Chemoselective and stereoselective reductions with modified borohydride reagents

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INTRODUCTION

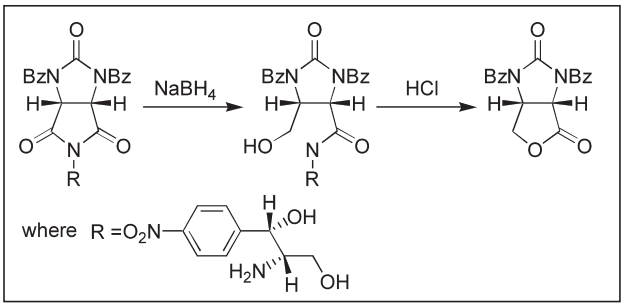
Sodium Borohydride ($NaBH_4$) is the preferred reducing agent for chemoselective reductions of aldehydes and ketones (1). It is sometimes forgotten, however, that Sodium Borohydride can be easily modified to form either a stronger or more selective reducing agent (2). And under the appropriate conditions, this versatility expands to include stereoselective reductions (3). This article will examine a few typical industrial examples showing Sodium Borohydride as a chemoselective and stereoselective reducing agent.

IMIDE REDUCTIONS

Reductions of esters, carboxylic acids, imides and amides are often carried out with very strong reducing agents such as Lithium Aluminum Hydride ($LiAlH_4$) (4). However, the strength of aluminum hydride reducing agents can cause loss of chemoselectivity or regioselectivity. In cases requiring selectivity, it may be beneficial to use $NaBH_4$ or its derivatives.

An applicable industrial example is the borohydride reduction step in Sumitomo's synthesis of *d*-Biotin (Figure 1). Biotin, also known as vitamin H, is an important nutrition additive for both humans and animals (5a). Reductive opening of the imide (with surprising regioselectivity) results in formation of the hydroxyamide in 65% yields after recrystallization (5b) The chiral R-group attached to the nitrogen atom of the imide induces the regioselectivity observed in this reaction. Thirty years after its initial application, this Sodium Borohydride reaction is still used industrially because of its cost-effectiveness.

Figure 1



CHEMOSELECTIVE HYDROXY ESTER REDUCTIONS

There are many laboratory methods and reducing agents to selectively reduce hydroxy esters (6). In the example shown in Figure 2, a β-hydroxymethyl ester is selectively reduced in the presence of another methyl ester (7). The chemoselectivity of this reaction is directed by condensation of the Lithium Triethylborohydride ($LiBHEt_3$) reagent with the hydroxyl function, forming a six-member transition state.

$LiBHEt_3$ is prepared by the reaction of triethyl boron with lithium hydride in a THF solution. Unfortunately, both the reaction conditions and the cost of the reducing agent limit large-scale application of this interesting conversion.

For these reasons, BASF

investigated alternative methods for the selective hydroxy ester reduction in their synthesis of R-Lipoic acid. Their retrosynthetic analysis relied upon the selective reduction of a β–hydroxy ester to an ester diol as shown in Figure 3 (8).

Using $NaBH_4$ in this application resulted in a cost-effective synthesis route suitable for large-scale production. This chemistry relies on initial reaction between $NaBH_4$ and the OH-group, forming an alkoxy borohydride intermediate (Figure 4). The electron donation by the alkoxy group results in a nucleophilic activation of the B-H bond. This activation makes the alkoxy borohydride a significantly stronger reducing agent than uncoordinated Sodium Borohydride.

For this reason, the ester group in the β-position to the hydroxyl group is selectively reduced versus the non-substituted ester. At ambient temperature the reaction is complete within 4-8 hours, with yields in excess of 90%. Further refinement of the reduction will enable BASF to carry out this reduction with virtually no excess borohydride.

