, 1	98	44:56
6		MAD	*t*-BuMgCl	0, 2.5	77	12:88
7		MAD	*t*-BuMgCl	−23, 3.5	76	10:90
8		MAD	*t*-BuMgCl	−42, 4	57	10:90
9		MAD + *t*-BuMgCl[e]		0, 3	72	16:84
10		MAD[f]	*t*-BuMgCl	0, 3	77	16:84
11		MAD	*t*-AmylMgCl	0, 4	60	29:71
12		MAD	*t*-BuMgBr	0, 3.5	69	22:78
13		DAD	*t*-BuMgCl	0, 3	70	45:55
14		MAD	*t*-BuMgCl	0, 2 25, 1	85	5:95
15		MAD	*t*-BuMgCl	−23, 4	86	5:95
16		MAD	*t*-BuMgCl	0, 3.5 25, 1	84	8:92
17		MAD	*t*-BuMgCl	−23, 4	85	7:93

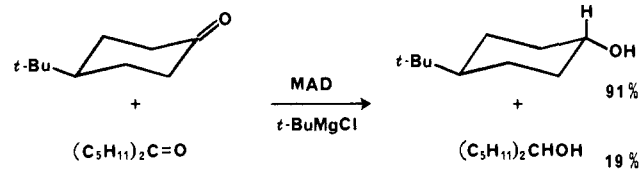
[a] Unless otherwise specified, reduction was carried out by adding the reducing agent (3 equiv) to a mixture of ketone (1 equiv) and Lewis acid (3 equiv). [b] Grignard reagents were used as an ethereal solution, while triisobutylaluminum in hexane was employed. [c] Isolated yield. [d] Determined by GLC analysis. [e] Initial treatment of MAD with *t*-BuMgCl at 0 °C for 30 min and subsequent addition of the ketone at 0 °C. [f] MAD was prepared in CH_2Cl_2.

Table IV. Cram/anti-Cram Selectivity in the Alkylation of α-Substituted Aldehydes[a]

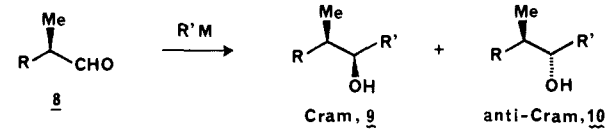
entry	aldehyde **8**	nucleophile	Lewis acid	yield[b] (%)	Cram (**9**): anti-Cram (**10**)[c]
1	R = Ph	MeMgI	none	64	72:28
2			MAT	96	7:93
3		EtMgBr	none	78	84:16
4			MAD	90	25:75
5			MAT	98	20:80
6			MAT[d]	90	13:87
7		BuMgBr	none	89	87:13
8			MAT	98	33:67
9		BuC≡CMgBr	none	64	78:22
10			MAT	96	41:59
11	R = 1-cyclohexenyl	MeMgI	none	64	79:21
12			MAT	84	2:98
13		EtMgBr	none	87	94:6
14			MAD	76	34:66
15			MAT	98	17:83
16		BuMgBr	none	88	94:6
17			MAT	97	26:74
18	R = cyclohexyl	MeMgI	none	81	82:18
19			MAD	88	22:78
20			MAT	75	23:77
21			MAT[d]	76	20:80
22		BuMgBr	none	81	89:11
23			MAT	89	77:23
24	R = $PhCH_2$	MeMgI	none	52	53:47
25			MAT	96	45:55
26		BuMgBr	none	68	50:50
27			MAT	94	39:61

[a] Alkylation was generally performed by using an aldehyde, Grignard reagent, and Lewis acid (1:3:3 molar ratio) at −78 °C for 1–2 h. [b] Isolated yield. [c] Determined by GLC analysis. [d] The reaction was carried out at −95 °C for 1–2 h.

demanding 2-undecanone, on treatment with MAD/EtMgBr at −78 °C for 2 h, gave rise to the desired ethylation product in 53% yield with 44% recovery of the starting ketone. In contrast, 6-undecanone afforded the ethylation product in only 15% yield with 80% of unreacted ketone. Similar treatment of ethyl phenylacetate with the MAD/EtMgBr system resulted in 95% recovery of the ester. Further, the cyclic ketone **1** can be reduced with moderate chemoselectivity in the presence of an acyclic one as illustrated below.



Amphiphilic Alkylation of α-Chiral Aldehydes. Even more significant is the application of the amphiphilic alkylation to α-chiral aldehydes having no ability to be chelated. Despite the numerous studies for achieving the Cram selectivity with ordinary α-chiral aldehydes,[20] the corresponding anti-Cram selectivity has not been easily realized for lack of appropriate methodologies.[2b,4,21] Indeed, the Cram/anti-Cram problem has been one of long-standing concern relating to the 1,2- and 1,3-asymmetric induction in acyclic systems.[2] A widely quoted example is the addition of organolithium and Grignard reagents to 2-phenylpropanal (**8**) (R = Ph) to form the Cram (erythro) product **9** (R = Ph, R′ = Me) and the anti-Cram (threo) product **10** (R = Ph, R′ = Me), generally in a ratio of about 2:1.[4] A recent attempt for obtaining Cram selectivity has revealed that the bulky organotitanium reagents are highly effective. With $MeTi(OR)_3$ (R = *i*-Pr, Ph) the ratios of Cram and anti-Cram product **9**:**10** turned out to be 88:12 ~ 93:7, which are much higher than those observed for MeLi or MeMgX (~2:1).[6g]



R = Ph: R′M =		
	MeLi, MeMgX	~2:1
	$MeTi(O\text{-}i\text{-}Pr)_3$	88:12
	$MeTi(OPh)_3$	93:7

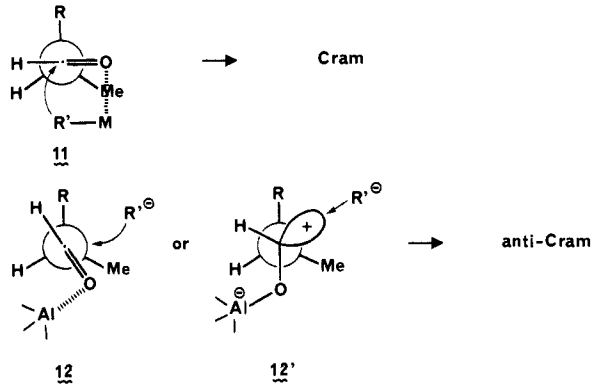
The stereochemistry of ordinary nucleophilic addition to the aldehyde **8** has been postulated to occur from a conformation that

(19) Chemoselective alkylation of carbonyl compounds with organotitanium reagents: Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: New York, 1986.

