

Organoaluminum reagents for selective reactions

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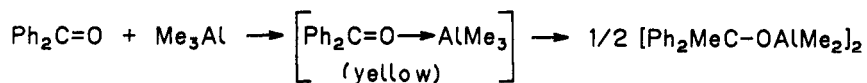
Abstract—With the aid of selected examples an overview is given of the development trends in highly discriminative reactions using organoaluminum compounds. 1) Bulky organoaluminum reagent, methylaluminum bis(2,6-di-*tert*-butyl-4-alkylphenoxide) has been successfully utilized for stereoselective activation of carbonyl moiety. 2) Development of some chiral Lewis acid catalysts is described. These catalysts are utilized for asymmetric cyclization and hetero-Diels-Alder reaction.

INTRODUCTION

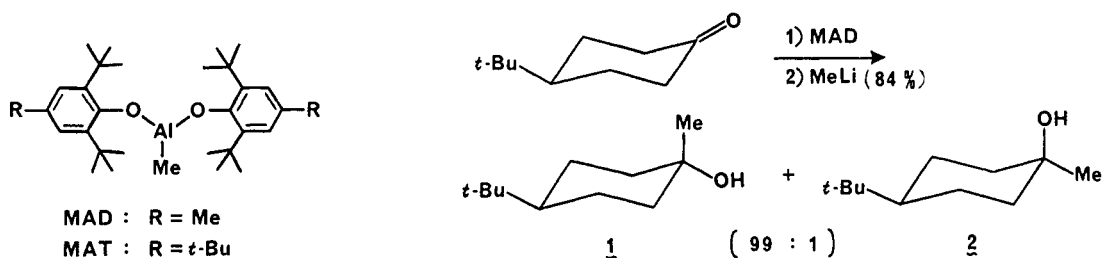
Although their role in the olefin oriented world of petrochemicals is well established, organoaluminum reagents are relatively newcomers as tools in selective organic synthesis. The characteristic properties of these reagents derived mainly from the high Lewis acidity of the organoaluminum monomers.¹ The unusually high Lewis acidity, indeed, appears to account for their great tendency to form 1:1 complexes, even with neutral bases such as ethers. These properties (commonly identified with oxygenophilicity) are of great value in the design of selective synthetic reactions. The coordination of a molecule invariably causes a change of reactivity, and the coordinated group may be activated or deactivated depending upon the type of reaction. These elements underlie the studies on synthetic methodology described herein.²

AMPHIPHILIC CARBONYL ALKYLATION

While the overall mode of reaction of trialkylaluminum reagents with carbonyl compounds parallels the reactions known for Grignard reagents, there are nevertheless significant differences. Thus, reaction of trialkylaluminum with a ketone (molar ratio 1:1) gives a long-lived monomeric 1:1 complex which very slowly decomposes unimolecularly to dimeric dialkylaluminum alkoxide.³ The synthetic utility of organoaluminum compounds in the sector has not yet been thoroughly investigated and it is probable that novel reactions will be found which have no parallel in the chemistry of the commonly used Grignard reagents.



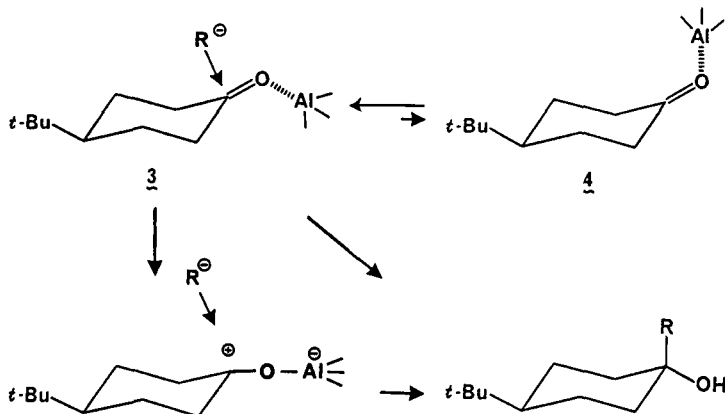
Treatment of 4-*tert*-butylcyclohexanone with methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) in toluene and subsequent addition of methyllithium in ether at -78°C gave rise to a mixture of isomeric methyl carbinols in 84% yield, 99% of which was found to be equatorial alcohol **1**. Use of MAT gave the similar stereoselectivity (ax/eq = 0.5:99.5). Methyllithium solely is reported to undergo preferential equatorial attack to furnish the axial/equatorial ratio of 79:21.⁴



