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Al-Isopropoxydiisobutylalane: A Study of the Effect of Solvent on the Rate and Stereoselectivity of Cyclic Ketone Reduction

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Abstract: The effect of solvent on the rate and stereoselectivity of cyclic ketone reduction by *Al*-isopropoxydiisobutylalane (DIBA^{i}OPr) has been investigated. In dichloromethane, DIBA^{i}OPr behaves as a bulky reducing agent, approaching the carbonyl group along an equatorial trajectory to produce the axial alcohol with >10:1 stereoselectivity. In sharp contrast, reduction in toluene gives the complementary outcome, affording the thermodynamically more stable isomer with >99:1 stereoselectivity.

The stereoselective reduction of cyclic ketones is an extremely important reaction in organic synthesis. In general, bulky reducing agents favor approach to the carbonyl group via an equatorial trajectory, resulting in formation of the axial alcohol, while small nucleophiles attack from the axial position to yield the equatorial alcohol (Figure 1).[1] Reductions that proceed through the establishment of an equilibrium will usually favor formation of the equatorial alcohol.

The thermodynamically less stable alcohol products (with an axial hydroxyl group) can often be prepared with extremely good stereocontrol, with the Selectride reagents developed by Brown most notable among the methods used to achieve this conversion.[2] Reagents for the preparation of the thermodynamically more stable alcohols (with an equatorial hydroxyl group) are not as well developed, although several valuable methods have been reported, including the classic Meerwein–Ponndorf–Verley reduction[3,4] and more recent catalytic variants,[5] lithium *n*-butylborohydride,[6] borane–THF complex,[7] activated sodium hydride,[8] the lithium aluminum hydride–aluminum trichloride complex,[9] and the use of very bulky aluminum Lewis acids in conjunction with Grignard reagents.[10]

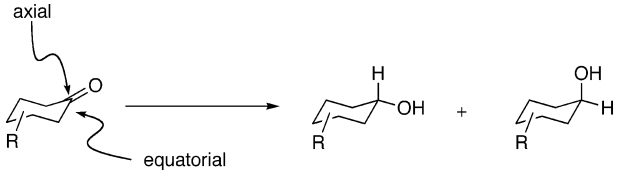

FIGURE 1. Diastereofacial attack on cyclohexanones.

Cha and Kwon recently published a new method for reducing cyclic ketones to the thermodynamically more stable alcohols using *Al*-isopropoxydiisobutylalane (DIBA^{i}OPr) in diethyl ether;[11] the reagent is readily prepared from diisobutylaluminum hydride and 2-propanol. The authors postulate that the reduction proceeds through a Meerwein–Ponndorf–Verley-type mechanism, supported by the fact that the relative proportion of the thermodynamically more stable alcohol increases over the course of the reduction.

Stereocontrol with this reagent is good to excellent, but a significant drawback is that long reaction times are required to achieve this, typically between 5 and 7 days. In an effort to reduce the reaction times and improve the stereoselectivity, we undertook an investigation into the solvent dependency of the reaction.

Results and Discussion. The reduction of a number of cyclic ketones was examined in a range of solvents varying in polarity from DMF to toluene. No reaction occurred in DMF and acetonitrile, but reduction was rapid in THF, dichloromethane, and toluene. The results for the latter three solvents are presented in Table 1.

The stereoselectivity of the reduction clearly shows a remarkable dependency on the solvent. Reaction in THF is essentially unselective, typically yielding approximately equal amounts of axial and equatorial alcohols after 6 h. Extending the reaction time improved the ratio in favor of the thermodynamically more stable alcohol. Thus, in the reduction of 4-*tert*-butylcyclohexanone, the ratio increased from 50:50 axial:equatorial after 6 h to 92:8 in favor of the axial product after 24 h.