(20) Recent attempt for obtaining excellent Cram selectivity: (a) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667. (b) Yamamoto, Y.; Maruyama, K. *Ibid.* **1985**, *107*, 6411. (c) Yamamoto, Y.; Yamada, J. *Ibid.* **1987**, *109*, 4395.

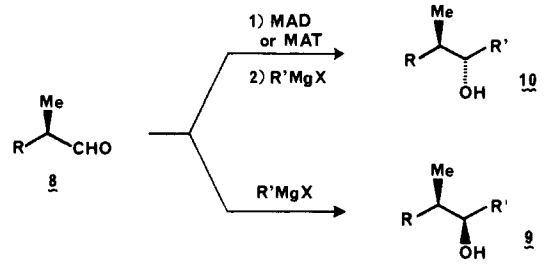
(21) So far only one method is reported to achieve the moderate anti-Cram selectivity. See ref 20b.

places the nucleophile (R′–M) in an antiperiplanar arrangement with the largest group (R) at the adjacent chiral center, leading to the Cram product **9** as depicted in model **11**.[22] In fact, the



11 **12** **12′**

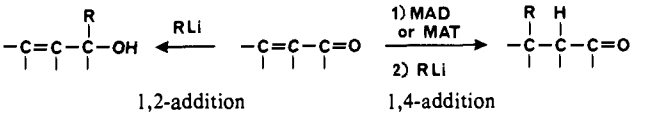
higher Cram selectivity was achievable by using the bulkier organometallics such as $MeTi(OR)_3$ compared to MeLi or MeMgX. The similar tendency was already observed in the organometallics-mediated alkylation of cyclic ketones.[6] In contrast, with an amphiphilic reaction system the alkylation should be expected to proceed by the initial formation of the sterically least hindered complex **12** or **12′** preferentially on treatment of **8** with MAD or MAT and subsequent attack of the nucleophile (R'^-) from the site opposite to the bulky aluminum reagent, affording the anti-Cram product **10** selectively. Thus, addition of the aldehyde **8** (R = Ph) to MAD in toluene at −78 °C gave a yellow aldehyde–MAD complex which on subsequent treatment with EtMgBr in ether afforded a mixture of Cram and anti-Cram product **9** (R = Ph; R′ = Et) and **10** (R = Ph; R′ = Et) in a ratio of 25:75



8 **10** **9**

(90% yield). This is in sharp contrast to the preferential Cram selectivity observed in ordinary alkylations (Cram/anti-Cram = 84:16 with EtMgBr solely). In addition, switching the modified aluminum reagent from MAD to MAT further enhanced the anti-Cram selectivity to 13:87. Other examples presented in Table IV clearly demonstrate the high synthetic utility of the new methodology in acyclic stereochemical control. It should be noted that the chemical yield can be also enhanced by the present amphiphilic alkylation. Use of organolithiums as nucleophiles gave less satisfactory results. In addition, the sp^2-carbon nucleophiles such as vinyl, phenyl, and enolate were introduced without any stereoselectivities. The anti-Cram selectivity tends to be lowered by changing the carbon nucleophile from Me^-, to Et^-, and Bu^-. 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 Me groups in the model **12** or **12′**.

Conjugate Addition of Organolithium to α,β-Unsaturated Carbonyl Compounds. The conjugate addition to α,β-unsaturated ketone is mostly effected by soft organometallics (Cu, Ni, Zr, Zn, Al, etc.),[23] and the sole use of organolithium reagent has never been developed for this purpose due to the hard nucleophilic character.[24] However, we have found that the conjugate addition of organolithium reagent to enone can be accomplished by combining use of MAD or MAT.[25] This new finding represents another, yet intriguing characteristic of the amphiphilic reaction systems in organic synthesis.



R = alkyl, vinyl, phenyl, enolate

Organolithium reagent normally adds to α,β-unsaturated ketone in a 1,2-fashion. For example, alkylation of 6-methyl-2-cyclohexenone with MeLi in ether at −78 °C gave rise to 1,2-adducts (cis/trans = ~1:1) in 75% yield. However, initial complexation of the enone with MAD (2 equiv) followed by treatment with MeLi (2 equiv) at −78 °C resulted in total reversal of selectivity, producing conjugate adducts, 2,5-dimethylcyclohexanone (cis/trans = 29:71),[26] exclusively in 68% yield. None of the 1,2-adducts were detected by TLC analysis. Notably, treatment of the enone with a mixture of MeLi and MAD at −78 °C afforded 1,2-adducts almost exclusively in 60% yield (cis/trans = ~1:1). This result implies that initial ate complex formation by the attack of MeLi to MAD followed by conjugate addition to the enone seems to be unlikely as similarly observed in the amphiphilic alkylation of cyclohexanones.[27] The reagent obtained by treatment of MAD with MeLi at 0 °C for 1 h was unreactive to the enone at −78 °C for 3 h. The effect of exact stoichiometry in the reagent was also examined with MAD/*t*-BuLi system. As revealed in Table V, 2 equiv of MAD/RLi each seems to be satisfactory for other alkylation experiments. The typical results summarized in Table VI show the following characteristic features. (1) The α,β-unsaturated ketone possessing the sterically less demanding carbonyl moiety, even when combined with MAD, is readily susceptible toward the nucleophilic attack of alkyllithium in a 1,2-fashion. The parent 2-cyclohexenone, 4-*tert*-butyl-2-cyclohexenone, and benzalacetone afforded only 1,2-adducts with MAD/RLi system (entries 11 and 21). Carvone, 2-methyl-2-cyclohexenone, and chalcone gave a mixture of 1,2- and 1,4-adducts depending on the steric and/or electronic effect of alkyllithiums (entries 12–16 and 23–25). The similar tendency was also observed in the cyclopentanone system (entries 19 and 20). In contrast, attempted alkylation of 2,6-dimethyl-2-cyclohexenone, 3,5-dimethyl-2-cyclohexenone, and (*E*)-4,4-dimethyl-1-phenyl-1-penten-3-one resulted in total recovery of the starting enones (entries 17, 18,

Table V. Effect of Stoichiometry in the Conjugate Butylation of the 6-Methyl-2-cyclohexenone/MAD Complex[a]

MAD (equiv)	*t*-BuLi[b] (equiv)	yield[c] (%)
1.5	1.5	52
2	2	73
3	3	77

[a] Alkylation was carried out in toluene at −78 °C for 30 min. [b] A pentane solution. [c] Isolated yield.

