

A Solution of Borane in Tetrahydrofuran. A Stereoselective Reducing Agent for Reduction of Cyclic Ketones to Thermodynamically More Stable Alcohols

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Recent developments in the area of stereoselective reduction of cyclic ketones have been exceptionally promising. The reagents developed for conversion of cyclic ketones to the thermodynamically less stable alcohols are extraordinary.¹ Moreover, the newly devised methods for conversion of cyclic ketones to the thermodynamically more stable alcohols are encouraging.²

A solution of borane in THF (BH₃–THF) represents a valuable reducing agent³ and has been widely used in organic synthesis. Nevertheless, the reagent has not attracted much attention in the stereoselective reduction of cyclic ketones because the stereoselectivity achieved by the reagent at 0 °C is poor.⁴ However, in the course of reexamining the reducing characteristics of BH₃–THF, we have found that the reagent reveals an unexpectedly high stereoselectivity in such cyclic ketone reductions at higher temperatures in THF to provide the corresponding thermodynamically more stable alcohols. This report describes such stereoselective reduction.

Results and Discussion

The reduction of representative cyclic ketones (10% excess) with BH₃–THF has been studied at different

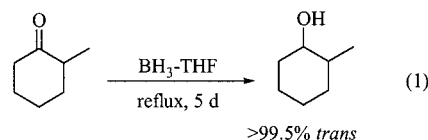
Table 1. Stereoselective Reduction of Cyclic Ketones with a Solution of Borane in Tetrahydrofuran (BH₃–THF)^a

ketone	reaction time (d)	ratio of more stable isomer ^b (%)			yields of alcohol (%) under reflux ^b
		0 °C	25 °C	reflux	
2-methylcyclohexanone	0.25	64	68	70	81
	3	64	68	92	88
	5		68	>99.5	100 (81)
3-methylcyclohexanone	0.25	80	82	83	81
	3	80	83	85	96
	5		84	>99.5	100
4-methylcyclohexanone	0.25	79	80	82	85
	3	79	82	85	99
	5		82	>99.5	100 (82)
4- <i>tert</i> -butylcyclohexanone	0.25	84			
	1	83	85	89	92
	5		86	90	99
3,3,5-trimethylcyclohexanone	0.25	27	37	45	74
	3	28	37	90	82
	7		38	>99.5	87
norcamphor	14			>99.5	100
	0.25	4			
	1	4	5	6	89
camphor	7		5	7	99
	0.25	38			
	1	39	40	49	64
	5	38	41	89	75
	7		42	97	92
	10		45	98	99

^a A 1:3.3 ratio for reagent to ketone was utilized. ^b Analyzed by GC with tridecane as an internal standard. The numbers in parentheses are isolated yields.

reaction temperature (i.e., 0 °C, 25 °C and reflux), and the reactivity and the isomeric ratios obtained of the product mixture are summarized in Table 1.

The most characteristic feature of the Table 1 is that the stereochemistry of reduction under reflux is dependent on the reaction time, while the reactions at 0 and 25 °C show no such a time dependence. Thus, under reflux, the stereoselectivity increases consistently with increase of the reaction time to afford the thermodynamically more stable isomer alcohols exclusively (eq 1), with the exception of norcamphor.⁵



This appears to be a situation that must rise where the thermodynamically less stable alcohol isomer, one of the two isomers produced by reduction with BH₃–THF, is converted to the more stable one by thermodynamically controlled isomer equilibration via a Meerwein–Ponndorf–Verley (MPV) type reduction (eq 2).⁶

(5) Fortunately, the reaction of alane derivatives^{2h–1} is favorable for norcamphor. Consequently, the two procedures complement each other.

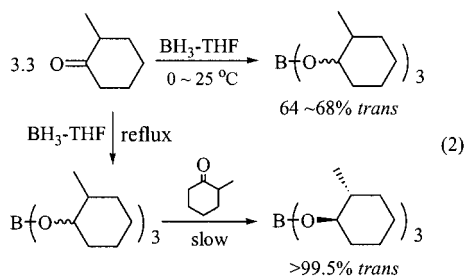
(6) Evidence for the MPV-type reaction of boron alkoxides is provided by the preliminary experiments that triisopropoxyboron readily reacts with simple ketones at room temperature or in refluxing THF under a stream of nitrogen to give the corresponding alcohols in high yields. For example, the reduction of 3 equiv of 2-heptanone yields 97% of 2-heptanol for 3 d at room temperature and for 1 d under reflux.

