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Chelation-Controlled Reduction of α - and β -Oxygenated Ketones with Lithium tri-*n*-Butylborohydride.

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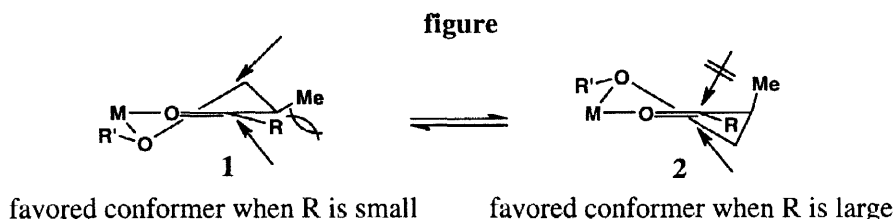
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Abstract: Lithium tri-*n*-butyl borohydride showed high selectivity in the reduction of α - and β -oxygenated ketones, giving a preponderance of the chelation controlled products. © 1998 Elsevier Science Ltd. All rights reserved.

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Several methods have been reported for the stereoselective hydride reduction of ketones [1]. Recently, we wanted to achieve the chelation-controlled reduction of α - and β -oxygenated ketones **3** and **5**. A well-known reagent, zinc borohydride [2], did not provide useful selectivity for this transformation. A closer look at the literature revealed that many established procedures [2, 3], are very efficient in providing the chelation controlled reduction product of phenones or *t*-butylketones. However, for methyl- or primary alkylketones, their efficiency is somewhat attenuated. Based on NMR evidence, DiMare *et al.* [3b] have suggested a lack of steric bias for ketones favoring type **1** over type **2** chelates (figure). We therefore reasoned that a bulky hydride such as a trialkyl borohydride could perhaps distinguish between the two faces of chelated ketones that have failed to provide sufficient bias for reduction with small hydride reagents (BH_4^- , BH_3CN^-). In this paper, we report efficient chelation-controlled reduction of methyl and primary alkyl ketones containing α - or β -oxygenated groups using lithium tri-*n*-butylborohydride.



When treated with $\text{Zn}(\text{BH}_4)_2$, α -alkoxyketone **3** or β -ketoester **5** gave moderate selectivity in favor of the chelation-controlled products **4 anti** and **6 syn** respectively (table 1, entries 1 and 10). Lithium tri-*s*-butylborohydride (L-Selectride[®]) was evaluated as a possible chelation-control reagent. In THF, this reagent is usually Felkin-Ahn selective [4]. This is also what we observed with **3** and **5** (table 1, entries 3 and 11). However, there have been a

number of reports showing that it could also provide the chelation-controlled product when used under modified conditions [5]. For example, when L-Selectride® (1 M in THF) is added to solutions of **3** or **5** in dichloromethane as a non-complexing co-solvent, shifts from Felkin-Ahn to chelation-controlled selectivity are observed (table 1, cf. entry 4 and 3, 12 and 11).

Table 1
Reduction of **3** and **5** with Various Borohydride Reagents.

entry	reduction of 3 , conditions ^a	ratio ^b (4 anti : 4 syn)	entry	reduction of 5 , conditions ^a	ratio ^b (6 syn : 6 anti)
1	Zn(BH ₄) ₂ , Et ₂ O, 0 °C	3 : 1	10	Zn(BH ₄) ₂ , Et ₂ O, 0 °C	2.5 : 1
2	Zn(BH ₄) ₂ (/Et ₂ O), CH ₂ Cl ₂ , -78 °C	6 : 1	11	<i>s</i> -Bu ₃ BHLi (/THF), THF, -78 °C	1 : 6
3	<i>s</i> -Bu ₃ BHLi (/THF), THF, -78 °C	1 : 28	12	<i>s</i> -Bu ₃ BHLi (/THF), CH ₂ Cl ₂ , -78 °C	4 : 1
4	<i>s</i> -Bu ₃ BHLi (/THF), CH ₂ Cl ₂ , -78 °C	10 : 1	13	<i>s</i> -Bu ₃ BHLi (/Et ₂ O-pentane), CH ₂ Cl ₂ , -78 °C	6 : 1
5	<i>s</i> -Bu ₃ BHLi (/Et ₂ O-pentane), CH ₂ Cl ₂ , -78 °C	30 : 1	14	Et ₃ BHLi (/THF), CH ₂ Cl ₂ , -78 °C	11 : 1
6	Et ₃ BHLi (/THF), CH ₂ Cl ₂ , -78 °C	28 : 1	15	Et ₃ BHLi (/Et ₂ O-pentane), CH ₂ Cl ₂ , -78 °C	25 : 1
7	Et ₃ BHLi (/Et ₂ O-pentane), CH ₂ Cl ₂ , -78 °C	50 : 1	16	<i>n</i> -Bu ₃ BHLi (/THF-pentane), CH ₂ Cl ₂ , -78 °C	3.5 : 1
8	<i>n</i> -Bu ₃ BHLi (/THF-pentane), CH ₂ Cl ₂ , -78 °C	23 : 1	17	<i>n</i> -Bu ₃ BHLi (/Et ₂ O-pentane), CH ₂ Cl ₂ , -78 °C	41 : 1
9	<i>n</i> -Bu ₃ BHLi (/Et ₂ O-pentane), CH ₂ Cl ₂ , -78 °C	>99 : 1			