(22) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (c) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162. See, also: Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908.

(23) (a) *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 7 and 8. (b) Posner, G. H. *Org. React.* **1972**, *19*, 1. (c) Watson, R. A.; Kjonaas, R. A. *Tetrahedron Lett.* **1986**, *27*, 1437, and references cited therein.

(24) For restricted examples in the conjugate addition of organolithium to enone, see: (a) Mulzer, J.; Hartz, G.; Kühl, U.; Brüntrup, G. *Tetrahedron Lett.* **1978**, 2949. (b) Lucchetti, J.; Dumont, W.; Krief, A. *Ibid.* **1979**, 2695. (c) Seebach, D.; Locher, R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 957. (d) Roux, M. C.; Wartski, L.; Seyden-Penne, J. *Tetrahedron* **1981**, *37*, 1927.

(25) Maruoka, K.; Nonoshita, K.; Yamamoto, H. *Tetrahedron Lett.* **1987**, *28*, 5723.

(26) Bartlett, P. D.; Schueller, K. E. *J. Am. Chem. Soc.* **1968**, *90*, 6077.

(27) Conjugate addition of lithium (*E*)-1-alkenyltrialkylaluminate to cyclopentenones has been developed in prostaglandin synthesis with limited synthetic utility in view of several side reactions including the undesired alkyl transfer, conjugate reduction, and anionic oligomerization of cyclopentenones: Bernady, K. F.; Weiss, M. J. *Tetrahedron Lett.* **1972**, 4083. Floyd, M. B.; Weiss, M. J. *Prostaglandins* **1973**, *3*, 921. Bernady, K. F.; Poletto, J. F.; Weiss, M. J. *Tetrahedron Lett.* **1975**, 765. Floyd, M. B.; Weiss, M. J. *J. Org. Chem.* **1979**, *44*, 71. Bernady, K. F.; Floyd, M. B.; Poletto, J. F.; Weiss, M. J. *Ibid.* **1979**, *44*, 1438. The $Ni(acac)_2$ catalyzed conjugate methylation of enones by lithium tetramethylaluminate has been also reported; Ashby, E. C.; Heinsohn, G. *J. Org. Chem.* **1974**, *39*, 3297.

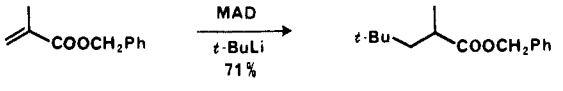
Table VI. Conjugate Addition of Alkyllithium to Enone in the Presence of MAD[a]

entry	enone	RM	1,4-adduct % yield[b] (c/t)[c]	1,2-adduct % yield[b]
1		MeLi	68 (29:71)[f]	
2		*n*-BuLi[d]	59 (17:83)[g]	
3		*t*-BuLi	73 (18:82)[f]	
4		PhLi	71 (33:67)[g]	
5		CH_2=C(O-*t*-Bu)OLi	87 (10:90)[g]	
6		EtMgBr[e]	35 (15:85)[f]	
7		BuC≡CLi	*h*	
8		MeLi	70	
9		PhLi	*h*	
10		Me_3SiC≡CLi	*h*	
11		MeLi		77[j]
12		MeLi	26	11
13		MeLi	65[i]	16
14		MeLi[e]	63[i]	31
15		*s*-BuLi	65[i]	12
16		CH_2=C(Me)Li	75[i]	
17		MeLi	*h*	
18		MeLi	*h*	
19		MeLi	74 (37:63)[g]	
20		*t*-BuLi	83 (24:76)[g]	
21	(*E*)-PhCH=CHC(=O)CH_3	MeLi		78
22	PhC≡CC(=O)CH_3	MeLi		85
23	(*E*)-PhCH=CHC(=O)Ph	MeLi	24	60
24		MeLi[e]	28	55
25		*t*-BuLi	77	9
26	(*E*)-PhCH=CHC(=O)Bu-*t*	MeLi	*h*	

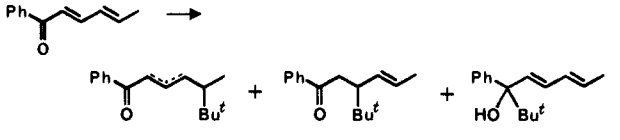
[a] Unless otherwise specified, alkylation was carried out at −78 °C by adding RLi (2 equiv) to the enone (1 equiv)–MAD (2 equiv) complex in toluene. [b] Isolated yield. [c] Ratio of the cis and trans isomers. [d] As an ethereal solution. Use of *n*-BuLi in hexane or THF gave the 1,4-adduct in 15% and 20% yield, respectively. [e] Use of MAT in CH_2Cl_2 in place of MAD. [f] Determined by GLC analysis. [g] Determined by ^{1}H NMR analysis. [h] Most recovery of the enone under the standard condition. [i] The high trans selectivity (>95%), which referred to the stereochemistries of the 3,5-dialkyl substituents, was observed. [j] Cis/trans = 14:86 by GLC analysis.

and 26). (2) A variety of alkyllithium reagents can be utilized. Introduction of the alkynyl group failed, however (entries 7 and 10). Grignard reagents as nucleophiles are less reactive with the enone–MAD complex, providing the conjugate adduct in much lower yield with some recovery of the enone (entry 6). (3) The stereochemistry in the conjugate addition is mostly governed by the size of alkyl substituents on the cycloalkenones, and the trans isomer always predominates over the cis. This selectivity is complementary to that in the organocopper-mediated conjugate addition of 6-methyl-2-cyclohexenone, in which the cis isomer is obtained as a major product (cis/trans = 7:3). (4) Use of nonpolar solvents such as toluene, CH_2Cl_2, ether, or their mixture gave consistently satisfactory results. (5) MAT may be equally employed in place of MAD (entries 6, 14, and 24).

