Al-Isopropoxydiisobutylalane. A Stereoselective Reducing Agent for Reduction of Cyclic Ketones to Thermodynamically More Stable Alcohols

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In recent years, new developments in the area of stereoselective reduction of cyclic ketones have been exceptionally encouraging. Especially, the reagents developed for conversion of cyclic ketones to the thermodynamically less stable alcohols are extraordinary.[1] However, although several useful reagents have been devised for converting cyclic ketones to the thermodynamically more stable alcohols,[2] generally acceptable synthetic methods for this conversion have still been lacking. In the course of a systematic study of the reducing characteristics of *Al*-alkoxydiisobutylalane, we have found that *Al*-isopropoxydiisobutylalane, one of these derivatives, reveals an excellent stereoselectivity in such cyclic ketone reductions to provide the corresponding thermodynamically more stable alcohols. This paper describes this stereoselective reduction.

Results and Discussion

Al-isopropoxydiisobutylalane (DIBAO^{i}Pr) is readily prepared by a simple reaction between diisobutylaluminum hydride (DIBAH) and isopropyl alcohol in ethyl ether(eq 1). The reactivity of this reagent in a stoichiometric amount toward representative cyclic ketones at 25 °C and the isomeric ratio of the product mixture are summarized in Table 1.

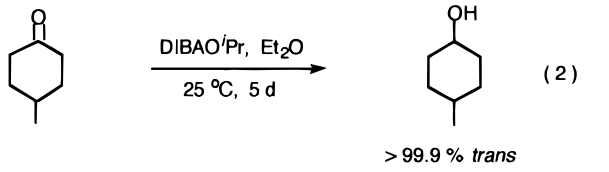
$$i\text{-Bu}_2\text{AlH} + i\text{-PrOH} \xrightarrow[0\ ^\circ\text{C}]{\text{Et}_2\text{O}} \underset{\textbf{DIBAO}^i\textbf{Pr}}{i\text{-Bu}_2\text{AlO}^i\text{Pr}} + \text{H}_2\uparrow \quad (1)$$

The most striking feature of the Table 1 is that the stereochemistry of reduction with DIBAO^{i}Pr is apparently dependent on the reaction time. The stereoselectivity increases consistently with increase of reaction time to afford the thermodynamically more stable isomer alcohols exclusively (eq 2), with the exception of camphor which is resistant to reduction under the reaction conditions. This seems to be a phenomenon that must rise where the thermodynamically less stable alcohol isomer, one of the two isomer produced by reduction with DIBAO^{i}Pr, is converted to the more stable one by thermodynamically controlled isomer equilibration *via* a Meerwein−Ponndorf−Verley type reduction.[3]

Table 1. Stereoselective Reduction of Cyclic Ketones with *Al*-Isopropoxydiisobutylalane (DIBAO^{i}Pr) in Ethyl Ether at 25 °C[a]

ketone	reaction time (h)	ratio of more stable isomer (%)[b]	yield of alcohol (%)[b]
2-methylcyclohexanone	3	49	51
	6	67	71
	24	85	92
	72	91	98
	96	94	99
	120	95	>99.9
	168	96	100 (82)
3-methylcyclohexanone	3	89	94
	6	91	98
	24	93	99
	72	93	>99.9
	96	94	100
	120	95	100
4-methylcyclohexanone	3	89	98
	24	92	99
	72	94	>99.9
	96	97	100
	120	>99.9	100
4-*tert*-butylcyclohexanone	6	91	98
	24	95	>99.9
	48	95	100
	72	97	100
	96	98	100 (84)
3,3,5-trimethylcyclohexanone	12	97	89
	24	98	94
	72	>99.9	99
	96	>99.9	100
norcamphor	6	85	43
	24	90	76
	48	92	89
	72	93	96
	96	95	>99.9
	120	97	100
camphor	24	31	7
	120	36	14
	168	37	23

[a] A 1:1 ratio for reagent to ketone was utilized. [b] Analyzed by GC. The numbers in parentheses are isolated yields.



