Chemoselective Reduction of Aldehydes over Ketones with Sodium Tris(hexafluoroisopropoxy)borohydride

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Abstract: Chemoselective reduction of aldehydes in the presence of ketones was achieved using sodium tris(hexafluoroisopropoxy)borohydride which can be stored as a THF solution.

Key words: reduction, sodium borohydride, hexafluoroisopropanol, aldehyde, ketone

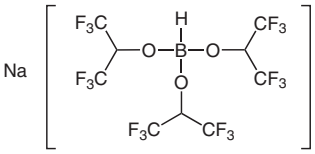

Figure 1 Chemical structure of $NaBH(HFIP)_3$

The chemoselective reduction of an aldehyde to a primary alcohol in the presence of ketone and other reducible functions is a considerably useful reaction in organic synthesis. Although $NaBH_4$ is widely used for reduction of aldehydes and ketones,[1] it is too reactive to chemoselectively reduce aldehydes in the presence of ketones under normal conditions. Therefore, chemoselective reduction of aldehydes using $NaBH_4$ has only been achieved at very low temperature[2] or by addition of other reagents such as thiols,[3] metal salts,[4] resins[5] or PEG.[6] However, a convenient alternative method is desirable in both academia and industry. In general, for such chemoselective reductions, the modified hydrides, formed by the replacement of hydride with sterically hindered substituents and/or electron-withdrawing groups, must be able to discriminate between the structural and electronic environment of the carbonyl groups. In this context, we examined sodium tris(hexafluoroisopropoxy)borohydride, $NaBH(HFIP)_3$, owing to the sterically hindered and electron-withdrawing nature of the hexafluoroisopropoxyl (HFIP) group (Figure 1). Although hexafluoroisopropanol (HFIP) has recently been used as a unique solvent,[7] and $NaBH(HFIP)_3$ was first prepared by Singaram and Williamson,[8] the use of $NaBH(HFIP)_3$ for chemoselective reduction of carbonyl functions has never been demonstrated. Here, we report the first chemoselective reduction of aldehydes over ketones using $NaBH(HFIP)_3$ in THF in HFIP.

We first slightly modified the preparation procedure of $NaBH(HFIP)_3$ reported by Singaram and Williamson. Thus, a mixture of $NaBH_4$ and an excess (6.0 equiv) of HFIP in dry THF (1 M for $NaBH_4$) was stirred at 0 °C for 15 hours, and then evaporated in vacuo in order to remove the excess HFIP and the solvent, THF, to give $NaBH(HFIP)_3$ as a white solid in almost quantitative yield. At this stage, we found that the solid $NaBH(HFIP)_3$ was too hygroscopic to be handled and stored under atmosphere for extended periods of time. Indeed, when we used the solid $NaBH(HFIP)_3$ for the following chemoselective reduction, good reproducibility was not obtained. Therefore, we prepared a 1 M $NaBH(HFIP)_3$ in THF solution by the immediate addition of dry THF after the removal of the excess HFIP and THF from the reaction mixture.

With the more stable 1 M $NaBH(HFIP)_3$ in THF in hand, we examined chemoselective reduction using the aldehyde **1** and the ketone **2**. From the results summarized in Table 1, it was shown that the aldehyde **1** was reduced using 3.0 equivalents of $NaBH(HFIP)_3$ in THF at 25 °C for 5 hours to afford the corresponding primary alcohol **3** in 95% yield (entry 4 in Table 1). In contrast, the reduction of the ketone **2** did not take place at all, and it was recovered quantitatively under the same reaction conditions. Although the actual role of HFIP as the solvent for the present chemoselective reduction reaction is not clear, its use is essential as the solvent for this reaction. These results clearly showed that $NaBH(HFIP)_3$ is a very useful and convenient new reagent for the chemoselective reduction of the aldehyde **1** over the ketone **2**.