Figure 2

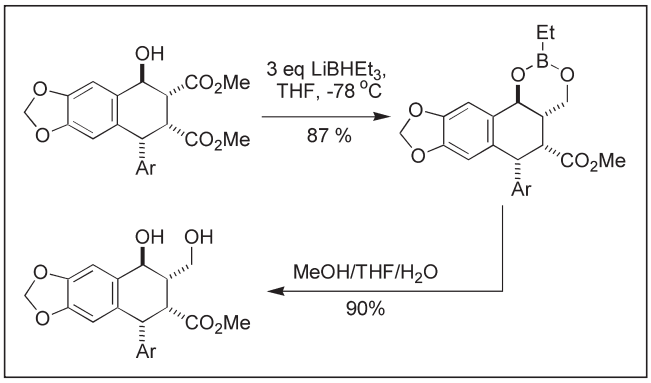


Figure 3

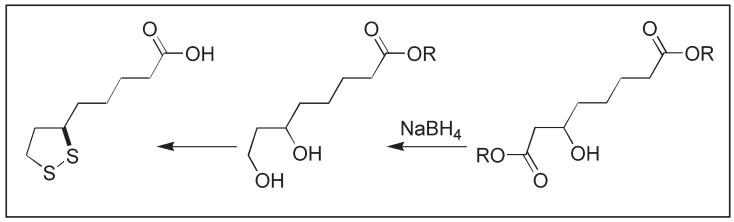


Figure 4

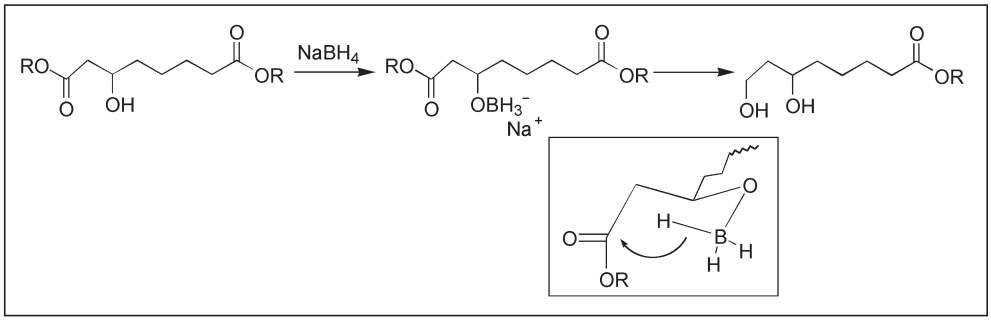


Figure 5

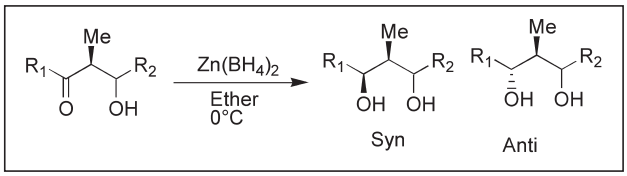


Table I

R_1	R_2	Syn:Anti
- Ph	- H	25:1
- CH_2=CMe	- H	25:1

STEREOSELECTIVE HYDROXY KETONE REDUCTIONS

A nearby electron-donating group can also enhance borohydride's stereoselectivity. In the example in Figure 5, a chiral center exists α- to both the carbonyl and hydroxyl groups. Addition of Zinc Borohydride [$Zn(BH_4)_2$] results in a carbonyl reduction with high diastereomeric excess (Table I) (9).

The stereoselectivity can be explained by formation of a six-membered chair-conformation transition state. As shown in Figure 6, geometric factors determine the preferential attack of borohydride to yield a syn-diol. The presence of a chiral methyl group adjacent to the carbonyl and alcohol functions drives the stereoselectivity. The methyl group forces the chair conformation used for hydride insertion.

Zinc borohydride is also a well-known chemoselective reducing agent in academic research. A barrier to its commercial use as a reducing agent is its limited storage stability. Fortunately for the industrial chemist, $Zn(BH_4)_2$ can be prepared *in situ* by addition of $ZnCl_2$ to either a THF slurry of $NaBH_4$ or to a $NaBH_4$ glyme solution (10).