^a The hydride reagent was added to a 0.03 M solution of ketone in the indicated solvent.

^b Ratios were determined by ¹H NMR and/or GC on the crude isolated products. Yields of purified products ≥70%.

At this point, we felt that complete removal of THF from the reaction mixtures could contribute to a significant increase in chelation-controlled selectivity. We prepared L-Selectride® in diethyl ether-pentane (0.35 – 0.5 M) [6]^{1, 2}. This THF-free reagent gave more chelation-controlled products than commercially available L-Selectride® 1M/THF (table 1, entries 5 and 13). Under the same reaction conditions³, Zn(BH₄)₂ did not generate the chelation product with the same efficiency (table 1, entry 2).

When a solution of lithium triethylborohydride (Super-Hydride® 1M in THF) was added to **3** or **5** in CH₂Cl₂, the chelation selectivity was superior to that of L-Selectride® under the same conditions (table 1, cf. entries 6 and 4, 14 and 12). Using the above-mentioned method, attempts to generate Super-Hydride® in Et₂O-pentane resulted in the generation of two colorless liquid phases that differed in their respective composition by the distribution of the borane species as suggested by ¹¹B NMR analysis. The lower phase was more concentrated and showed mainly a singlet at –15.5 ppm that we attributed to *t*-Bu(Et)₃BLi⁴. The upper phase contained the desired hydride but was dilute. It was used for reduction of **3** and **5** and

¹ This procedure originally involved the addition of an equimolar amount of *t*-BuLi (1.7 M/pentane) to a –78 °C THF solution of *s*-Bu₃B.

² ¹¹B NMR gave the expected doublet for L-Selectride® at –6.7 ppm (referenced to BF₃ at 0 ppm).

³ Dichloromethane as co-solvent and –78 °C.

⁴ This tetraalkylborate species may have been obtained by direct addition of *t*-BuLi to Et₃B, a side reaction that was not observed in THF at –78 °C (see ref. 6b). This change in the reactivity of *t*-BuLi was attributed to a difference in its aggregation state between THF and Et₂O (see Bauer W, Winchester WR, von Rague Schleyer P. *Organometallics*, 1987, 6, 2371).

showed noticeable enhancement in the chelation-controlled selectivity compared to a THF solution of Super-Hydride[®] (table 1, entries 7 and 15).

We also attempted the generation of *n*-Bu₃BHLi, in THF and in Et₂O-pentane⁵. The THF preparations showed, by ¹¹B NMR, two doublets in a 1 to 4 ratio at -11.3 and -14.5 ppm corresponding to *s*-Bu(*n*-Bu)₂BHLi and *n*-Bu₃BHLi respectively⁶. In addition to two doublets, the ether preparation showed a singlet at -15.8 ppm that was again attributed to lithium tetraalkylborate. The two solutions were used to reduce **3** and **5**. While the THF solution did not perform significantly better than L-Selectride[®] or Super-Hydride[®] under analogous conditions (table 1, entries 8 and 16), the ether-pentane solution performed extremely well giving the highest ratios observed so far (table 1, entries 9 and 17)⁷.

To verify that this method is not limited to the substrates shown above, we have submitted a variety of α - and β -oxygenated ketones **7** to **12** to our optimized conditions and have compared the results to those obtained with Zn(BH₄)₂. For most of the cases studied, lithium tri-*n*-butylborohydride performed significantly better than Zn(BH₄)₂ in giving useful levels of the chelation-controlled products (table 2)⁸.