With these favorable results in hand, we next examined the generality of the chemoselective reduction using several aldehydes **5**–**7**, **11**, **13** and ketones **8**–**10**, **12**, **14**, **15**. These results are summarized in Table 2. We found that the aldehydes **5**–**7** possessing benzyl, trityl, and benzoyl groups, as well as **1**, were smoothly reduced by $NaBH(HFIP)_3$ in THF in HFIP to give the corresponding primary alcohols in high yields, while the corresponding ketones **8**–**10** were either not reduced at all or only slightly reduced. At this stage, it was confirmed that an ester group was not reduced by $NaBH(HFIP)_3$ and THF as indicated in entry 4 in Table 2. Furthermore, not only aliphatic substrates but also aromatic ones were applicable for the present chemoselective reduction. Thus, as shown in entries 5 and 6, only the aromatic aldehydes **11** and **13** were effectively reduced by $NaBH(HFIP)_3$ in THF, while the aromatic ketones **12** and **14** were recovered almost un-

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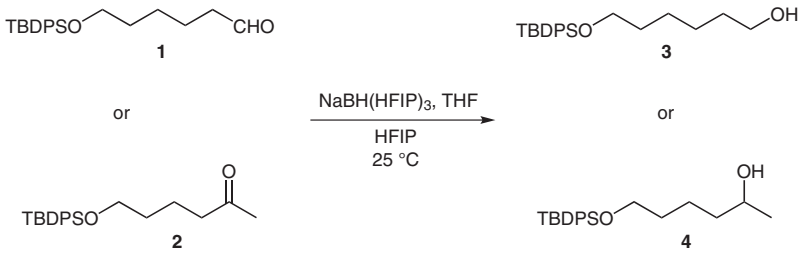
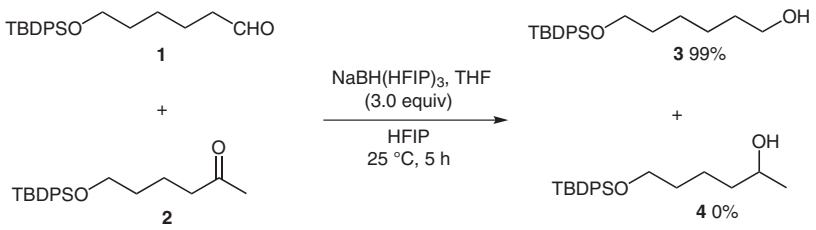
Table 1 Chemoselective Reductions of Aldehyde **1** over Ketone **2** Using $NaBH(HFIP)_3$[a]



Entry	$NaBH(HFIP)_3$ (equiv)	Time (h)	Yield (%)[b]			
			1	**3**	**2**	**4**
1	5.0	24	0	95	98	0
2	3.0	24	0	97	99	0
3	1.5	24	46	53	99	0
4	3.0	5	0	95	98	0
5	3.0	3	5	92	99	0
6	3.0	1	31	69	98	0

[a] The reaction using **1** or **2** was separately performed.
[b] Isolated yields after purification by column chromatography.



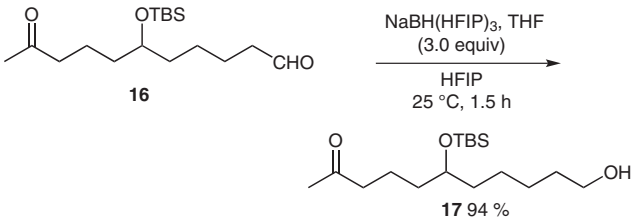
Scheme 1 Chemoselective reduction of aldehyde **1** in the presence of **2**

changed under similar reaction conditions. In addition, the chemoselective reduction of the aldehyde **1** over the ethyl ketone **15** was also achieved as shown in entry 7 in Table 2.

We further examined the chemoselective reductions using a mixture of the aldehyde **1** and the ketone **2** in the same reaction flask, and using the compound **16** possessing both aldehyde and ketone functionalities in the same molecule. It was found that even with the aldehyde **1** and the ketone **2** mixed in the same reaction flask, identical results (yield and chemoselectivity) were obtained using $NaBH(HFIP)_3$ in THF as shown in Scheme 1. Furthermore, only the aldehyde group in compound **16**[9] was reduced using $NaBH(HFIP)_3$ in THF without the reduction of the ketone functionality to give the keto-alcohol **17**[9] in high yield (Scheme 2).