"STATIN-TYPE" CHEMISTRY (11)

Some of the today's largest selling drugs are a series of HMG-CoA reductase inhibitors or "statins", such as fluvastatin, atorvastatin or pravastatin. All of these anti-cholesterol drugs contain an identical side chain, ε-ene-β,δ-dihydroxy-methyl ester. For a number of the statins, this synthon is obtained by Sodium Borohydride reduction of the corresponding β-ene-δ-hydroxy-β-carboxy-methyl ester (Figure 7).

The hydroxy ketone chemistry described in the previous section is inadequate for this application due to the absence of a stereocenter adjacent to the ketone and hydroxyl groups. Narasaka and others have published an alternative technology that addresses this synthesis problem (12). He discovered that a combination of $NaBH_4$ with an organoborane compound, such as Bu_3B or Et_3B (Figure 8), produces diastereomeric yields exceeding 80% (Table II).

The stereoselectivity can be explained by either preferential axial $NaBH_4$ attack on a six-member ring transition-state intermediate (the cyclohexanone model, orbital perturbation), or by the steric hindrance

Figure 6

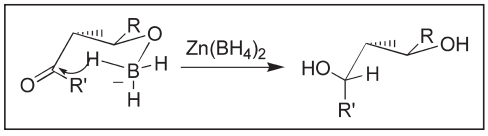


Figure 7

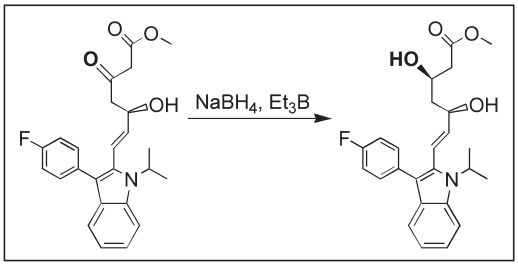
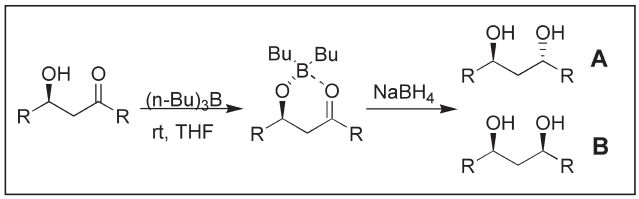


Figure 8



from the butyl groups of the borane (Figure 9).

Researchers at Pfizer (Warner Lambert), Bayer and Novartis have developed the $NaBH_4$ / organoborane combination for diastereoselective hydroxy ketone reductions to where this approach dominates reduction methods for "statin-type" molecules (12b). The $NaBH_4$ / organoborane combination produces excellent diastereoselective yields, without requiring transition metal separation (necessary when using catalytic hydrogenation) It also does not require the use and recovery of chiral auxiliary ligands.

STEREOSELECTIVE ENAMINE KETONE REDUCTIONS

Abbott Laboratories uses a similar technique in the production of ritonavir, which requires reducing both an enamine and a carbonyl function with the creation of two chiral centers. Both reductions use Sodium Borohydride in a one-pot sequence (13).

The enamine reduction uses a borane reagent, which is generated *in situ* from Sodium Borohydride upon addition of methanesulfonic acid (Figure 10). The postulated borane reagent is DME:BH_3 (DME = dimethoxyethane or monoglyme), an unstable borane complex that readily exchanges with the R-NH_2 group to form an R-NH_2:BH_3 complex.

Commercially available boranes used for large-scale industrial applications are mainly THF:BH_3 and [amine]:BH_3. The first reduction step of the above ritonavir sequence reveals one of the disadvantages of borane chemistry. Some interesting borane complexes, such as DME:BH_3 in the case of ritonavir, cannot be offered commercially due to their limited stability. *In situ* generation of boranes from $NaBH_4$ overcomes this hurdle and expands the range of available BH_3-complexing solvents.