Some additional examples are listed below, which also include the results in the absence of modified organoaluminum reagents for comparison.⁵

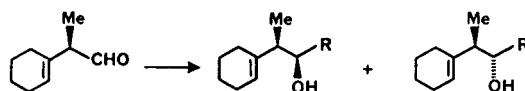
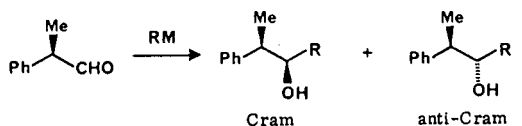
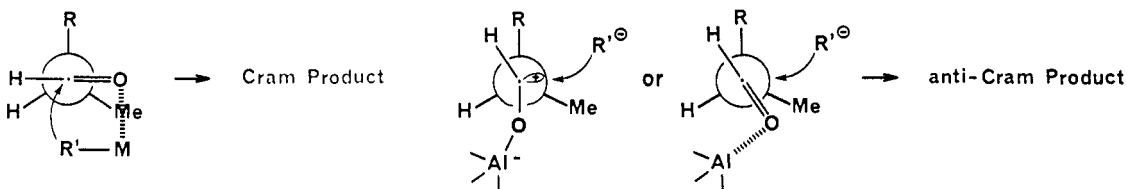
	\rightarrow		+	
		Yield (%)		Ratio
EtMgBr	none	95		48 : 52
	MAD	91		0 : 100
BuMgBr	none	58		56 : 44
	MAD	67		0 : 100
AllylMgBr	none	86		48 : 52
	MAD	90		9 : 91
	\rightarrow		+	
		Yield (%)		Ratio
MeLi	none	88		94 : 6
	MAD	90		6 : 94
MeMgI	MAT	35		3 : 97
	\rightarrow		+	
		Yield (%)		Ratio
MeLi	none	97		73 : 27
	MAD	98		2 : 98
	MAT	98		1 : 99
	\rightarrow		+	
		Yield (%)		Ratio
MeLi	none	77		75 : 25
	MAD	82		1 : 99

The exceedingly high equatorial selectivity observed herein may be ascribed to the eminent affinity of the oxygenophilic MAD and MAT for carbonyl oxygen. Thus, treatment of 4-*tert*-butylcyclohexanone with MAD or MAT would produce the stable 1:1 complex 3 or 4. Here the bulky aluminum reagent upon coordination has resulted in the preferential formation of the sterically favored isomer 3 rather than the alternative 4. Then the nucleophile appears to attack the carbonyl carbon of complex 3 from the sterically less hindered side leading to the equatorial alcohol 1 in accord with the experimental findings. The initial ate complex formation by the attack of nucleophile seems unlikely, since exposure of the ketone with a pretreated mixture of nucleophile with aluminum reagent at low temperature gave rise to the results similar to those in the sole addition of nucleophile.