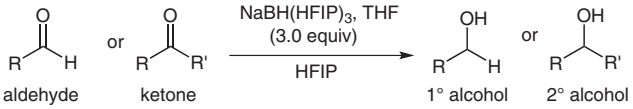
Finally, we tested whether 1 M $NaBH(HFIP)_3$ in THF was stable for an extended period of time. Thus, we stored $NaBH(HFIP)_3$ in THF at –30 °C in a refrigerator for three months, and we examined the time course of the chemoselective reduction using the stored $NaBH(HFIP)_3$ in THF over the same period. From the results shown in Table 3, it was confirmed that $NaBH(HFIP)_3$ in THF worked well for at least three months, and similar satisfactory results were obtained in terms of the reduction efficiency and chemoselectivity.

In conclusion, we found that $NaBH(HFIP)_3$, easily prepared from $NaBH_4$ and HFIP, chemoselectively reduced aldehydes in the presence of ketones. Furthermore, the $NaBH(HFIP)_3$ in THF solution was stable for at least three months with no decrease in efficiency. The reaction is very simple and convenient. As reduction reactions of carbonyl groups are very important steps in organic synthesis, this chemoselective reduction method should find wide application in both academia and industry.



Scheme 2 Chemoselective reduction of the aldehyde group over the ketone function in **16**

Table 2 Chemoselective Reductions of Aldehydes over Ketones Using $NaBH(HFIP)_3$[a]



Entry	Aldehyde	Ketone	Temp (°C)	Time (h)	Yield (%)[b] 1° Alcohol	2°Alcohol
1	**1**	**2**	25	5	95	0
2	**5**	**8**	0	2	87	12
3	**6**	**9**	25	5	91	0
4	**7**	**10**	25	0.3	89	9
5	**11**	**12**	25	24	93	2
6	**13**	**14**	0	0.5	82	14
7	**1**	**15**	25	5	93	0

[a] The reaction using aldehyde or ketone was separately performed.
[b] Isolated yields after purification by column chromatography.

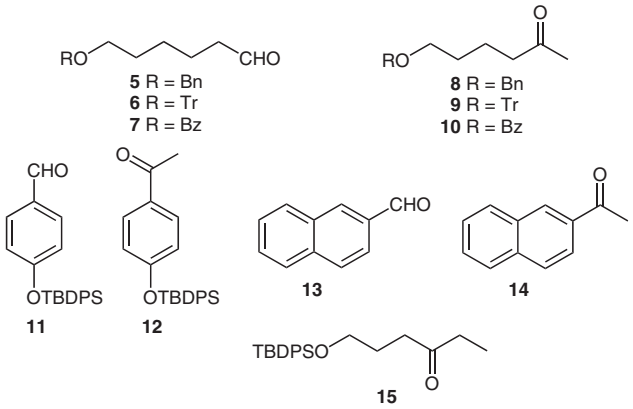


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Table 3 Chemoselective Reductions of Aldehyde **1** over Ketone **2** Using the Stored $NaBH(HFIP)_3$[a]

Entry	Shelf life (weeks)	Yield (%)[b] **3**	**4**
1	0	95	0
2	1	96	0
3	2	94	0
4	3	92	0
5	4	98	0
6	12	90	0

[a] The reaction using **1** or **2** was separately performed.
[b] Isolated yields after purification by column chromatography.

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(9) Analytical Data of Compounds **16** and **17**
Compound 16: ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.036 (6 H, s), 0.88 (9 H, s), 1.26–1.70 (10 H, m), 2.13 (3 H, s), 2.42 (2 H, t, *J* = 7.1 Hz), 2.43 (2 H, dt, *J* = 7.3, 1.8 Hz), 3.65 (1 H, tt, *J* = 5.6 Hz), 9.77 (1 H, t, *J* = 1.8 Hz).
Compound 17: ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.037 (6 H, s), 0.88 (9 H, s), 1.25–1.68 (13 H, m), 2.13 (3 H, s), 2.42 (2 H, t, *J* = 7.4 Hz), 3.63 (1 H, m), 3.64 (2 H, t, *J* = 6.5 Hz).