In a similar fashion, organolithiums were found to undergo the conjugate addition to α,β-unsaturated esters in the presence of MAD, while without MAD the reaction gave a number of side products.



The present approach clearly demonstrates an illustration of the ability of the amphiphilic system by using MAD or MAT in order to alter the normal rules in reactivity and selectivity of organolithium reagents in the alkylation of enones. Application of the amphiphilic system to polyethylenic ketone is carried out in comparison with the organocopper reaction which is known to undergo α,ω conjugate addition.[23b] Treatment of (*E*,*E*)-1-phenyl-2,4-hexadien-1-one with MAD/*t*-BuLi or MAT/*t*-BuLi yielded the 1,6-adduct predominantly accompanied by 1,4- and 1,2-adducts.



MAD/*t*-BuLi: 73% yield (77:19:4)
MAT/*t*-BuLi: 95% yield (87:13:0)

Conclusions

The amphiphilic reaction has been increasingly important in organic synthesis for obtaining unusual reactivity and selectivity not observable in ordinary electrophilic and/or nucleophilic reactions. Several recent reports indicated that boron trifluoride etherate (BF_3·OEt_2) facilitated the addition of moderately basic main-group nucleophiles like organolithiums, Grignard reagents, and enolates to a variety of electrophiles which include (i) cleavage of epoxides with RLi–BF_3·OEt_2,[28] (ii) aldol-type reaction of acetals

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with lithium enolate–BF_3·OEt_2,[29] and (iii) alkylation of imines with RLi, RMgX, or lithium enolate–BF_3·OEt_2.[30,31] Others observed that trimethylsilyl chloride and its analogues promoted the selective 1,4-addition of organocopper compounds to carbonyl substrates without contamination of 1,2-addition.[32] Apparently the choice of Lewis acid is crucial for generating new amphiphilic systems. Oxygenophilic aluminum compounds seems to be quite suitable for this purpose. According to this line, initial effort was already reported in our laboratory in developing amphiphilic reduction of imines with the Me_3Al–$LiAlH_4$ system that allowed the hitherto difficult trans reduction of cyclic imines.[33] This methodology has been successfully applied to the straightforward synthesis of *trans*-2,6-dialkylpiperidine alkaloids.[34] In addition, the bulky, oxygenophilic organoaluminum reagents, MAD and MAT, have proved to exhibit exceptionally high diastereoface-differentiating ability (i.e., equatorial and anti-Cram selectivity) in carbonyl alkylation and reduction and unusual 1,4-selectivity in the addition of organolithium reagents to α,β-unsaturated carbonyl compounds. Hence, the concept of the amphiphilic systems has the growing tendency to be accepted and is further expected to possess the vast synthetic potential in selective organic synthesis.

Experimental Section

Preparation of Ketones. 4-Phenyl-3-butyn-2-one[28c] and 2-phenylcyclopentanone[35] were available by the literature procedure. Most enones were synthesized by a selenenylation–selenoxide elimination sequence according to Reich's method.[36]

2-(3-Butenyl)cyclohexanone.[37] To a solution of *N*-cyclohexylidene cyclohexylamine[38] (5.37 g, 30 mmol) in THF (90 mL) was added a 1.56 M hexane solution of *n*-BuLi (19.2 mL, 30 mmol) at 0 °C. The resulting yellow solution was stirred at 0 °C for 30 min. Then 4-bromo-1-butene (3 mL, 30 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 6 h and hydrolyzed with $(COOH)_2$·$2H_2O$ (7.56 g, 50 mmol) in water at room temperature for 1.5 h. The crude product was extracted with ether, dried, and concentrated. The residual oil was purified by column chromatography on silica gel (ether/hexane = 1:9 then 1:5 as eluant) to give the title ketone (4.05 g, 89% yield): ^{1}H NMR (CCl_4) δ 5.39–6.09 (1 H, m, –CH–C), 4.71–5.14 (2 H, m, –C=CH_2); IR (liquid film) 3090, 1713, 1643, 997, 910 cm^{-1}. 2-Butylcyclopentanone was obtained in a similar manner.

(*E*,*E*)-1-Phenyl-2,4-hexadien-1-one. To a solution of diisopropylamine (1.72 g, 17 mmol) in THF (20 mL) was added a 1.6 M hexane solution of *n*-BuLi (10 mL, 16 mmol) at 0 °C. After 20 min, the LDA solution was cooled to –78 °C and treated with acetophenone (1.8 g, 15 mmol) in THF (5 mL) at this temperature. The solution was stirred at –78 °C for 5 min, and crotonaldehyde (1.41 mL, 17 mmol) was then added. The whole mixture was stirred at –78 °C for 10 min and worked up with water. After extraction with ether, the combined extracts were dried, concentrated, and purified by column chromatography on silica gel (ether/hexane = 1:2 then 1:1 as eluant) to give the aldol product (2.3 g, 81% yield). The aldol product was dissolved in benzene (20 mL) and heated under reflux for 20 min in the presence of catalytic *p*-TsOH to give, after usual workup and purification by column chromatography on silica gel (AcOEt/hexane = 1:15 as eluant), the title dienone (1 g, 48% yield): ^{1}H NMR (CCl_4) δ 7.76–8.01 (2 H, m, Ar–H), 7.32–7.52 (3 H, m, Ar–H), 6.07–7.40 (4 H, m, C=C–H), 1.90 (3 H, d, J = 5 Hz, CH_3). Anal. ($C_{12}H_{12}O$) C, H.

