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Hindered Organoboron Groups in Organic Synthesis. 16.[1] Preparation and Use of Lithium Ditripylethylhydroborate for the Diastereoselective Reduction of Cyclohexanones

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Abstract. Preparations of lithium and potassium ditripylethylhydroborates are outlined. The lithium salt reduces substituted cyclohexanones with diastereoselectivities comparable with the most selective reagents known, but with the advantages that low temperatures are not required and the corresponding borane is air stable and can be quantitatively recovered.

Hindered alkylbis(2,4,6-triisopropylphenyl)boranes, ($Trip_2BR$) (**1**) and aryldditripylboranes (**2**), ($Trip_2BAr$) are easily synthesised in good yields[2] by reaction of readily available[1,2] ditripylfluoroborane with either Grignard reagents (R = *p*-alkyl) or alkyllithiums (R = *s*, *t*-alkyl) and aryllithiums. Reaction of (**1**) with either *t*-butyllithium[3,4] or activated potassium hydride[5] gives rise to the corresponding lithium or potassium hydroborates. Sodium and lithium hydrides do not react in comparable conditions.

Unhindered reductants such as sodium tetrahydroborate[6,7,8] and borane THF[9] tend to reduce cycloalkanones so as to yield the more stable (equatorial) alcohol (Table 1) by attack from the more hindered face of the molecule. As the reductant becomes more hindered[10] there is increasing attack from the less hindered face to give the less stable alcohol. The most selective reagents to do this are lithium tri-*s*-butylhydroborate[11] and lithium trisiamylhydroborate.[12] We decided to investigate the effect of the ditripylboryl group on such reductions and chose lithium and potassium ditripylethylhydroborates (**3**) and (**4**) as our test reagents, though considerably more hindered alkylditripylboranes are available, if required. Using THF solutions of (**3**) and (**4**) at room temperature, reductions were almost instantaneous and slightly exothermic. The results (Table 1) show that (**3**) is directly comparable in its stereoselectivity[#] with the most selective known reagents. The latter, however, require low temperatures (-78°C) to attain the high diastereoselectivities recorded for the 3- and 4-methylcyclohexanones.[11,12] The potassium salt (**4**) appears to be considerably less selective than the lithium salt, unlike the corresponding lithium and potassium tri-*s*-butylhydroborates.[11,13] This could be a genuine cation effect,

[#]Lithium ditripylmethylhydroborate gives approximately the same results.

but could be due to the presence of a small amount (<5%) of potassium ethyltripyldihydroborate ($KBEtTripH_2$) shown (^{11}B nmr) to be produced by detripylation in the reaction of activated KH with ditripylethylborane. The two hydroborates could not be separated.

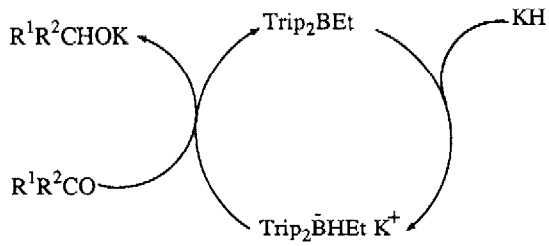
Table 1. Diastereoselectivities in reductions of cyclohexanones

Cyclo-hexanone	Less Stable Alcohol	% Less stable alcohol produced						
		$NaBH_4$[7]	$LiBHBu^n_3$[10]	Li9BBNH$_2$[10]	$LiBu^s_3BH$[11]	$LiSia_2BH$[12]	*$LiTrip_2BEtH$*	*$KTrip_2BEtH$*
2-Me	cis	27	85	97	99.9	99.7	>99[a]	-
3-Me	trans	12	-	59	95[b]	99.6[b]	99[c]	82
4-Me	cis	11	-	52	90[b]	99[b]	97.5[d]	85
4-Bu^t	cis	13	-	54	96.5[b]	99.4[b]	>99[d]	-

[a] Isolated yield of 90%. [b] Reaction at -78°C. [c] Isolated yield of 85%. [d] Yields of 97%.

