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A NEW, STEREOCONTROLLED SYNTHESIS OF EQUATORIAL ALCOHOLS BY THE AMBIPHILIC REDUCTION OF CYCLOHEXANONES

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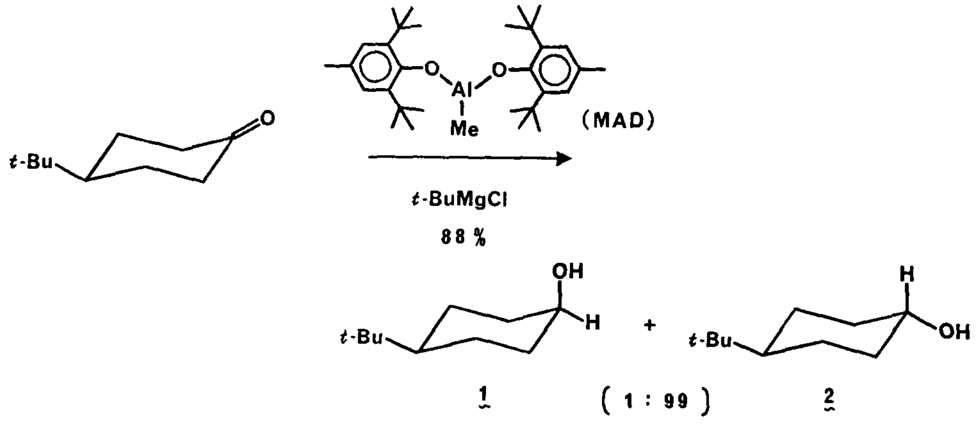
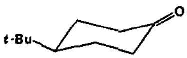
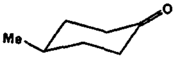
Summary: Ambiphilic reduction of cyclohexanones with methylaluminum bis(2, 6-di-tert-butyl-4-methylphenoxide) and tert-butylmagnesium chloride provides the corresponding equatorial alcohols with high stereoselectivity.

In connection with our recent project on the utility of ambiphilic systems in organic synthesis,[1] we wish to report a conceptually new, ambiphilic reduction of cyclohexanones leading to the highly stereocontrolled synthesis of equatorial alcohols.[2] This method is based on the stereoselective activation of carbonyl moiety using methylaluminum bis(2, 6-di-tert-butyl-4-methylphenoxide)[3] (abbreviated to MAD) and subsequent reduction of the resulting ketone-MAD complex with tert-alkylmagnesium halide.



Treatment of 4-tert-butylcyclohexanone with MAD in toluene[3] at 0°C followed by addition of tert-butylmagnesium chloride in ether at this temperature gave rise to a mixture of axial and equatorial alcohols, 1 and 2, in 88% yield. GC analysis indicated the ratio of the ax/eq alcohol to be 1:99.

Table I. Stereoselective Reduction of Cyclohexanones.[a]

entry	ketone	Lewis acid[b]	reducing agent[c]	temp., °C (time, h)	yield, %[d]	ratio (ax/eq)[e]
1		MAD	t-BuMgCl	0 (2.5)	88	1 : 99
2		MAD + t-BuMgCl [f]		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 [f]		0 (3)	72	16 : 84
10		MAD [g]	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 reducing agent (3 equiv) to a mixture of ketone (1 equiv) and Lewis acid (3 equiv).

[b] MAD: Methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide).

DAD: Dimethylaluminum 2,6-di-tert-butyl-4-methylphenoxide.

[c] Grignard reagents were used as ethereal solution, while triisobutylaluminum in hexane was employed.

[d] Isolated yield.

[e] Determined by GC analysis.

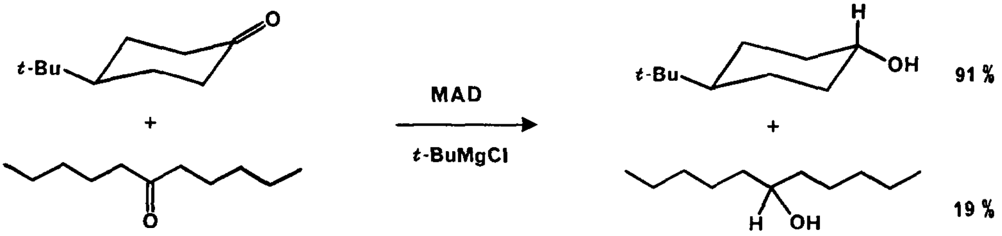
[f] Initial treatment of MAD with t-BuMgCl at 0°C for 30 min and subsequent addition of the ketone at 0°C.

