## UNUSUAL CONJUGATE ADDITION OF ORGANOLITHIUM REAGENT TO $\alpha, \beta$ -UNSATURATED KETONE

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Abstract: The conjugate addition of organolithium reagent to  $\alpha,\beta$ -unsaturated ketone has been accomplished with methylaluminum bis(2,6-di-tert-butyl-4-alkylphenoxide) (MAD and MAT). Here combination of alkyllithium and MAD (or MAT) constitutes an amphiphilic system that allows to exhibit unusual selectivity in the alkylation of enones with alkyllithium.

Conjugate addition to  $\alpha,\beta$ -unsaturated ketone is mostly effected by soft organometallics (Cu, Ni, Zr. Zn, Al, etc.)<sup>1</sup> and the sole use of organolithium has never been developed in view of its hard nucleophilic character.<sup>2</sup> Here we wish to report an unusual example in the conjugate addition of organolithium reagent to  $\alpha$ .  $\beta$ -unsaturated ketone.

A nucleophilic reaction to electrophilically activated substrate by combination with certain reactive nucleophile and Lewis acid, i.e. amphiphilic reaction,<sup>3</sup> 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  $BF_2 \cdot OEt_2$ facilitated the addition of moderately basic main-group nucleophiles like organolithiums, Grignard reagents, and lithium enolates to a variety of electrophiles.<sup>4-7</sup> Others observed the efficiency of Me<sub>3</sub>SiCl and its analogues as Lewis acid in the organocopper-mediated conjugate addition to carbonyl compounds as well as deprotonation of ketones and esters. $^{8,9}$ Apparently, the choice of Lewis acid is crucial for generating new amphiphilic systems. Oxygenophilic organoaluminum compound that is capable of forming a stable 1:1 complex with carbonyl substrate seems to be quite expectable for this purpose.<sup>10</sup> In fact, we have already reported that the exceptionally bulky, oxygenophilic organoaluminum reagents, methylaluminum bis(2,6-di-tert-butyl-4-alkylphenoxide) (MAD and MAT), have proved to exhibit the excellent diastereoface-differentiating ability (i.e. equatorial and <u>anti-Cram</u> selectivity) in carbonyl alkylation and reduction.<sup>3,11</sup> Yet another, new example is the MAD- or MAT-facilitated conjugate addition of organolithium reagent to  $\alpha_{,\beta}$ -unsaturated ketone.



Organolithium reagent normally adds to  $\alpha, \beta$ -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 =  $\sim 1:1$ ) 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,