An advantage of using lithium ditripylethylhydroborate (**3**) is that it is very stable in solution. A major drawback to using (**3**), however, is its high molecular weight which is such that to reduce 25g of 2-methylcyclohexanone just over 100g of reagent is required. However, alkylditripylboranes are very stable to both hydrolysis and aerial oxidation and hence a simple aqueous work-up is possible. Chromatography on silica with pentane gives a recovery of 96 - 100% of ditripylethylborane ready to be recycled. The product alcohol is then eluted with ether. This simple non-destructive work-up contrasts with the oxidative procedure used with tri-*s*-alkylhydroborates which completely degrades the boron species.

In view of the stability of ditripylethylborane, it seemed possible that it could catalyse the KH reduction of ketones (Scheme)



Scheme

Indeed, the addition to activated KH of ditripylethylborane (1 - 2% with respect to ketone) followed by addition of ketone in THF gives complete reduction in *ca.* 5 min. in conditions in which KH alone simply enolises the ketone. Thus phenyl ethyl ketone was quantitatively reduced to 1-phenylpropan-1-ol. The methylcyclohexanones gave excellent yields of the alcohols but with low diastereoselectivities (Table 2), presumably due to the excess KH present. Lowering the temperature does not improve the situation as longer times have to be used. If KH is added to lithium ditripylethylhydroborate solutions, the results of reductions are similar to those in Table 2. The reason for this reduction in diastereoselectivity is not yet clear.

Table 2. $Trip_2BEt$ catalysed reduction of methylcyclohexanones by KH

Cyclohexanone	% Less stable alcohol[a]	Yield (%)[a]
2-Me	27.4	99
3-Me	20.4	100
4-Me	18.5	98

[a] Estimated by capillary g.c.

B-Ethylditripylborane (1, R = Et). A solution of ditripylfluoroborane (2) (9.6g, 22 mmol)[2] in THF (15 ml) was transferred *via* double ended needle under argon pressure to a stirred, previously prepared solution of EtMgI (75 mmol in 32 ml. of THF) under argon. Once addition was complete, the mixture was heated under reflux for 3h. and then allowed to stand at room temperature for 16 h. The excess Grignard reagent was quenched by careful addition, with good stirring, of saturated aqueous NH_4Cl. Diethyl ether (60 ml) was added and the supernatent decanted into a separating funnel. The inorganic residue was dissolved in water and added to the funnel. The layers were separated, the organic layer was washed with brine (2 x 30 ml) and the combined aqueous extracts shaken with ether (30 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Crystallisation from ethanol gave B-ethylditripylborane, m.p. 104°C (7.87g, 80%).

Preparation of lithium ditripylethylhydroborate and reduction of *t*-butylcyclohexanone. A dry 100 ml round-bottomed flask connected to a bubbler was charged with ditripylethylborane (3g, 6.7 mmol) and then flushed for 5 min. with argon. Tetrahydrofuran (50 ml) was added and the solution stirred whilst *t*-butyllithium (4.5 ml. of a 1.5M solution, 6.75 mmol) was added slowly by syringe. There was a gently exothermic reaction which gave a pale green solution which was stirred for 10 min. at room temperature. The resultant solution showed a doublet in the ^{11}B nmr at -13.6 δ (d, J = 39 Hz) which collapsed on decoupling the proton signals.

The solution so prepared was transferred by double-ended needle to a stirred solution of 4-*t*-butylcyclohexanone (0.5g, 3.2 mmol) in THF and the mixture stirred overnight at room temperature The reaction was quenched with a mixture of water (30 ml) and diethyl ether (30 ml) and the separated organic layer washed further with brine (3 x 50 ml). The combined aqueous extracts were washed with ether (40 ml) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was transferred to a dry silica gel column which was eluted with pentane to give pure ditripylethylborane (2.89 g, 96%). The column was eluted with pentane : ether mixtures (50 : 50 → 0 : 100) to give the product as a white solid, (0.49g, 97%), essentially a single isomer by capillary g.c. and ^{13}C nmr.

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