

- 1985, 45, 844.
3. (a) Shin, H.-C.; McFarlane, E. F. *Korean Biochem. J.* **1993**, 26, 163. (b) Shin, H.-C.; McFarlane, E. F. *J. Biochem. Mol. Biol.* **1995**, 28, 546.
 4. Kirschner, D. A.; Ganser, A. L.; Donald, L. D. C. In *Myelin*; Morell, P. Ed.; Plenum Press: New York, U.S.A., 1984; p 51.
 5. James, G. E.; Moore, W. J. *J. Neurochem.* **1980**, 34, 1334.
 6. Weise, M.; Hsieh, D.; Hoffman, P. M.; Powers, J. M.; Brostoff, S. W. *J. Neurochem.* **1980**, 35, 393.
 7. Emerson, M. F.; Holtzer, A. J. *Phys. Chem.* **1965**, 69, 3718.
 8. Tanford, C.; Reynolds, J. A. *Biochim. Biophys. Acta* **1976**, 457, 133.
 9. Makino, S. *Adv. Biophys.* **1979**, 12, 131
 10. (a) Pitt-Rivers, R.; Impiombato, F. S. A. *Biochem. J.* **1968**, 109, 825. (b) Reynolds, J. A.; Tanford, C. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, 66, 1002. (c) Nelson, C. A. *J. Biol. Chem.* **1971**, 246, 3895. (d) Takagi, T.; Tsujii, K.; Shirahama, K. *Biochem. J.* **1975**, 77, 939.
 11. Smith, R.; McDonald, B. *Biochim. Biophys. Acta* **1979**, 554, 133.
 12. (a) Brostoff, S. W.; Levitt, S.; Powers, J. M. *Nature* **1977**, 268, 752. (b) Kadlubowski, M.; Hughes, R. A. C. *Nature* **1979**, 277, 140. (c) Curtis, B. M.; Fiorno, I. S.; Smith, M. E. *Brain Res.* **1979**, 175, 389.
 13. Ballin, R. H. M.; Thomas, P. K. *J. Neurosci.* **1969**, 8, 1.
 14. (a) Shin, H.-C.; McFarlane, E. F.; Pollard, J. D.; Watson, E. G. S. *Neurosci. Lett.* **1989**, 102, 309. (b) Ros-tami, A.; Brown, M. J.; Lisak, R. P.; Sumner, A. J.; Zweiman, B.; Pleasure, D. E. *J. Neuropathol. Exp. Neurol.* **1982**, 41, 372. (c) Ishaque, A.; Szymanska, I.; Ramwani, J.; Eylar, E. H. *Biochim. Biophys. Acta* **1981**, 669, 28.
 15. Nagai, Y.; Uchida, T.; Takeda, S.; Ikuta, F. *Neurosci. Lett.* **1978**, 8, 247.
 16. Shin, H.-C.; Stuart, B.; McFarlane, E. F. *Biochem. Biophys. Res. Commun.* **1996**, 224, 5.

Reexamination of Al-Isopropoxydiisobutylalane as a Stereoselective Reducing Agent for Reduction of Cyclic Ketones to Thermodynamically More Stable Alcohols

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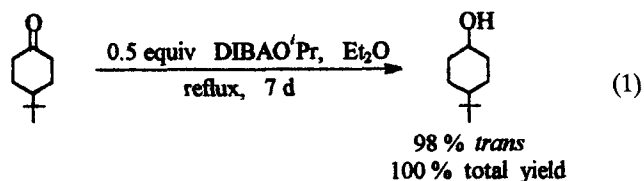
Very recently, we reported that Al-isopropoxydiisobutylalane (DIBAO'Pr) reveals an excellent stereoselectivity in the reduction of representative cyclic ketones in ethyl ether at 25° to provide the corresponding thermodynamically more stable alcohols.¹ In this report, we examined only the reaction in which an equimolar mixture of reagent and ketone is involved. However, we soon realized that, like triisobutylaluminum (TIBA),² the isobutyl group of DIBAO'Pr is also involved in this reduction. Thus, when 2 equiv of ketone was treated with 1 equiv of DIBAO'Pr in refluxing ethyl ether, the first equiv of ketone was reduced readily and the second one was also reduced in a relatively slow rate. This apparently improves the procedure appeared in the previous report.¹ Herein we describe an improved procedure for reduction of cyclic ketones to thermodynamically more stable alcohols using DIBAO'Pr.