Unprecedented anti-Cram selectivity was also achieved in the MAD or MAT mediated alkylation of α -chiral aldehydes. Thus, addition of α -phenylpropionaldehyde to MAT in dichloromethane at -78°C gave a yellow complex which on subsequent treatment with methylmagnesium iodide in ether afforded a mixture of Cram and anti-Cram products in a ratio of 7:93. Some selected examples are shown on this page.⁵

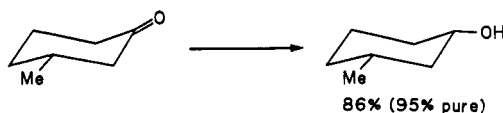
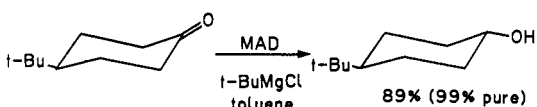
The present anti-Cram selectivity may be rationalized by the initial formation of the sterically least hindered complex preferentially on treatment with MAD or MAT, and subsequent attack of the nucleophile from the side opposite the aluminum reagent.



nucleophile	Lewis acid	yield, %	Cram/ <u>anti</u> -Cram
MeMgI	—	64	72 : 28
	MAT	96	7 : 93
EtMgBr	—	78	84 : 16
	MAD	90	25 : 75
BuMgBr	MAT	90	13 : 87
	—	89	87 : 13
BuMgBr	MAT	98	33 : 67

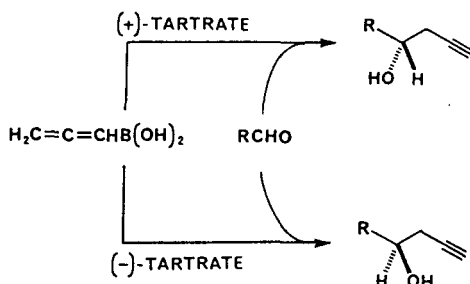
nucleophile	Lewis acid	yield, %	Cram/ <u>anti</u> -Cram
MeMgI	—	64	79 : 21
	MAT	84	2 : 98
EtMgBr	—	87	94 : 6
	MAD	76	34 : 66
BuMgBr	MAT	98	17 : 83
	—	88	94 : 6
BuMgBr	MAT	97	26 : 74

In contrast, treatment of 4-tert-butylcyclohexanone with MAD in toluene at 0°C followed by addition of tert-butylmagnesium chloride in ether at this temperature gave rise to produce the equatorial alcohol in high yield and with high selectivity (99% pure). As revealed below, this reaction is applicable to a variety of cyclohexanones.

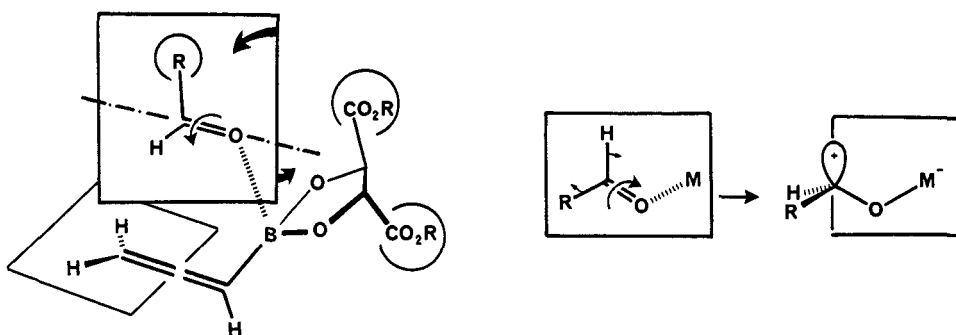


ASYMMETRIC ACTIVATION OF CARBONYL GROUP

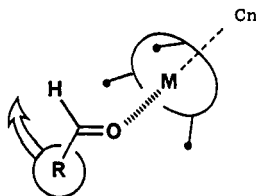
In principle, using the chiral Lewis acid catalyst, it should be possible to activate carbonyl compounds asymmetrically. In our early work, we focused on a regio- and stereoselective synthesis of β -hydroxyl acetylene using allenyl boronic esters. In an enantioface differentiating reaction, the chiral nucleophile adds to the carbonyl group of aldehydes, thus allowing the preparation of the chiral alcohols.⁷