$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	entry	enone	RLi	1,4 adduct % yield <sup>b</sup> (c/t) <sup>C</sup>	1,2 adduct % yield <u>b</u>
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1	ç.	MeLi	68 (29:71) <sup>g</sup>	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2	$\searrow$	<u>n</u> -BuLi <u>d</u>	59 (17:83) <u>h</u>	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3		<u>t</u> -BuLi	73 (18:82) <u>g</u>	
5 $CH_2=C(OBu^{t})OLi^{\underline{C}}$ 87 (10:90) <sup><u>h</u></sup> 6 $\stackrel{\bullet}{\downarrow}$ MeLi       70         7 $\stackrel{\bullet}{\downarrow}$ MeLi       0 $77^{\underline{h}}$ 8 $\stackrel{\bullet}{\downarrow}$ MeLi       0 $77^{\underline{h}}$ 8 $\stackrel{\bullet}{\downarrow}$ MeLi       26       11         9 $\stackrel{\bullet}{\downarrow}$ MeLi       65 <sup><u>1</u></sup> 16         10 $\stackrel{\bullet}{\downarrow}$ MeLi       65 <sup><u>1</u></sup> 12         12 $\stackrel{\bullet}{\Box}$ MeLi       65 <sup><u>1</u></sup> 12         13 $\stackrel{\bullet}{\downarrow}$ MeLi       j.       12         14 $\stackrel{\bullet}{\downarrow}$ MeLi       1       1         15 $\stackrel{\bullet}{\downarrow}$ MeLi       0       78         16 $\stackrel{\bullet}{\downarrow}$ MeLi       0       78         16 $\stackrel{\bullet}{\downarrow}$ MeLi       24       60         18       ( <u>E</u> )-PhCH=CHC(=O)CH <sub>3</sub> MeLi       0       78         18       ( <u>E</u> )-PhCH=CHC(=O)CH <sub>3</sub> MeLi       24       60         18       ( <u>E</u> )-PhCH=CHC(=O)CH <sub>3</sub> MeLi       24       60         19 <u>i</u> -BuLi       77       9       9     <	4		PhLi	71 (33:67) <u>h</u>	
6	5		CH <sub>2</sub> =C(OBu <sup>t</sup> )OLi <u>e</u>	87 (10:90) <u>h</u>	
7	6	$\rightarrow$	MeLi	70	
8 $+$ MeLi       26       11         9 $+$ MeLi $65^{\frac{1}{2}}$ 16         10 $+$ MeLi $63^{\frac{1}{2}}$ 31         11 $\pm$ $5^{-1}$ 12       12         12 $CH_2=C(Me)Li$ $75^{\frac{1}{2}}$ 12         13 $+$ MeLi $1$ $1$ 14 $+$ $+$ MeLi $1$ 15 $+$ $+$ $ 1$ 16 $+$ $+$ $ 1$ 17       (E)-PhCH=CHC(=0)CH_3       MeLi $0$ $78$ 18       (E)-PhCH=CHC(=0)CH_3       MeLi $24$ $60$ 19       MeLi $28$ $55$ $52$ 20 $t$ $t$ - $t$ - $77$ $9$	7	Ļ	MeLi	0	77 <u>k</u>
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	8	+ U	MeLi	26	11
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	9	Ŷ	MeLi	65 <u>i</u>	16
11 $\downarrow$ $\underline{S}$ -BuLi $65^{\underline{i}}$ 12         12 $CH_2=C(Me)Li$ $75^{\underline{i}}$ 12         13 $\downarrow$ MeLi $\underline{i}$ 14 $\downarrow$ MeLi $\underline{j}$ 15 $\downarrow$ MeLi $74$ ( $37:63$ ) <sup><math>\underline{h}</math></sup> 16 $\downarrow$ $\underline{j}$ MeLi $83$ ( $24:76$ ) <sup><math>\underline{h}</math></sup> 17       ( <u>E</u> )-PhCH=CHC(=O)CH_3       MeLi       0       78         18       ( <u>E</u> )-PhCH=CHC(=O)Ph       MeLi       24       60         19       MeLi <sup><math>\underline{f}</math></sup> 28       55         20 <u>t</u> -BuLi       77       9	10		MeLi <u>f</u>	63 <u>i</u>	31
12 $CH_2=C(Me)Li$ $75^{1}$ 13 $\downarrow$ $MeLi$ $I$ 14 $\downarrow$ $MeLi$ $I$ 15 $\downarrow$ $MeLi$ $74$ ( $37:63$ ) <sup>h</sup> 16 $\downarrow$ $L^{-BuLi}$ $83$ ( $24:76$ ) <sup>h</sup> 17       (E)-PhCH=CHC(=O)CH_3       MeLi $0$ $78$ 18       (E)-PhCH=CHC(=O)Ph       MeLi $24$ $60$ 19       MeLi <sup>f</sup> $28$ $55$ 20       t-BuLi $77$ $9$	11	$\mathbf{Y}$	<u>s</u> -BuLi	65 <u>-</u>	12
13 $\stackrel{\circ}{\downarrow}$ MeLi       j         14 $\stackrel{\circ}{\downarrow}$ MeLi       j         15 $\stackrel{\circ}{\downarrow}$ MeLi       74 (37:63) <sup>h</sup> 16 $\stackrel{\circ}{\downarrow}$ $\stackrel{\circ}{t}$ -BuLi       83 (24:76) <sup>h</sup> 17       (E)-PhCH=CHC(=O)CH <sub>3</sub> MeLi       0       78         18       (E)-PhCH=CHC(=O)Ph       MeLi       24       60         19       MeLif       28       55         20       t-BuLi       77       9	12		CH <sub>2</sub> =C(Me)Li	75 <u>i</u>	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	13	Ļ	MeLi	Ĺ	
15       9       MeLi       74 $(37:63)^{h}$ 16 $t$ -BuLi       83 $(24:76)^{h}$ 17       (E)-PhCH=CHC(=O)CH <sub>3</sub> MeLi       0       78         18       (E)-PhCH=CHC(=O)Ph       MeLi       24       60         19       MeLif       28       55         20       t-BuLi       77       9	14	Ļ	MeLi	Ţ	
16 $\underline{t}$ -BuLi       83 (24:76) <sup>h</sup> 17       (E)-PhCH=CHC(=O)CH <sub>3</sub> MeLi       0       78         18       (E)-PhCH=CHC(=O)Ph       MeLi       24       60         19       MeLi <sup>f</sup> 28       55         20       t-BuLi       77       9	15	Q	MeLi	74 (37:63) <u>h</u>	
17       (E)-PhCH=CHC(=0)CH <sub>3</sub> MeLi       0       78         18       (E)-PhCH=CHC(=0)Ph       MeLi       24       60         19       MeLi <sup>f</sup> 28       55         20       t-BuLi       77       9	16	Physic	<u>t</u> -BuLi	83 (24:76) <u>h</u>	
18 $(\underline{E})$ -PhCH=CHC(=O)PhMeLi246019MeLi $\frac{f}{}$ 285520 $\underline{t}$ -BuLi779	17	( <u>E</u> )-PhCH≠CHC(=O)CH <sub>2</sub>	MeLi	0	78
19         MeLif         28         55           20 <u>t</u> -BuLi         77         9	18	 (E)-PhCH≠CHC(=O)Ph	MeLi	24	60
20 <u>t</u> -BuLi 77 9	19		MeLi <u>f</u>	28	55
	20		<u>t</u> -BuLi	77	9

