Reexamination of Aluminum Hydride as a Stereoselective Reducing Agent for Reduction of Cyclic Ketones to Thermodynamically More Stable Alcohols

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Aluminum hydride, a very interesting and valuable reducing agent, has been widely used in numerous applications in organic syntheses.[1] Jorgenson first reported the comparison in the reducing properties between lithium aluminum hydride and aluminum hydride on the reduction of cinnamaldehyde,[2] and Brown and Yoon reported a systematic study on the reducing properties of aluminum hydride in THF.[3] Finally, Cha and Brown introduced a very stable solutions of aluminum hydride - triethylamine complex (AHTEA) and showed this complex possesses actually the same reducing properties as does aluminum hydride alone. Nevertheless, we have believed that this reagent can not be applicable for the stereoselective reduction of cyclic ketones, because the stereoselectivity achieved by the reagent at 0° is quite similar to that by lithium aluminum hydride and hence is insignificant.[3-b] However, in the course of reexamining the reducing characteristics of aluminum hydride, we have found that this reagent possesses a potentiality to be used as a stereoselective reducing agent to provide thermodynamically more stable alcohols. This report describes such stereoselective reduction.

Results and Discussion

The reduction of representative monocyclic and bicyclic ketones by aluminum hydride has been studied at different reaction temperature (0°, 25° and reflux) and the reactivity and the isomeric ratio of the product mixture are summarized in Table 1. When the reduction of monocyclic ketones was carried out at 0°, the thermodynamically more stable isomer alcohol were produced preferentially. For example, the reduction of 2-methylcyclohexanone in THF at 0° yields a mixture of *cis*- and *trans*-2-methylcyclohexanol in the ratio of 26 : 74. On the contrary, the reduction of bicyclic ketones such as norcamphor and camphor at 0° afforded the thermodynamically less stable alcohols predominantly (Table 1). Thus, the reduction of norcamphor yields a mixture of *exo*- and *endo*- norborneol in the ratio of 20 : 80; the reduction of camphor yields a mixture of *exo*- and *endo*-borneol in the ratio of 81 : 19. However, when the reduction of excess cyclic ketones (3.3 equiv) with aluminum hydride was carried out for a long period of time at 25° or under reflux, the stereoselectivity shifted in favor of being produced the thermodynamically more stable isomer alcohols. For example, the reduction of 2-methylcyclohexanone yields a mixture of *cis*- and *trans*-2-methylcyclohexanol in the ratio of 12 : 88. Especially, in the case of norcamphor a dramatic change of isomeric ratio was observed. Thus, in the reduction of norcamphor the isomeric ratio of 20 : 80 changes to be 83 : 17 to produce the thermodynamically more stable isomer predominantly. Very much the same is true to all other cases of cyclic ketones examined.

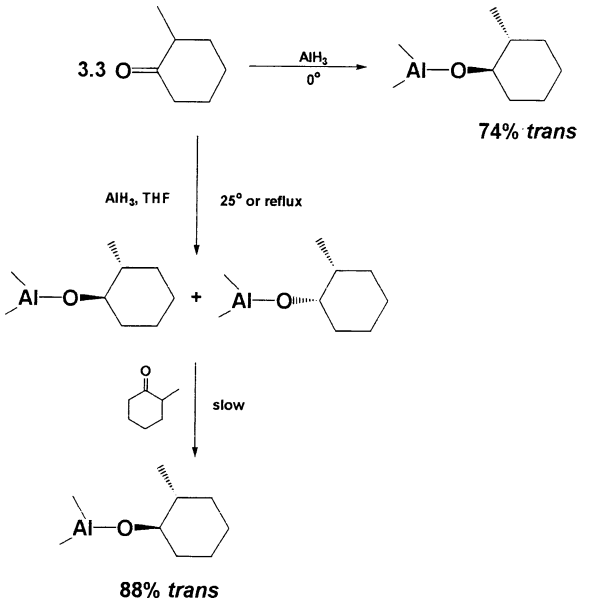
Table 1. Stereochemistry in the Reduction of Cyclic Ketones with Aluminum Hydride in Tetrahydrofuran[a]

Ketone	Time (d)	Ratio of more stable isomer (%)[b]		
		At 0°	At 25°	Under reflux
2-Methylcyclohexanone	0.15	74	75	79
	0.25		78	
	1		84	86
	3		86	87
	7		88	88
	10		88	
3-Methylcyclohexanone	0.25	80	82	85
	1		85	84
	3		86	85
	7		86	
4-Methylcyclohexanone	0.25	78	81	83
	1		84	85
	3		84	86
4-*tert*-Butylcyclohexanone	0.25	80	83	86
	1		85	86
	3		85	86
3,3,5-Trimethylcyclohexanone	1	75	88	93
	3		92	96
	7		95	97
	10		96	97
Norcamphor	0.25	20	20	46[c]
	1		30	57[c]
	3		77	82[c]
	7		81	83[c]
Camphor	1	19	21	30[d]
	3		19	31[d]
	5		20	34[d]

[a]Ten % excess (3.3 equiv) of Ketone was reacted. [b]GC yield. [c]Turn to be turbid. [d]Turn to be turbid and precipitated.