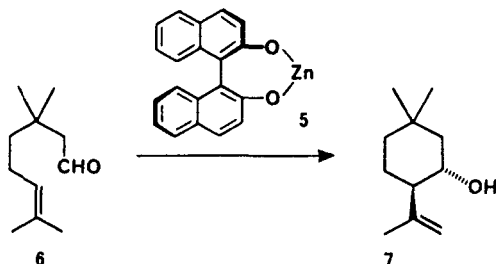
A detailed knowledge of the structure of the transition state of this reaction is, of course, a prerequisite for understanding the mechanism and thus the process of asymmetric induction in these nucleophilic addition reactions. Whereas the structure of the Lewis acid-carbonyl complexes are known to exist as an anti-coplanar complexation,⁸ definite structural information with respect to the transition state is still lacking. However, based on the anti-coplanar complex structure, we have postulated the rotation of O-C bond prior to C-C bond formation for the present reaction as shown below.



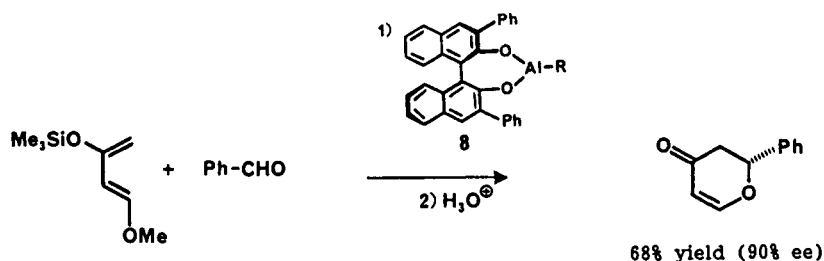
The reaction scheme as shown above demonstrates that the symmetry element on metal center does have a significant effect on the direction of the rotation, i.e. clockwise or anticlockwise, and thus on the asymmetric induction of the reaction. After these considerations, we think it is possible to further expand the synthetic utility of the main group organometallic reagent as a powerful tool in asymmetric synthesis.



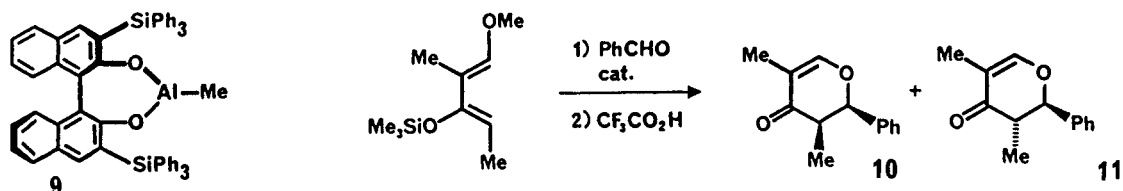
The chiral zinc reagent **5** was prepared in situ from dimethylzinc and optically pure (R)-(+)-1,1'-bi-2-naphthol in methylene chloride at -78°C for 3 h. Cyclization of 3-methylcitronellal **6** with the reagent **5** was effected at -78°C for 20 min and at 0°C for 20 min to furnish the single isomer in 91% yield which was characterized analytically and spectrometrically to be pure trans alcohol **7**. The optical purity of **7** was substantiated by GC after converting to its MTPA ester to be 90% ee.⁹



Similarly, the chiral aluminum reagent **8** was prepared from the corresponding diphenylbinaphthol and trialkylaluminum. The activation of carbonyl compound with this reagent in the presence of Danishefsky's diene gave the high asymmetric C-C bond formation as shown below.¹⁰