Preparation of Aldehydes: 2-(1-Cyclohexenyl)propanal.[39] To a solution of LDA (prepared from diisopropylamine (2.31 mL, 16.5 mmol) and *n*-BuLi (9.15 mL, 15 mmol) in THF (30 mL) at 0 °C for 20 min) was added *N*-propylidene *tert*-butylamine (2.3 mL, 15 mmol) at 0 °C, and the mixture was stirred at 0 °C for 20 min. Cyclohexanone (1.24 mL, 12 mmol) was added at 0 °C, and the mixture was stirred there for 20 min. Then methanesulfonyl chloride (1.16 mL, 15 mmol) was added at 0 °C, and the whole mixture was stirred at 0 °C for 30 min. After hydrolysis with aqueous $(COOH)_2$, the crude product was extracted with ether, dried, and concentrated. The residual oil was purified by column chromatography on silica gel (ether/hexane = 1:7 as eluant) to give the title aldehyde (745 mg, 45% yield): ^{1}H NMR (CCl_4) δ 9.40 (1 H, d, J = 2 Hz, CHO), 5.53 (1 H, m, =C–H), 2.83 (1 H, qd, J = 6.5, 2 Hz, C=C–CH), 1.47–2.26 (8 H, m, CH_2), 1.12 (3 H, d, J = 6.5 Hz, CH_3); IR (liquid film) 1727 cm^{-1} (CHO).

2-Cyclohexylpropanal.[40] 2-(1-Cyclohexenyl)propanal (662 mg, 4.8 mmol), obtained above, was hydrogenated in THF (15 mL) over 10% Pd/C (150 mg) under H_2 (1 atm) at room temperature for 15 h. The mixture was filtered and concentrated to give an oil which was purified by column chromatography on silica gel (ether/hexane = 1:5 as eluant) to furnish the title aldehyde (563 mg, 85% yield): ^{1}H NMR (CCl_4) δ 9.56 (1 H, d, J = 2 Hz, CHO), 1.01 (3 H, d, J = 6.5 Hz, CH_3).

2-Methyl-3-phenylpropanal.[40] To a solution of LDA (90 mmol) in THF (120 mL) was added *N*-propylidene *tert*-butylamine (13.6 mL, 90 mmol) at 0 °C. After 20 min, benzyl bromide (8.3 mL, 90 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 1.5 h and at room temperature for 3 h. This was hydrolyzed with aqueous $(COOH)_2$ to furnish the title aldehyde (7.10 g, 69% yield) after purification by column chromatography on silica gel (ether/hexane = 1:8 as eluant): ^{1}H NMR (CCl_4) δ 9.59 (1 H, s, CHO), 7.12 (5 H, s, Ar–H), 2.36–3.32 (3 H, m, CH_2CH), 1.01 (3 H, d, J = 6 Hz, CH_3).

Preparation of MAD.[12] To a solution of 2,6-di-*tert*-butyl-4-methylphenol (2 equiv) in toluene was added at room temperature a 2 M hexane solution of Me_3Al (1 equiv). The methane gas evolved immediately. The resulting mixture was stirred at room temperature for 1 h and used as a solution of MAD in toluene without any purification.

Preparation of MAT. To a solution of 2,4,6-tri-*tert*-butylphenol (2 equiv) in CH_2Cl_2 was added at room temperature a 2 M hexane solution of Me_3Al (1 equiv). The mixture was stirred at room temperature for 1 h and used as a solution of MAT in CH_2Cl_2. Since MAT tends to solidify in toluene at low temperature, CH_2Cl_2 is recommended as a solvent for the preparation of MAT. Other modified organoaluminum reagents were prepared in situ from Me_3Al and the corresponding phenols in either toluene or CH_2Cl_2 at room temperature for 1 h.

General Method for Amphiphilic Alkylation of Cyclohexanones and α-Chiral Aldehydes. To a solution of MAD in toluene or MAT in CH_2Cl_2 (3 mmol in 10 mL of solvent) at –78 °C was added carbonyl compound (1 mmol) followed by an ethereal solution of MeLi or RMgX (3 mmol). The solution was maintained at –78 °C for 2 h. The reaction mixture was poured into 1 N HCl, and the organic layer was washed with brine. The combined ether extracts were, after concentration, purified by column chromatography on silica gel (ether/hexane as eluant) to give a mixture of diastereomeric alcohols as listed in Tables II and IV. The isomeric ratio was determined by capillary GLC by comparison with authentic samples which were prepared by the alkylation of the carbonyl compound with MeLi or RMgX (3 equiv) at –78 °C for 1 h.[1] The GLC retention times of each isomer using a capillary column of PEG-HT (0.25 × 25 000 mm) at the indicated column temperature are as follows. Alkylation of cyclic ketones: methylation of **1**: 13.7 min (axial alcohol), 18.5 min (equatorial alcohol) at 100 °C; ethylation of **1**: 8.5 min (axial alcohol), 9.8 min (equatorial alcohol) at 130 °C; butylation of **1**: 16.6 min (axial alcohol), 17.3 min (equatorial alcohol) at 130 °C; allylation of **1**: 11.7 min (axial alcohol), 13.3 min (equatorial alcohol) at 130 °C; methylation of 2-methylcyclohexanone: 6.4 min (axial alcohol), 8.3 min (equatorial alcohol) at 100 °C; methylation of 3-methylcyclohexanone: 10.1 min (axial alcohol), 13.4 min (equatorial alcohol) at 80 °C; butylation of 3-methylcyclohexanone: 10.9 min (axial alcohol), 11.9 min (equatorial alcohol) at 110 °C; allylation of 3-methylcyclohexanone: 8.2

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min (axial alcohol), 9.2 min (equatorial alcohol) at 110 °C; methylation of 2-(3-butenyl)cyclohexanone: 5.2 min (axial alcohol), 6.2 min (equatorial alcohol) at 130 °C; methylation of 2-butylcyclopentanone: 3.2 min (axial alcohol), 3.7 min (equatorial alcohol) at 130 °C; propylation of 3-methylcyclopentanone: 11.8 min (axial alcohol), 12.3 min (equatorial alcohol) at 80 °C. Alkylation of substituted aldehydes: methylation of **8** (R = Ph): 7.2 min (erythro isomer), 8.1 min (threo isomer) at 150 °C; ethylation of **8** (R = Ph): 8.2 min (threo isomer), 9.4 min (erythro isomer) at 150 °C; butylation of **8** (R = Ph): 8.1 min (threo isomer), 9.0 min (erythro isomer) at 150 °C; hexynylation of **8** (R = Ph): 10.6 min (erythro isomer), 11.4 min (threo isomer) at 200 °C; methylation of **8** (R = 1-cyclohexenyl): 7.1 min (threo isomer), 8.2 min (erythro isomer) at 150 °C; ethylation of **8** (R = 1-cyclohexenyl): 6.1 min (threo isomer), 7.0 min (erythro isomer) at 150 °C; butylation of **8** (R = 1-cyclohexenyl): 7.4 min (threo isomer), 8.3 min (erythro isomer) at 160 °C; methylation of **8** (R = cyclohexyl): 7.2 min (erythro isomer), 7.7 min (threo isomer) at 140 °C; butylation of **8** (R = cyclohexyl): 10.6 min (erythro isomer), 11.4 min (threo isomer) at 150 °C; methylation of **8** (R = benzyl): 8.4 min (threo isomer), 8.9 min (erythro isomer) at 170 °C; butylation of **8** (R = benzyl): 10.7 min (threo isomer), 11.6 min (erythro isomer) at 180 °C.