(2)

> 99.9 % *trans*

Experimental Section[4]

Preparation of *Al*-Isopropoxydiisobutylalane (DIBAO-^{i}Pr) in Ethyl Ether. The following procedure served for the preparation of the reagent. An oven-dried, 200-mL, round-

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(2) (a) Eliel, E. L.; Rerick, M. *J. Am. Chem. Soc.* **1960**, *82*, 1367. (b) Eliel, E. L.; Martin, R. J. L.; Nasipuri, D. *Organic Syntheses*; Wiley: New York, 1973; Coll. Vol. 5, p 175. (c) Abramovitch, R. A.; Marsh, W. C.; Saha, J. G. *Can. J. Chem.* **1965**, *43*, 2631. (d) Mestroni, G.; Zassinovich, G.; Camus, A.; Martinelli, F. *J. Organomet. Chem.* **1980**, *198*, 87. (e) Toros, S.; Kollar, L.; Heil, B.; Marko, L. *J. Organomet. Chem.* **1983**, *255*, 377. (f) Spogliarich, R.; Mestroni, G.; Graziani, M. *J. Mol. Catal.* **1984**, *22*, 309. (g) Maruoka, K.; Sakurai, M.; Yamamoto, H. *Tetrahedron Lett.* **1985**, *26*, 3853. (h) Sarkar, A.; Rao, B. R.; Ram, B. *Synth. Commun.* **1993**, *23*, 291. (i) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378. (j) Fort, Y. *Tetrahedron Lett.* **1995**, *36*, 6051.

(3) (a) A similar time dependence was reported by Haubenstock and Davidson (*J. Org. Chem.* **1963**, *28*, 2772) as observed in the reduction of excess 3,3,5-trimethylcyclohexanone with triisobutylaluminum (TIBA). (b) Heinsohn, G. E.; Ashby, E. C. *J. Org. Chem.* **1973**, *38*, 4232.

(4) All reactions were performed under a dry N_2 atmosphere. All chemicals used were commercial products of the highest purity available; ethyl ether was dried over 4-Å molecular sieves and distilled from sodium−benzophenone ketyl prior to use. ^{27}Al NMR spectra were recorded on a Bruker AMX 300 spectrometer, and the chemical shifts are reported in parts per million with reference to $Al(H_2O)_6^{3+}$. Gas chromatographic analyses were carried out with a Varian 3300 chromatograph using a 50 m HP 20 M capillary column.

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bottomed flask, equipped with a side arm, 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. To this flask was added 14.22 g of *i*-Bu_2AlH (100 mmol) and 25 mL of ethyl ether, and the flask was cooled to 0 °C in an ice−water bath. A 6.31 g amount of isopropyl alcohol (105 mmol) was added to the solution of *i*-Bu_2AlH dropwise with vigorous stirring at 0 °C. After the complete evolution of hydrogen, the reagent solution was brought to room temperature. The solution was then diluted with ethyl ether to make a total volume of 100 mL to be 2 M. ^{27}Al NMR of the solution showed a broad singlet centered at δ 160.

Reduction of Cyclic Ketones. The following procedure was used to explore the stereoselectivity of this reagent. In a 50-mL, round-bottomed flask was placed 5.0 mL of the 2.0 M solution of the reagent in ethyl ether (10.0 mmol). The flask was maintained at 25 °C by immersion in a water bath. To the flask was added 10 mL of 2-methylcyclohexanone solution in ethyl ether (1.0 M in ketone), and the reaction mixture was stirred at 25 °C. 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 are listed in Table 1.

Isolation of Alcohols. The following procedure is for the larger scale reaction. In the assembly previously described was placed 25 mL of 2.0 M reagent solution (50 mmol). Into the solution was injected 25 mL of a 2.0 M solution of 2-methylcyclohexanone (5.6 g, 50 mmol) in ethyl ether, and the reaction mixture was stirred for 7 days at room temperature. The mixture was then hydrolyzed with 50 mL of 3 N HCl, until the gelatinous precipitate was dissolved, and saturated with NaCl. The separated organic layer was washed three times with 3 N NaOH (3 × 20 mL) and dried over anhydrous K_2CO_3. All the volatile materials were evaporated under reduced pressure to yield almost pure 2-methylcyclohexanol (>98% purity). Fractional distillation gave 4.7 g (82% yield) of essentially pure 2-methylcyclohexanol, bp 166−168 °C (754 mm). GC examination revealed the presence of 4% *cis*- and 96% *trans*-2-methylcyclohexanol.

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