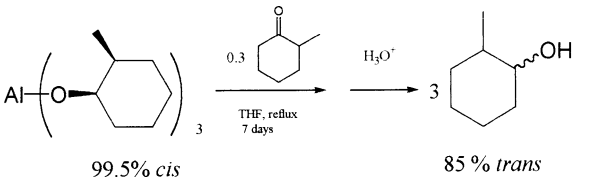
The most striking feature of the Table 1 is that the stereochemistry of reduction with aluminum hydride is apparently dependent on the reduction time, similar to the case of diisobutylaluminum hydride (DIBAH)[4] and *Al*-isopropoxydiisobutylalane (DIBAO^{i}Pr).[5] The stereoselectivity increases consistently with increase of reaction time to afford the ther-

modynamically more stable isomer alcohols predominantly, with the exception of camphor. This seems to be a phenomenon that must rise where the thermodynamically less stable alcohol isomer, one of the two isomers produced by reduction with aluminum hydride, is converted to the more stable one by thermodynamically controlled isomer equilibration *via* a Meerwein-Ponndorf-Verley (MPV) type reduction[6,7] (Eq. 1). The exceptional case of camphor seems to happen, apparently due to its too large steric requirement to meet the MPV type reduction.



(1)

Support for the above explanation is provided by the fact that the reaction of trialkoxyaluminum, formed from aluminum hydride and 3 equiv of *cis*-2-methylcyclohexanol(a 99.5% isomeric purity), in the presence of 0.3 equiv of 2-methylcyclohexanone for 7 days under reflux gives *trans*-2-methylcyclohexanol in a 85% isomeric purity upon hydrolysis (Eq. 2). This is an interesting example which shows a possibility for isomer conversion from thermodynamically less stable alcohols to more stable ones. We are examining this possibility in detail.



(2)

In general, the stereoselectivity of this system is somewhat lower than that obtained by DIBAH[4] and DIBAO^{i}Pr[5-a] systems : the latter systems yield 92-93% *trans*-isomer in the reduction of 2-methylcyclohexanone. This difference can be rationalized as resulting from the enhanced steric requirement of isobutyl group directly bound to aluminum atom. Thus, the difference in the thermodynamic stabilities between the more stable alkoxy moiety and the less stable alkoxy moiety is increased by the isobutyl group, when compared to the case of aluminum hydride itself. However, aluminum hydride has the advantage of an economical point of view in such stereoselective reduction, because all the three equivalents of hydride are involved in this reaction.

Experimental Section

All reactions were performed under a dry N_2 atmosphere. All chemicals used were commercial products of the highest purity available; THF was dried over 4 Å molecular sieve and distilled from sodium-benzophenone ketyl prior to use. A solution of aluminum hydride in THF was prepared by the reaction of lithium aluminum hydride with methanesulfonic acid, according to the reported procedure.[8] Gas chromatographic analysis were carried out with a Varian 3300 Chromatograph using TB^{TM}-WAX capillary column (30 m).

Stereoselective Reaction. The following procedure was utilized to examine the stereoselectivity of aluminum hydride. An oven-dried, 50 mL, round-bottomed flask, equipped with a sidearm, a condenser, and an adaptor connected to a mercury bubbler, was cooled to room temperature under a stream of nitrogen and maintained under a static pressure of nitrogen. The flask was then immersed in the water bath 25° or heated to be under gentle reflux. To this flask was added 5.0 mL of a 2.0 M solution of the reagent in THF (10 mmol) and 33 mmol of ketone examined was injected as a neat into the flask dropwise with vigorous stirring. After the appropriate time intervals, the reaction aliquot was withdrawn and then quenched by addition of 3 N HCl. The aqueous layer was saturated with $MgSO_4$, and the organic layer was dried over anhydrous K_2CO_3. The isomeric ratio of alcohol product analyzed by GC using a capillary column is listed in Table 1.

Reduction of Tri(2-methylcyclohexyloxy)aluminum in the Presence of 2-methylcyclohexanone. The following procedure was used to convert *cis*-2-methylcyclohexanol to *trans*-2-methylcyclohexanol. Into a 50 mL flask, dried thoroughly as described above, 5.0 mL of a 2.0 M solution of aluminum hydride in THF (10 mmol) was introduced and the flask was cooled to 0°. To this 30 mmol of *cis*-2-methylcyclohexanol (a 99.5% isomeric purity) was injected as a neat dropwise with stirring. After the complete addition, the reaction mixture was allowed to stir for an additional 1 h at room temperature and then 3 mmol of 2-methylcyclohexanone was added. After 7 days under reflux the mixture was quenched by addition of 3 N HCl. After the usual workup procedure, the alcohol product was subjected to GC analysis to show the presence of *cis*- and *trans*-2-methylcyclohexanols in a isomeric ratio of 15 : 85.

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