Reaction of 4-*tert*-Butylcyclohexanone (1) with a Mixture of MeLi and MAD. To a solution of MAD (3 mmol) in toluene (10 mL) was added at −78 °C a 1.5 M ethereal solution of MeLi (2 mL, 3 mmol). After 10 min, the ketone **1** (154 mg, 1 mmol) was added at − 78 °C. The mixture was stirred at −78 °C for 1 h, poured into 1 N HCl, and extracted with ether. The combined ethereal extracts were dried, concentrated, and purified by column chromatography on silica gel (ether/hexane = 1:8 as eluant) to furnish a mixture of axial and equatorial alcohols (133 mg, 78% yield), the ratio of which was determined by capillary GLC to be 84:16.

Attempted Alkylation of 2-Phenylcyclopentanone. To a solution of MAD (1.5 mmol) in toluene (5 mL) was added at −78 °C 2-phenylcyclopentanone (80 mg, 0.5 mmol) in toluene (1 mL). After 10 min, a 1.5 M ethereal solution of MeLi (1 mL, 1.5 mmol) was added at −78 °C. The mixture was stirred at −78 °C for 1 h and at −45 °C for 1 h resulting in recovery of most of the starting ketone.

Alkylation of 3-Cholestanone with MeLi. To a solution of 3-cholestanone (348 mg, 0.9 mmol) in ether (15 mL) and CH_2Cl_2 (6 mL) was added at −78 °C a 1.5 M ethereal solution of MeLi (1.8 mL, 2.7 mmol). The resulting mixture was stirred at −78 °C for 30 min and poured into water. The organic layer was extracted with ether. The combined extracts were dried and concentrated. The crude products were separated by column chromatography on silica gel (ether/hexane = 1:3 to 1:2, 1:1, and 2:1 as eluant) to furnish 3β-methylcholestan-3α-ol (264 mg, 66% yield) and then 3α-methylcholestan-3β-ol (96 mg, 24% yield).[42] 3β-Methylcholestan-3α-ol: ^{1}H NMR (CCl_4) δ 0.91 (3 H, s, CH_3), 0.87 (9 H, d, J = 6 Hz, CH−CH_3), 0.72 (3 H, s, CH_3), 0.64 (3 H, s, CH_3); IR (CCl_4) 3630, 1458, 1445, 1375, 1170, 1110, 1040, 950, 895 cm^{-1}. 3α-Methylcholestan-3β-ol: ^{1}H NMR (CCl_4) δ 0.91 (3 H, s, CH_3), 0.86 (9 H, d, J = 6 Hz, CH−CH_3), 0.80 (3 H, s, CH_3), 0.64 (3 H, s, CH_3); IR (CCl_4) 3633, 1463, 1443, 1380, 1155, 1095, 1015, 940, 925, 913 cm^{-1}.

Alkylation of 3-Cholestanone with the MAD/MeLi System. To a solution of MAD (2 mmol) in toluene (8 mL) was added at −78 °C 3-cholestanone (258 mg, 0.67 mmol) in toluene (2 mL). After 10 min, a 1.37 M ethereal solution of MeLi (1.46 mL, 2 mmol) was added at this temperature. The mixture was stirred at −78 °C for 2 h and poured into 1 N HCl. After extraction with ether, the combined extracts were dried, concentrated, and purified by column chromatography on silica gel (ether/hexane = 1:3 to 1:2, 1:1, and 2:1 as eluant) to give 3β-methylcholestan-3α-ol (6 mg, 2% yield) and 3α-methylcholestan-3β-ol (257 mg, 96% yield).[42] The amphiphilic alkylation of 3-cholestanone with MeLi/MAT system was carried out in a similar manner as described above.

Reaction of 4-*tert*-Butylcyclohexanone (1) with the MAD/*i*-PrMgBr System. To a solution of MAD (1.5 mmol) in toluene (5 mL) was added at −78 °C the ketone **1** followed by a 1.63 M ethereal solution of *i*-PrMgBr (0.92 mL, 1.5 mmol). The mixture was stirred at −78 °C for 1.5 h and at −45 °C for 1.5 h. The solution was poured into 1 N HCl and extracted with ether. The combined extracts were dried, concentrated, and purified by column chromatography on silica gel (ether/hexane = 1:4 to 1:1 as eluant) to furnish 4-*tert*-butylcyclohexanol (69 mg, 44% yield) as a mixture of axial and equatorial isomers.[43] The isomeric ratio of axial and equatorial alcohols was determined to be 2:98 by GLC analysis: t_R (axial) = 5.9 min, t_R (equatorial) = 6.0 min (25-m PEG-HT capillary column at 150 °C).

General Method for Amphiphilic Reduction of Cyclohexanones. To a solution of MAD (3 mmol) in toluene (10 mL) were added successively substituted cyclohexanone (1 mmol) and an ethereal solution of *t*-BuMgCl (3 mmol) at −78 °C. The mixture was stirred under the conditions as described in Table III and poured into 1 N HCl. The ethereal extracts were dried and concentrated. The residual liquid was chromatographed on silica gel (ether/hexane as eluant) to furnish a mixture of axial and equatorial alcohols as illustrated in Table III. The isomeric ratio was determined by capillary GLC by comparison with authentic samples which were prepared by the literature procedure.[15b] The GLC retention times of axial and equatorial alcohols using 25-m PEG-HT column (column temperature, 80 °C) follow: 2-methylcyclohexanol: 10.6 min (axial), 11.0 min (equatorial); 3-methylcyclohexanol: 13.5 min (axial), 14.9 min (equatorial); 4-methylcyclohexanol: 13.8 min (axial), 15.2 min (equatorial).