[g] MAD was prepared in CH_2Cl_2.

Notably, reaction of 4-tert-butylcyclohexanone with tert-butylmagnesium chloride in the absence of MAD produced the complex reaction mixtures. It should be added that initial treatment of MAD with tert-butylmagnesium chloride at 0°C for 30 min followed by addition of 4-tert-butylcyclohexanone gave the similar stereoselectivity (ax/eq = 2:98). This implies that the interaction of MAD (as electrophile for the ketone) with tert-butylmagnesium chloride (as nucleophile) is negligible under the conditions disclosed above, and hence these two reagents constitute an ambiphilic system in the reduction of 4-tert-butylcyclohexanone.

As revealed in Table I, this reaction is applicable to a variety of cyclohexanones. As an oxygenophilic aluminum reagent, MAD is superior to dimethylaluminum 2,6-di-tert-butyl-4-methylphenoxide[4] (abbreviated to DAD) (entries 3 and 13). A series of reducing agents were examined by combination with MAD. Among these, tert-butylmagnesium chloride was found to be most satisfactory. tert-Amylmagnesium chloride and tert-butylmagnesium bromide were less effective (entries 11 and 12). Phenethylmagnesium chloride afforded a number of by-products. Use of complex metal hydride reagents such as lithium aluminum hydride, lithium borohydride, lithium triethylborohydride, and lithium tri-sec-butylborohydride gave unsatisfactory results. In contrast to the conventional methodology for the synthesis of equatorial alcohols using dichloroaluminum hydride under thermodynamic conditions,[5,6] this reaction is irreversible and the products are kinetically controlled.

In addition to the high equatorial selectivity, the present ambiphilic reduction has proved to exhibit moderate chemoselectivity in the reduction of carbonyl moieties. Thus, 4-tert-butylcyclohexanone can be reduced chemoselectively in the presence of acyclic ketone as illustrated below.



A typical experimental procedure is provided by the reduction of 4-tert-butylcyclohexanone. To a solution of 2,6-di-tert-butyl-4-methylphenol (1.322 g, 6 mmol) in toluene (10 mL) was added a 2 M hexane solution of trimethylaluminum (3 mmol) and the resulting clear solution was stirred at 25°C for 1 h.[3] The mixture was cooled to 0°C and 4-tert-butylcyclohexanone (154 mg, 1 mmol) followed by a 1.3 M ethereal solution of tert-butylmagnesium chloride (3 mmol) were added at this temperature. The solution was stirred at 0°C for 2.5 h and poured into 1 N HCl. The ethereal extracts were dried over Na_2SO_4 and concentrated. The residual liquid was chromatographed on silica gel to furnish a mixture of **1** and **2** (137 mg, 88% yield). The isomeric ratio of **1** and **2** was determined to be 1:99 by GC analysis: (25-m PEG-HT capillary column, 150°C) t_R (**1**) = 5.39 min; t_R (**2**) = 5.97 min.

REFERENCES AND NOTES

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4. DAD was prepared by treatment of 2,6-di-tert-butyl-4-methylphenol with trimethylaluminum (1:1 molar ratio) at room temperature for 1 h.
5. (a) Eliel, E. L.; Rerick, M. N. J. Am. Chem. Soc. 1960, 82, 1367. (b) Eliel, E. L.; Martin, R. J. L.; Nasipuri, D. Org. Synth. Coll. Vol. 1973, 5, 175.
6. Attempted reduction of cyclohexanones with dichloroaluminum hydride in ether at 0°C under kinetic conditions afforded a mixture of axial and equatorial alcohols with low stereoselectivity: 4-tert-butylcyclohexanone (96%, ax/eq = 18:82); 2-methylcyclohexanone (95%, 44:56); 3-methylcyclohexanone (94%, 27:73).

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