Table I. Conjugate Addition of Alkyllithium to Enone in the Presence of MADa

<sup>a</sup> 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. <sup>b</sup> Isolated yield. <sup>c</sup> Ratio of the cis and trans isomers. <sup>d</sup> As an ethereal solution. Use of <u>n</u>-BuLi in hexane gave 1,4 adduct in only 15% yield. <sup>e</sup> Prepared from CH<sub>3</sub>COOBu<sup>t</sup> and LDA in ether at -78°C. <sup>f</sup> Use of MAT in CH<sub>2</sub>Cl<sub>2</sub> in place of MAD. <sup>g</sup> Determined by GC analysis. <sup>h</sup> Determined by <sup>1</sup>H NMR analysis. <sup>i</sup> The high trans selectivity (>95%), which referred to the stereochemistries of the 3,5-dialkyl substituents, was observed. <sup>j</sup> Total recovery of the enone under the standard condition. <sup>k</sup> Cis/trans = 14:86 by GC analysis.

conjugate adducts, 2,5-dimethylcyclohexanone (cis/trans = 29:71)<sup>12</sup> exclusively in 68% producing 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  $-78^{\circ}$ C afforded 1,2 adducts almost exclusively in 60% yield (cis/trans =  $\sim$ 1:1). This result implies that the initial ate complex formation by the attack of MeLi to MAD followed by conjugate addition to the enone seems to be unlikely,  $^{13}$  The effect of exact stoichiometry in the reagent was also examined with MAD/t-BuLi system, and yields of the conjugate adducts with each 1.5, 2, and 3 equiv of MAD/t-BuLi under the similar conditions are 52, 73, and 77%, respectively. Hence, each 2 equiv of MAD/RLi can be satisfactorily utilized for other alkylation experiments. The preliminary results summarized in Table I show the following (1) The  $\alpha$ , $\beta$ -unsaturated ketone possessing the sterically less demanding carbonyl moiety, features. 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 7 and 17). Carvone, 2-methyl-2cyclohexenone, and chalcone gave a mixture of 1,2 and 1,4 adducts depending on the steric and/or electronic effect of alkyllithiums (entries 8-12 and 18-20). The similar tendency was also observed in the cyclopentenone system (entries 15 and 16). In contrast, attempted alkylation of 2,6-dimethyl-2-cyclohexenone and 3,5-dimethyl-2-cyclohexenone resulted in total recovery of the starting enones (entries 13 and 14). (2) A variety of alkyllithium reagents can be utilized. In addition, alkylation with lithium enolate appeared feasible (entry 5). Introduction of alkynyl group failed, however. Grignard reagents as nucleophile are less reactive to the enone-MAD complex, providing the conjugate adduct in much lower yield with some recovery of the enone. (3) The stereochemistry in the conjugate addition is mostly governed by the size of alkyl substituents on the cycloalkenones, and the trans isomer always predominated 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.<sup>14</sup> (4) Use of nonpolar solvents such as toluene,  $CH_2Cl_2$ , ether, or their mixtures gave consistently satisfactory results. (5) MAT may be equally employed in place of MAD (entries 10 and 19).

The following procedure for the synthesis of 2,5-dimethylcyclohexanone is illustrative. To a solution of 2,6-di-<u>tert</u>-butyl-4-methylphenol (440 mg, 2 mmol) in toluene (5 mL) was added a 2 M hexane solution of  $Me_3Al$  (0.5 mL, 1 mmol) and the resulting colorless solution was stirred at room temperature for 1 h. The mixture was then cooled to  $-78^{\circ}C$  and 6-methyl-2-cyclohexenone (55 mg, 0.5 mmol) was added at this temperature to give the enone-MAD complex as an orange solution. Subsequent treatment of this complex with a 1.5 M ethereal solution of MeLi (0.67 mL, 1 mmol) at  $-78^{\circ}C$  induced the immediate disappearance of the orange color. The reaction mixture was stirred at  $-78^{\circ}C$  for 30 min and worked up with 10% HCl. The ethereal extracts were dried over  $Na_2SO_4$  and evaporated. The residue was purified by column chromatography on silica gel (ether/hexane, 1:8 as eluant) to give 2,5-dimethylcyclohexanone (43 mg, 68% yield) as a colorless oil. The cis/trans ratio was determined by capillary GC to be 29:71.<sup>12</sup>

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