MAD-Mediated Reduction of 4-*tert*-Butylcyclohexanone (1) with Various Reducing Agents. The reduction of the ketone **1** was examined with various reducing agents in the presence of MAD, the result being summarized in the text and Table III. Thus, the ketone **1** (1 mmol) followed by a reducing agent (3 mmol) was added to a solution of MAD (3 mmol) in toluene (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and then treated as described in the general method for amphiphilic reduction of cyclohexanones.

Attempted Reduction of Cyclohexanones with Cl_2AlH under Kinetic Conditions. Reduction of substituted cyclohexanones with Cl_2AlH (2 equiv: prepared according to ref 17) in ether at 0 °C for 1 h afforded a mixture of axial and equatorial alcohols with low stereoselectivity: 4-*tert*-butylcyclohexanone (96%; axial/equatorial = 18:82); 2-methylcyclohexanone (95%; 44:56); 3-methylcyclohexanone (94%; 27:73).

Chemoselectivity in the MAD-Mediated Alkylations. The chemoselectivity in the amphiphilic alkylation of the carbonyl substrate was examined with the MAD/EtMgBr system. Thus, the carbonyl substrate (1 mmol) and an ethereal solution of EtMgBr (3 mmol) were added successively to a solution of MAD (3 mmol) in toluene at −78 °C. The resulting mixture was stirred at −78 °C for 2 h and worked up with 1 N HCl. The crude product was purified by column chromatography on silica gel (ether/hexane as eluant). Benzaldehyde and cyclohexanone gave the corresponding ethylation product quantitatively, while 2- and 6-undecanone afforded a mixture of ethylation product (53% and 15%, respectively) and unreacted ketone (44% and 80%, respectively). In case of ethyl phenylacetate, no ethylation product was isolated, and the starting ester was recovered in 95% yield.

Chemoselective Reduction of Cyclic Ketone in the Presence of Acyclic Ketone. To a solution of MAD (1.5 mmol) in toluene (5 mL) was added at −25 °C a mixture of 4-*tert*-butylcyclohexanone (**1**) (74 mg, 0.5 mmol) and 6-undecanone (85 mg, 0.5 mmol) in toluene (1 mL). After 5 min, a 1.46 M ethereal solution of *t*-BuMgCl (1.03 mL, 1.5 mmol) was added at this temperature. The mixture was stirred at −25 °C for 1 h and poured into 1 N HCl. Extraction with ether followed by separation by column chromatography on silica gel (ether/hexane = 1:4 to 1:1 as eluant) gave 6-undecanol (16 mg, 19% yield) and 4-*tert*-butylcyclohexanol (71 mg, 91% yield). GLC analysis of the latter showed the axial/equatorial ratio to be 1:99.

General Method for Conjugate Addition of Organolithium to Enone. To a solution of MAD (1 mmol) in toluene (5 mL) was added enone (0.5 mmol) at −78 °C to yield the enone–MAD complex as a yellow-to-orange solution. Subsequent treatment of this complex with organolithium (1 mmol) at −78 °C induced the immediate disappearance of the color. The reaction mixture was stirred at −78 °C for 30 min and worked up with 1 N HCl. The ethereal extracts were dried over Na_2SO_4 and evaporated. The residue was separated by column chromatography on silica gel (ether/hexane as eluant) to give the 1,4-adduct and/or the 1,2-adduct depending on the kind of alkyllithium and enone substrate employed. The results are indicated in Table VI.

Reaction of 6-Methyl-2-cyclohexenone with a Mixture of MeLi and MAD. To a solution of MAD (1 mmol) in toluene (5 mL) was added a 1.5 M ethereal solution of MeLi (0.67 mL, 1 mmol) at −78 °C. After 5 min, 6-methyl-2-cyclohexenone (55 mg, 0.5 mmol) was added. The resulting mixture was stirred at −78 °C for 30 min and worked up with 1 N HCl. Extraction with ether and purification by column chromatography (ether/pentane = 1:5 to 1:1 as eluant) gave the 1,2-adduct (38 mg, 60%), the isomeric ratio of which was about 1:1 by ^{1}H NMR analysis: ^{1}H NMR (CCl_4) δ 1.16, 1.03 (3 H, s, CH_3–CO), 0.95, 0.91 (3 H, d, J = 5.2 Hz, CH_3–CH).

Stereochemistry of Conjugate Adducts. The cis/trans ratio of 2,5-dimethylcyclohexanone was determined by capillary GLC analysis [t_R (cis) = 5.0 min, t_R (trans) = 4.5 min at 80 °C with 25-m PEG-HT column] by using an authentic sample which was prepared according to