By contrast, the reductions performed in dichloromethane generally gave good-to-excellent ratios in favor of the thermodynamically less stable alcohol. Particularly noteworthy are the ketones bearing bulky groups at the 2-position, 2-*tert*-butylcyclohexanone and menthone, and 2-methylcyclopentanone, all of which afforded the thermodynamically less stable alcohol essentially exclusively. These results suggest that in this solvent DIBA^{i}OPr behaves as a bulky reducing agent,

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TABLE 1. Reductions in THF, Dichloromethane, and Toluene[a]

	THF		dichloromethane		toluene	
ketone	ratio of alcohols axial:equatorial[b]	yield (%)[c]	ratio of alcohols axial:equatorial[b]	yield (%)[d]	ratio of alcohols axial:equatorial[b]	yield (%)[d]
2-methylcyclohexanone	25:75	89	91:9	71 (7)	1:99	69
3-methylcyclohexanone	36:64	95	91:9	74 (8)	1:99	74
4-methylcyclohexanone	50:50	97	93:7	67 (5)	1:99	75
2-*tert*-butylcyclohexanone	31:69	90	99:1	85	1:99	87
4-*tert*-butylcyclohexanone	50:50	97	97:3[e]	83 (3)	1:99	73
3,3,5-trimethylcyclohexanone	48:52	94	95:5	83 (5)	1:99	67
menthone	34:66	92	99:1	77	1:99	89
norcamphor			92:8	78 (7)	1:99	77
camphor			8:92	83 (7)	58:42	50 (36)
5α-cholestan-3-one			77:23	60 (10)	2:98[f]	78
2-methylcyclopentanone			99:1[g]	73	19:81[g]	75 (10)

[a] Reactions performed for 6 h at 25 °C, except where stated. [b] Ratios were measured by ^{1}H NMR or GC on the crude mixture after workup. [c] Combined isolated yield: major and minor isomers were not separated. [d] Isolated yields of major (minor) isomers following column chromatography. [e] Reaction performed at −78 °C; ratio at 25 °C was 71:29. [f] Ratio measured by HPLC. [g] Ratio expressed as cis:trans.

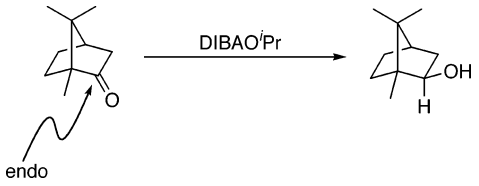

FIGURE 2. Reduction of camphor is from the endo face.

approaching the carbonyl group along an equatorial trajectory to produce the axial alcohol. The one exception to this is the reduction of camphor, where the equatorial alcohol is produced by hydride delivery from the less hindered endo face as expected (Figure 2).

Extending the reaction time in dichloromethane resulted in equilibration to the thermodynamically more stable alcohol. Thus, for the reduction of 3,3,5-trimethylcyclohexanone, reaction was complete after 6 h, with an axial:equatorial alcohol ratio of 95:5. After 3 days the ratio of axial:equatorial had switched to 6:94, and after 7 days there was less than 2% axial alcohol present.

Performing the reductions in toluene gave dramatically different results. The reductions were complete after 6 h at room temperature, and, remarkably, the ratio of equatorial to axial alcohol, in all examples except camphor and 2-methylcyclopentanone, was better than 99:1, with no axial alcohol detectable by ^{1}H NMR or GC analysis. The stereoselectivity for the reduction of camphor by DIBA^{i}OPr in toluene was similar to that obtained by Cha and Kwon in diethyl ether, but whereas in ether the reaction was only 23% complete after 7 days, in toluene the reaction had gone to completion within 6 h. The results for 2-methylcyclopentanone are in line with earlier work in which reductions of cyclopentanones under equilibrating conditions afforded modest diastereoselectivities.[12,13]

One important feature of the reductions in ether, THF, and dichloromethane was that the ratio of equatorial:axial alcohol increased over time. To see whether the same was true for the reductions in toluene, the reduction of 2-methylcyclohexanone was monitored over time. After 2 h, 60% of the starting ketone remained, with 40% having been reduced to equatorial alcohol. After 4 h, 75% of the ketone had been reduced to equatorial alcohol, and 25% remained unchanged. Reduction was complete after 6 h. At no stage was there any axial alcohol visible by ^{1}H NMR.