The reactivity of DIBAO'Pr in a half stoichiometric amount toward representative cyclic ketones under reflux in ethyl ether and the isomeric ratio of the product mixture are summarized in Table 1.

When the reduction of excess cyclic ketone with the reagent was carried out at 25°, 1 equiv of ketone was reduced in a relatively fast rate but the reduction of further equiv of ketone was insignificant, indicating the involvement of only the isopropoxy moiety of DIBAO'Pr in this reduction.

However, when the reduction was repeated in refluxing ethyl ether, the unreacted ketone was also reduced slowly. Finally, all of the cyclic ketones examined, with the exception of camphor, underwent complete reduction with a half stoichiometric amount of DIBAO'Pr in 10-15 days. Camphor is resistant to reduction under the reaction conditions.

The most interesting feature of the Table is that the stereochemistry of reduction with DIBAO'Pr is apparently dependent on the reaction time, as described in the previous paper.¹ The stereoselectivity increases consistently with increase of reaction time to afford the thermodynamically more stable isomer alcohols exclusively (Eq. 1).



This seems to be a phenomenon that must arise where the thermodynamically less stable alcohol isomer, one of the two isomers produced by reduction with DIBAO'Pr, is converted to the more stable one by thermodynamically con-

Table 1. Stereoselective Reduction of Excess Cyclic Ketones with *Al*-Isopropoxydiisobutylalane (DIBAOⁱPr) in Ethyl Ether under Reflux^a

Reaction	Ratio time (d)	Ratio of more stable isomer (%) ^b	Yield of alcohol (%) ^b
2-methylcyclohexanone	1	87	76
	3	89.5	87
	5	90	92
	7	92	93
	10	93	96
	15	93.5	99
3-methylcyclohexanone	20	93.5	100
	1	91	81
	3	92	92
	5	92	97
	7	93	98
	10	94	>99.9
4-methylcyclohexanone	15	95	100
	1	92	87
	3	93.5	94
	5	94	97
	7	95	98
	10	97	100
4-tert-butylcyclohexanone	1	91	82
	3	94.5	94
	5	97	97
	7	98	>99.9
	10	98	100
3,3,5-trimethylcyclohexanone	1	93	78.5
	3	94	89
	5	94.5	90
	7	96	97
	10	98	100
norcamphor	1	68	58
	3	81	73
	5	86	80
	7	89	95
	10	91.5	98
	15	92	100
camphor	1	35	2.5
	3	37	5
	5	49	6
	7	42.5	6.5
	10	56	10.5
	15	69	20

^a A 1:2 ratio for reagent to ketone was utilized. ^b Analyzed by GC.

trolled isomer equilibration *via* a Meerwein-Ponndorf-Verley type reduction.² The difference between this system (ketone:reagent=2:1) and the previous system (ketone:reagent=1:1) is that which moiety in DIBAOⁱPr is participated in the isomer equilibration. This system involves one isobutyl group as well as the isopropoxy group; only the isopropoxy moiety is involved in the previous case. A similar time dependence was also reported by Haubenstock and Davidson as observed in the reduction of excess of 3,3,5-trimethyl-cyclohexanone with TIBA.³

The following procedure was used to explore the stereoselectivity of this reagent. In a pre-dried 50-mL, round-bottom flask was placed 5.0 mL of a 2.0 M solution of the reagent in ethyl ether (10.0 mmol). To the flask was added 10 mL of 2-methylcyclohexanone solution in ethyl ether (2.0 M, 20.0 mmol), and the reaction mixture was heated to be under gentle reflux with 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 MgSO₄ and the organic layer was dried over anhydrous K₂CO₃. The isomeric ratio of alcohol product analyzed by GC using a capillary column are listed in Table 1.

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References

1. Cha, J. S.; Kwon, O. O. *J. Org. Chem.* **1997**, *62*, 3019.
2. (a) Ashby, E. C.; Yu, S. H. *J. Org. Chem.* **1970**, *35*, 1043. (b) Heinsohn, G. E.; Ashby, E. C. *Ibid.* **1973**, *38*, 4232. (c) Winterfeldt, E. *Synthesis* **1975**, 617.
3. Haubenstock, H.; Davidson, E. B. *J. Org. Chem.* **1963**, *28*, 2772.