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the reported procedure.[26] Further, this conjugate adduct (cis/trans = 21:79) was treated with a solution of sodium methoxide in methanol under reflux for 4 h. The mixture was poured into pentane and water, and the pentane layer was analyzed by GLC. This showed that 20% of the cis isomer had been converted to the more stable trans isomer.[26] Authentic samples for 5-alkyl-2-methylcyclohexanone (R = Et, *n*-Bu, *t*-Bu, and Ph) are prepared by the conjugate addition of R_2CuLi to 6-methyl-2-cyclohexenone. Their stereochemical assignments were made by the base-catalyzed conversion of the cis/trans mixtures to the stable trans isomer.[26] The isomeric ratio of 5-alkyl-2-methylcyclohexanone (R = Et and *t*-Bu) were determined by capillary GLC analysis: 5-ethyl-2-methylcyclohexanone: t_R (trans) = 10.1 min, t_R (cis) = 10.7 min at 80 °C; 5-*tert*-butyl-2-methylcyclohexanone: t_R (trans) = 17.5 min, t_R (cis) = 18.2 min at 80 °C. In contrast, the cis/trans ratio of 5-alkyl-2-methylcyclohexanone (R = *n*-Bu, Ph, and CH_2COO-*t*-Bu) were established by comparison with the doublet peaks of the 2-methyl group in 500 MHz ^1H NMR: 5-*n*-butyl-2-methylcyclohexanone: δ 1.02 (trans), 1.06 (cis); 2-methyl-5-phenylcyclohexanone: δ 1.09 (trans), 1.17 (cis); *tert*-butyl (4-methyl-3-oxocyclohexyl)acetate: δ 1.02 (trans), 0.91 (cis). In the conjugate addition to (*S*)-(−)-carvone with MAD/MeLi, the high trans selectivity (>95%), which referred to the stereochemistries of the 3,5-dialkyl substituents, was confirmed by GLC comparison with the authentic material of (3*S*,5*S*)-5-isopropenyl-2,3-dimethylcyclohexanone. This material was synthesized by the conjugate addition of Me_2CuLi to carvone.[44] The stereochemical assignments at the 3,5-dialkyl substituents in 3-*sec*-butyl-5-isopropenyl-2-methylcyclohexanone and 3,5-diisopropenyl-2-methylcyclohexanone were made in a similar manner as described above. Authentic *trans*-3-methyl-4-triphenylsiloxycyclopentanone was prepared by the conjugate addition of Me_2CuLi (4 equiv) in ether to 4-triphenylsiloxy-2-cyclopentenone at −78 °C for 30 min: ^1H NMR (CCl_4) δ 7.25–7.63 (15 H, m, Ph), 4.12 (1 H, q, *J* = 5.2 Hz, CH–O), 2.21 (2 H, d, *J* = 6.2 Hz, $CH_2C{=}O$), 0.92 (3 H, d, *J* = 6.2 Hz, CH_3CH). On the other hand, the conjugate adduct derived by the reaction of 4-triphenylsiloxy-2-cyclopentenone with MAD/MeLi exhibited the CH–O peaks at δ 4.12 (q, *J* = 5.2 Hz) and 4.45 (m) corresponding to the trans and cis isomers in a ratio of 63:37. In a similar manner, the trans/cis ratio of 3-*tert*-butyl-4-triphenylsiloxycyclopentanone was established by ^1H NMR analysis to be 76:24: ^1H NMR (CCl_4) δ 4.72 (m, cis CH–O), 4.43 (m, trans CH–O).

Conjugate Addition of *t*-BuLi to Benzyl Methacrylate. The reaction was carried out in a similar manner as described in the conjugate addition of organolithium to enone. The crude product was purified by column chromatography on silica gel (ether/hexane = 1:30 as eluant) to give benzyl 2,5,5-trimethylhexanoate in 71% yield: ^1H NMR (CCl_4) δ 7.25 (5 H, s, Ar–H), 5.00 (2 H, s, $ArCH_2$), 1.12 (3 H, d, *J* = 6.5 Hz, CH_3), 0.83 (9 H, s, *t*-Bu); IR (liquid film) 1737, 1454, 1369, 1188, 1151, 696 cm^{-1}. Anal. ($C_{13}H_{22}O_2$) C, H.

Reaction of (*E*,*E*)-1-Phenyl-2,4-hexadien-1-one with MAD/*t*-BuLi. The MAD-mediated conjugate addition of *t*-BuLi to the dienone was carried out in a like manner as described in the general method for conjugate addition of organolithium to enone. The ratio of 1,6-, 1,4-, and 1,2-adducts was determined by ^1H NMR analysis of their mixture based on the peaks of isolated C=C–H (δ 5.09–6.27), $C{=}C{-}CH_2{-}C{=}O$ (δ 3.51–3.69), and $C{=}C{-}CH_3$ (δ 1.54, *J* = 5 Hz).

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A Model for the Diastereofacial Differentiation in the Alkylation of Endocyclic Enolate

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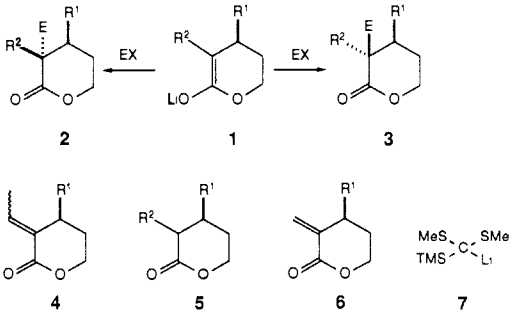
Abstract: There is a consensus of opinion that an alkylation of endocyclic enolates **1** with an asymmetric center at the β-position affords the products **2** with an entry of electrophile E trans to the substituent (R^1). A series of endocyclic enolates **1** with nonchiral exo-allylic substituents (R^2) varying from methyl to $CH_2C(SMe)_2SiMe_3$ have been examined with respect to their diastereofacial differentiation in alkylation (trans to R^1 (**2**) and/or cis to R^1 (**3**)). The complete reverse of diastereofacial differentiation was realized in the alkylation of **1** with bulky nonchiral exo-allylic substituent ($R^2 = CH_2C(SMe)_2SiMe_3$), providing **3** in an extremely high selectivity. On the other hand, the usual, but higher diastereofacial differentiation was realized in the alkylation of **1** with a vinyl substituent ($R^2 = CH{=}CH_2$). It was found that the reverse and normal diastereofacial differentiations can be simply rationalized by considering the conformation of **1** as shown in A.

An intriguing facet of alkylation of **1** is the manner through which the asymmetric center renders the face of the adjacent enolate π-system stereochemically nonequivalent.[1] The preferred production of **2** arising from alkylation trans to R^1 is the established understanding and, in fact, constitutes an important protocol in complex synthesis.[2] We now report the unprecedented and extremely efficient diastereofacial differentiation in the alkylation of **1**, providing **3** with an entry of electrophile cis to R^1, based on the notion of controlling stereochemistry by the *nonchiral* exo-allylic substituent with the specific conformation.[3] Furthermore

Scheme I



molecular mechanics calculations were performed on **1** and appear to be generally consistent with the experimental results. The *reverse* of diastereofacial differentiation demonstrated here requires a revision of the common understanding above (see Scheme I).

Results

A series of endocyclic enolates **1** with nonchiral exo-allylic substituents (R^2) varying from methyl to $CH_2C(SMe)_2SiMe_3$ have

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