The stereoselectivity and rate of the toluene reductions decreased if ether was added to the reactions. Thus, a solution of DIBA^{i}OPr in toluene was prepared as before, and diluted with 20 times its volume of ether before addition of 3,3,5-trimethylcyclohexanone. After 24 h the reduction was essentially complete, with a product ratio of 93:7 in favor of the equatorial alcohol, a result broadly in line with (although slightly less stereoselective than) that of Cha and Kwon.

A 1:1 ratio of ketone to reducing agent appeared to be crucial to achieve optimum stereoselectivity, with excess DIBA^{i}OPr proving to be detrimental to the product ratio. Reducing the amount of DIBA^{i}OPr, while not affecting the ratio of product alcohols, did result in the recovery of ketone, suggesting that at this temperature only one hydride is transferred per molecule of DIBA^{i}OPr.[14]

Meerwein−Ponndorf−Verley and related aluminum reductions proceed via initial coordination of the carbonyl oxygen to the aluminum. The solvent dependency of Meerwein−Ponndorf−Verley-type reductions was reported by Krohn,[15] following an earlier investigation by Lardicci.[16] These studies concluded that Meerwein−Ponndorf−Verley-type equilibrations are slowest in solvents such as ether and THF that are capable of coordinating to the metal, thereby competing for the aluminum with the carbonyl group. Reactions were found to be fastest in toluene and cyclohexane, although solubility of the substrate often limits use of the latter. The reductions with DIBA^{i}OPr in toluene do appear to be proceeding through a Meerwein−Ponndorf−Verley-type equilibration process. When the reaction was monitored over time, none of the axial alcohol product was detected, suggesting that equilibration is fast relative to

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hydride transfer. As in the earlier work of Eliel with lithium aluminum hydride−aluminum trichloride complex,[9] the species being equilibrated will be the aluminum alkoxide complexes rather than the free alcohols. Attempts to convert the free alcohol *cis*-4-*tert*-butylcyclohexanol into the thermodynamically more stable trans isomer by treatment with DIBA^{i}OPr in toluene met with failure, but when excess 4-*tert*-butylcyclohexanone was added to the mixture, complete equilibration occurred within 6 h to give the trans isomer and unreacted ketone.

In dichloromethane, DIBA^{i}OPr behaves as a bulky reducing agent, approaching the carbonyl group along an equatorial trajectory to produce the axial alcohol. Although the rate of reduction is not significantly decreased, it does appear that the rate of equilibration of the resultant aluminum alkoxides is reduced relative to the rates in the other solvents studied.

In conclusion, the stereoselectivity of the reduction of cyclic ketones by DIBA^{i}OPr is strongly dependent on reaction solvent. The use of toluene as solvent is optimal for reduction of cyclohexanones to the corresponding equatorial alcohols, achieving equatorial:axial ratios as high as those previously reported by Cha and Kwon in diethyl ether, but in dramatically shorter reaction times. In dichloromethane, reduction is rapid and the axial alcohol is strongly favored. These observations should extend the usefulness of this important reagent.

Experimental Section[17]

Preparation of DIBA^{i}OPr in Toluene. Isopropyl alcohol was added dropwise over 30 min to a stirred solution of diisobutylaluminum hydride in toluene (1 M solution, 10 mL, 10 mmol) at 0 °C. After complete evolution of hydrogen, the reagent solution was stirred at room temperature for 1 h to give a solution of DIBA^{i}OPr (0.93 M) in toluene.

Reduction of Cyclic Ketones. A solution of DIBA^{i}OPr in toluene (0.93 M, 8.00 mL, 7.43 mmol) was added to a solution of the ketone (7.43 mmol) in toluene (20 mL), and the reaction mixture was stirred for 6 h at room temperature. Diethyl ether (20 mL) and HCl (3 M, 10 mL) were added and the mixture was stirred for 30 min; a solution of NaOH (3 M, 15 mL) was added and stirring continued for 1 h. The organic phase was separated and the aqueous phase extracted with ether (3 × 50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford the crude alcohols, which were further purified by flash column chromatography on silica gel.

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(17) All reactions were performed in flame-dried glassware under an atmosphere of nitrogen. Toluene was distilled from sodium, THF was distilled from sodium and benzophenone, and dichloromethane was distilled from calcium hydride.