Table 2
Reduction of a variety of oxygenated ketones with *n*-Bu₃BHLi and Zn(BH₄)₂.

ketone ^a	entry	conditions ^b	chelation (a) : Felkin-Ahn (b)		
			ratio ^c	products	
	1	A	24 : 1		
	2	B	1 : 2		
	3	A	43 : 1		
	4	B	2.1 : 1		
	5	A	4.4 : 1		
	6	B	3.7 : 1		
	7	A	6.5 : 1		
	8	B	1.5 : 1		
	9	A	37 : 1		
	10	B	3.6 : 1		
	12	A	67 : 1		
	13	B	48 : 1		

^a Except for **7**, the racemates were used.

^b A) *n*-Bu₃BHLi (Et₂O-pentane), CH₂Cl₂, -78 °C. B) Zn(BH₄)₂, Et₂O, 0 °C.

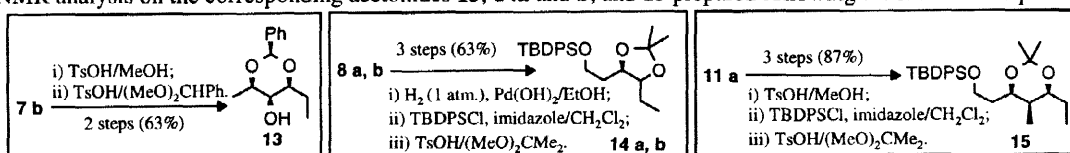
^c Ratios determined by ¹H NMR and/or GC on crude isolated products. Yields of purified products \geq 70%.

⁵ The reaction had to be initiated at -40 °C due to the lack of solubility of *n*-Bu₃B in Et₂O at -78 °C.

⁶ This 4 to 1 ratio of hydride is consistent with a 96 to 4 distribution of *n*- and *s*-butyl chains present in the commercial tri-*n*-butylborane. This corresponds to the observed regioselectivity in the BH₃ hydroboration of 1-butene.

⁷ Excess reagent (3 eq.) was used to drive the reactions to completion, consistent with a 1 to 2 ratio of hydride to tetraalkylborate.

⁸ All new compounds displayed satisfactory spectroscopic data. The relative configuration of compounds **7a**, **8a**, **8b** and **11a** was established by ¹H or ¹³C (Rychnovsky SD, Yang G, Powers JP. *J. Org. Chem.* **1993**, *58*, 5251, and references cited therein) NMR analysis on the corresponding acetonides **13**, **14a** and **b**, and **15** prepared following the indicated sequences.



In conclusion, we have compared three lithium tri-alkylborohydrides to $\text{Zn}(\text{BH}_4)_2$ in the reduction of a variety of α - and β -oxygenated ketones. In general, Et_2O -pentane solutions of trialkylborohydride added to dichloromethane solutions of the substrates at low temperature give more chelation-controlled product than $\text{Zn}(\text{BH}_4)_2$. Lithium tri-*n*-butylborohydride appears to be the best reagent of the three and constitutes a good complement to existing methods. In addition, we have observed that the reactivity of *t*-BuLi towards tri-*n*-alkylboranes varies from THF to diethyl ether, the later giving also rise to the formation of a by-product assigned as the corresponding lithium tetraalkylborate.

Preparation of *n*-Bu₃BHLi (*/Et*₂O-pentane) [6b]: In a dry 100 mL round-bottom-flask equipped with a three-way stop-cock (for N₂ inlet and septum) were introduced anhydrous Et₂O (40 mL) and *n*-Bu₃B (Aldrich, 5 mL, 20.5 mmol) under N₂. The resulting solution was chilled to -40°C (external) and *t*-BuLi (Aldrich, 1.3 M /pentane, 15.7 mL, 1.0 eq.) was added dropwise via syringe. The cold temperature bath was then removed and the pale yellow reaction mixture was allowed to reach ambient temperature and was stirred for an additional hour. Within 20 min., the yellow color faded. The reagent, obtained as a clear colorless solution, could be kept for weeks at ambient temperature without noticeable degradation.

Reduction of **11**: To a -78°C solution of ketone **11** (0.03M / CH₂Cl₂) under N₂ was added the hydride solution slowly via syringe. After 30 min., the reaction was quenched with MeOH (excess) at -78°C. After concentration under reduced pressure, the crude mixture was diluted with THF (to ca. 0.03M) and treated at ambient temperature with NaOH (10 eq., 10 M) and H₂O₂ (10 eq., 30%) overnight. After partition between Et₂O and water, the crude reaction isolate was dried and analyzed (GC). Purification by flash chromatography gave the desired alcohols **11 a** (*syn*) and **11 b** (*anti*) in 70% yield.

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