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

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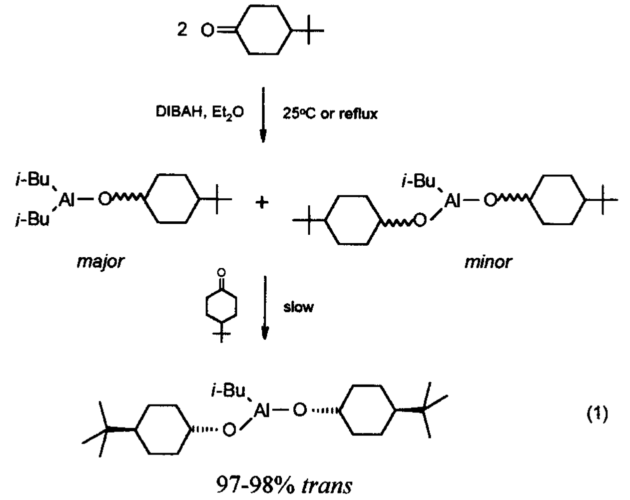
Abstract: The reducing property of diisobutylaluminum hydride (DIBAH) has been reexamined as a stereoselective reducing agent for reduction of representative cyclic ketones. When the reduction of excess cyclic ketone with DIBAH was carried out at 0 °C in ethyl ether, only 1 equiv of the free hydride was involved to show a low stereoselectivity. However, when performed at 25 °C or under reflux in ethyl ether, one isobutyl group as well as the free hydride was also involved in this reduction: the first equiv of ketone was reduced rapidly and the second one reduced, in a relatively slow rate. In addition, the stereoselectivity increases consistently with increase of reaction time to afford the thermodynamically more stable isomer alcohols exclusively.

Diisobutylaluminum hydride (DIBAH) has secured its place as one of the most widely used reducing agents in organic synthesis.[1] 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 °C is insignificant.[2,3] However, in the course of reexamining the reducing characteristics of DIBAH, we have found that this reagent reveals an unexpectedly high stereoselectivity along with the utilization of 2 equiv of ketone in such cyclic ketone reduction at 25 °C or under reflux in ethyl ether to provide the corresponding thermodynamically more stable alcohols. This paper describes this stereoselective reduction.

When the reduction of excess cyclic ketone with DIBAH was carried out at 0 °C, only the free hydride was involved and hence only 1 equiv of ketone reduced to show a low stereoselectivity. For example, the reduction of 2-methylcyclohexanone in toluene[2] or ethyl ether[3] at 0 °C yields a mixture of *cis*- and *trans*-2-methylcyclohexanol in the ratio of approximate 1:1. However, when the reduction was repeated at 25 °C or under reflux in ethyl ether, one isobutyl group as well as the free hydride of DIBAH was also involved: DIBAH reduced 2 equiv of ketone, the first one being reduced rapidly and the second reduced in a relatively slow rate. The reactivity of DIBAH in a half stoichiometric amount toward representative cyclic ketones at 25 °C or under reflux and the isomeric ratio of the product mixture are summarized in Table 1.

The most interesting feature of the Table is that the stereochemistry of reduction with DIBAH is apparently dependent on the reaction time, similar to the case of *Al*-isopropoxydiisobutylalane (DIBAO^{i}Pr).[4,5] The stereoselectivity increases consistently with increase of reaction time to afford the thermodynamically more stable isomer alcohols exclusively, 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 DIBAH, is converted to the more stable one by thermodynamically controlled isomer equilibration *via* a Meerwein-Ponndorf-Verley type reduction[1,6] (eq 1).

The reducing power of DIBAO^{i}Pr is so mild that it can reduce only aldehydes and ketones effectively.[7] Therefore, DIBAO^{i}Pr can be applied for stereoselective reduction of cyclic ketones in the presence of other reducible functional groups in a molecule. On the contrary, DIBAH is a strong reducing agent which can reduce most common organic functionalities.[2] However, DIBAH has the advantage of an economical point of view in such stereoselective reductions[8], particularly in cases where no other readily reducible functional groups is present in a molecule.



The following procedure was utilized to examine the stereoselectivity of DIBAH.[9] An oven-dried, 50 mL, round-bottom 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 5.0 mL of a 2.0 M solution of the reagent in ethyl ether (10.0 mmol) and the flask was cooled to 0 °C by use of an ice-water bath. To the flask was added slowly 10.0 mL of ketone solution in ethyl ether (2.0 M, 20.0 mmol). The ice-water bath was then removed and the flask was maintained at 25 °C by immersion in a water bath (or 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 $MgSO_4$, 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.

The following procedure is for the larger scale reaction. In the assembly previously described was placed 12.5 mL of 2.0 M DIBAH solution (25 mmol) and the flask was cooled to 0 °C. Into the solution was injected slowly 25 mL of a 2.0 M solution of 3-methylcyclohexanone (5.6 g, 50 mmol) in ethyl ether. The reaction mixture was then heated to be under gentle reflux with stirring. After 7 days, the mixture was 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 x 20 mL) and dried over anhydrous K_2CO_3. All the volatile materials were evaporated under reduced pressure to yield almost pure 3-methylcyclohexanol (> 98% purity). Fractional distillation gave 4.8 g (83% yield) of essentially pure 3-methylcyclohexanol, bp 163-164 °C (756 mm). GC examination revealed the presence of 96% *cis*- and 4% *trans*-3-methylcyclohexanol.

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Table 1. Stereoselective Reduction of Excess Cyclic Ketones with Diisobutylaluminum Hydride (DIBAH) in Ethyl Ether[a]

ketone	time(d)	at 25 °C		under reflux	
		ratio of more stable isomer(%)[b]	yield of alcohol(%)[b]	ratio of more stable isomer(%)[b]	yield of alcohol(%)[b]
2-methylcyclohexanone	1	78	74	85	90
	3	87	85	89	98
	5	90	91	90	99
	7	91	94	92	99
	10	92	97	93	>99.9
	15	92	>99.9	93	100
3-methylcyclohexanone	1	88	84	90	92
	3	91	95	93	95
	5	93	98	94	97
	7	95	>99.9	96	100(83)
	10	95	100		
4-methylcyclohexanone	1	91	89	92	95
	3	93	97	93	99
	5	94	98	95	>99.9
	7	94	99	95	100
	10	94	100		
4-*tert*-butylcyclohexanone	1	90	90	93	92
	3	94	96	96	98
	5	96	98	96	99
	7	97	>99.9	98	100(85)
	10	97	100		
3,3,5-trimethylcyclohexanone	1	90	80	95	87
	3	94	85	98	96
	5	98	88	99.5	99
	7	98	93	>99.9	100
	10	98	100		
norcamphor	1	41	70	67	81
	3	62	79	83	95
	5	81	92	89	98
	7	89	97	94	>99.9
	10	95	>99.9	96	100
	15	95	100		
camphor	1	18	64	20	73
	3	19	65	30	77
	5	23	70	33	80
	7	28	76	35	82
	10	36	81	40	86

[a] A 1:2 ratio for reagent to ketone was utilized

[b] A percent conversion of ketone to alcohol analyzed by GC. The numbers in parentheses are isolated yields

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(9) 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-A 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.