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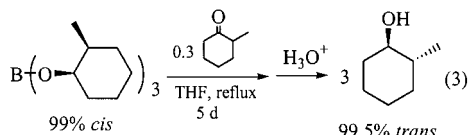
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Support for the above explanation is provided by the fact that the reaction of trialkoxyborane, formed from 3 equiv of *cis*-2-methylcyclohexanol (a 99% isomeric purity) and $\text{BH}_3\text{-THF}$, in the presence of 0.3 equiv of 2-methylcyclohexanone for 5 days under reflux, gives *trans*-2-methylcyclohexanol in 99.5% isomeric purity upon hydrolysis (eq 3).⁷ This is an interesting example which shows a possibility for isomer conversion from the thermodynamically less stable alcohols to the more stable ones. We are examining this possibility in detail.



The same reactions with a solution of borane–dimethyl sulfide (BMS) in THF under reflux were also carried out for comparison, and the isomeric ratios of the product mixture are summarized in Table 2. The stereoselectivity, however, shows no dependence on the reaction time.

Experimental Section⁸

Reduction of Cyclic Ketones. The following procedure was used to explore the stereoselectivity of the reagent.⁹ 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. To this flask was added 10.0 mL of the 1.0 M solution of the reagent in THF (10.0 mmol) and 3.70 g of 2-methylcyclohexanone (33 mmol). Tridecane was added as an internal standard.

The reaction was brought to gentle reflux. After the appropriate time intervals, the reaction aliquots were withdrawn and then quenched by addition of 3 N HCl. The aqueous layer was

(7) In the case of the reaction without added 2-methylcyclohexanone under reflux, the *cis*-alcohol was recovered without change of isomeric purity.

(8) 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 sieves and distilled from sodium–benzophenone ketyl prior to use. Gas chromatographic analyses were carried out with a Varian CP-3380 chromatograph using a 30 m DB-WAX capillary column.

(9) A solution of $\text{BH}_3\text{-THF}$ was prepared from NaBH_4 and Me_2SO_4 in THF; BMS was purchased from Aldrich Chemical Co.

Table 2. Stereoselective Reduction of Cyclic Ketones with a Solution of $\text{BH}_3\text{-SMe}_2$ (BMS) in Tetrahydrofuran under Reflux^a

ketone	reaction time (d)	ratio of more stable isomer ^b (%)
2-methylcyclohexanone	7	59
	14	59
3-methylcyclohexanone	7	82
	14	81
4-methylcyclohexanone	7	79
	14	80
4- <i>tert</i> -butylcyclohexanone	3	76
	7	76
3,3,5-trimethylcyclohexanone	14	76
	3	44
norcamphor	7	53
	14	81
camphor	3	7
	7	7
	14	7
	3	44
	7	45
	14	51

^a A 1:3:3 ratio for reagent to ketone was utilized. ^b Analyzed by GC.

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 Tables 1 and 2.

Isolation of Alcohols. The following procedure is for larger scale reactions. In the assembly previously described was placed 20 mL of 1.0 M $\text{BH}_3\text{-THF}$ solution (20 mmol). Into the solution was injected 7.4 g of 2-methylcyclohexanone (66 mmol). The reaction was brought to gentle reflux, and the reaction mixture was stirred for 5 d. The mixture was then hydrolyzed with 20 mL of 3 N HCl and saturated with NaCl. The separated organic layer was dried over anhydrous K_2CO_3 . All the volatile materials were evaporated under reduced pressure and fractional distillation gave 5.5 g (81% yield) of essentially pure 2-methylcyclohexanol, bp 165–167 °C (759 mm). GC examination revealed the presence of a trace amount of *cis*- and >99.5% *trans*-2-methylcyclohexanol.

Reaction of Tris(2-methylcyclohexyloxy)boron in the Presence of 2-Methylcyclohexanone. The following procedure served for conversion of the thermodynamically less stable isomer alcohol to the more stable one. In a 50-mL flask was placed 5.0 mL of a 1.0 M solution of $\text{BH}_3\text{-THF}$ (5.0 mmol). To this, 1.71 g of *cis*-2-methylcyclohexanol (a 99% isomeric purity, 15 mmol) was injected dropwise with stirring at room temperature. After the complete addition, the reaction mixture was allowed to stir for an additional 1 h at that temperature, and then 0.17 g of 2-methylcyclohexanone (1.5 mmol) was added. After being stirred for 5 d under reflux, the mixture was 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 . GC analysis indicated the presence of *trans*-2-methylcyclohexanol in a purity of higher than 99.5%.

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