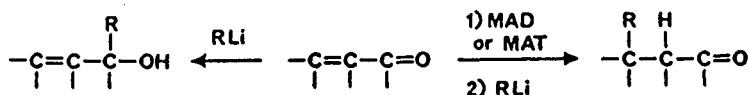


The sterically even more hindered, optically pure catalyst **9**, requisite for the present purpose, can be synthesized in two steps from (R)-(+)-3,3'-dibromobinaphthol. Thus, the dibromobinaphthol was converted with Ph₃SiCl/imidazole in DMF to bis-silyl ether in 95% yield, which on treatment with *t*-BuLi underwent a remarkably smooth 1,3-rearrangement to furnish the optically pure binaphthol almost quantitatively. Reaction of the binaphthol in toluene with trimethylaluminum produced the chiral organoaluminum reagent **9** as a wine-red solution.¹⁰ The chiral aluminum reagent of type **9** was found to be highly effective as a chiral Lewis acid catalyst for the asymmetric hetero-Diels-Alder reaction. A mixture of benzaldehyde and siloxydiene in toluene was treated under the influence of catalytic **9** (10 mol%) at -20°C for 2 h to furnish, after exposure of the resulting adducts to trifluoroacetic acid in dichloromethane, *cis*-dihydropyridone **10** (77%) and its *trans* isomer **11** (7%). The major *cis* adduct was shown to be 95% ee.



















CONJUGATE ADDITION OF ORGANOLITHIUM TO UNSATURATED CARBONYL GROUP

Conjugate addition to α,β -unsaturated ketone is mostly effected by soft organometallics and the sole use of organolithium has never been developed in view of its hard nucleophilic character. However, we have found that the conjugate addition of organolithium reagent to enone can be accomplished by combining use of MAD or MAT. This finding represents another, yet intriguing characteristic of the amphiphilic reaction systems in organic synthesis.¹¹



Organolithium reagent normally adds to enone 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 followed by treatment with MeLi at -78°C resulted in total reversal of selectivity, producing conjugate adducts, 2,5-dimethylcyclohexanone (*cis/trans* = 3:7) exclusively in 68% yield. None of the 1,2 adducts were detected. 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 cycloalkanone. 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 results are summarized in Table 1.¹¹

Table I. Conjugate Addition of Alkylolithium to Enone in the Presence of MAD^a

entry	enone	RLi	1,4 adduct % yield ^b (c/t) ^c	1,2 adduct % yield ^b	entry	enone	RLi	1,4 adduct % yield ^b (c/t) ^c	1,2 adduct % yield ^b
1		MeLi	68 (29:71) ^g		9		MeLi	65 ⁱ	16
2		<i>n</i> -BuLi ^d	59 (36:64) ^g		10		MeLi ^f	63 ⁱ	31
3		<i>t</i> -BuLi	73 (32:68) ^g		11		<i>s</i> -BuLi	65 ⁱ	12
4		PhLi	71 (28:72) ^g		12		CH ₂ =C(Me)Li	75 ⁱ	
5		CH ₂ =C(OBu ^t)OLi ^e	87 (10:90) ^h		13		MeLi	↓	
6		MeLi	70		14		MeLi	↓	
7		MeLi		77 ^k	15		MeLi	74 (37:63) ^h	
8		MeLi	26	11	16		<i>t</i> -BuLi	83 (24:76) ^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. The stereochemistries (cis/trans) were determined in part by independent synthesis of conjugate adducts of enones using organocopper reagents. ^b Isolated yield. ^c Ratio of the cis and trans isomers. ^d As an ethereal solution. Use of *n*-BuLi in hexane gave 1,4 adduct in only 15% yield. ^e Prepared from CH₃COOBu^t and LDA in ether at -78°C . ^f Use of MAT in CH₂Cl₂ in place of MAD. ^g Determined by GC analysis. ^h Determined by ¹H NMR analysis. ⁱ The high trans selectivity (>95%), which referred to the stereochemistries of the 3,5-dialkyl substituents, was observed. ^j Total recovery of the enone under the standard condition. ^k Cis/trans = 14:86 by GC analysis.

CONCLUSIONS

Although many of the results discussed in this review are preliminary and fragmentary, it has become increasingly clear that the amphiphilic approach using bulky organometallic reagent is widely applicable to selective reactions. Many of these reactions promise to provide viable alternatives to classical reactions involving carbonyl compounds. Additional efforts are being made to further delineate their full scope and synthetic potential.

Acknowledgements

We are deeply indebted to our coworkers, whose names appear in our papers cited in this review. We also wish to acknowledge the financial support from the Ministry of Education, Japanese Government.

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