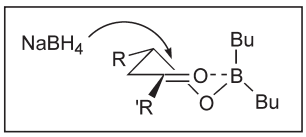
As for the second step, the literature provides many alternatives that exploit the presence of a chiral OH-group, or as in this case NH_2-group, in β-position for the diastereoselective reduction of the carbonyl group.

In the example in Figure 11, the diastereomeric excess appears to be high (> 98%) for a large number of equivalents) of Sodium Borohydride. The low yields might be caused by the way the compound is isolated; as the hydrochloride solid (14).

Table II

R	T °C	Time h	A/B	Yield %
Bz		2	98:2	94
n-Bu	-100	3	96:4	74
	-78	2	88:12	73
C_6H_{11}	-100	6	84:16	90
	-78	6	73:27	94
	-78	36	88:12	84

Figure 9



Researchers at Abbott Laboratories have investigated the synthesis problem of obtaining both good chemical yield and good diastereoselectivity. They showed that addition of a protic co-solvent, e.g. 2-propanol, improved diastereoselectivity (Figure 12). It is believed that after hydroboration of the C-C double bond, the boron remains bonded to the molecule and forms a propoxyamino borane. The propoxyamino borane serves as a stereodriver in the subsequent $NaBH_4$ ketone reduction (15). The isolated yield is 96%.

Figure 10

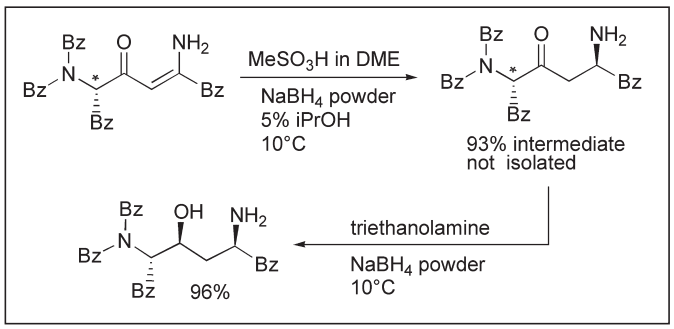


Figure 12

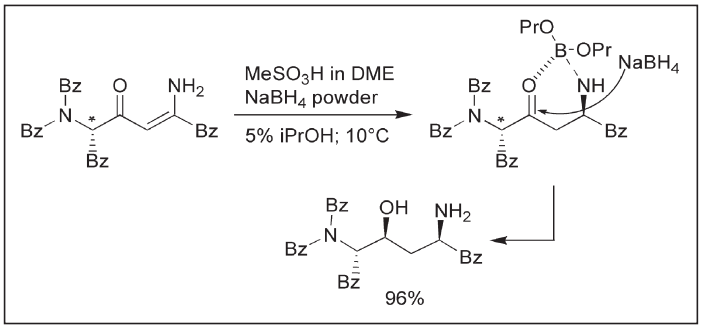
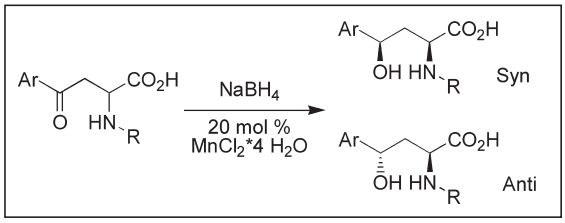


Figure 11



substitutents (Table III). However the chemical yield never exceeds 80%, despite using a large excess (8 hydride

Table III

Ar	R	Temperature °C	Yield %	Syn/Anti
Ph	Bz	20	77	>97:3
4-$MeOC_6H_4$	Bz	18	79	96:4
4-$MeOC_6H_4$	2-Furylmethyl	20	65	>97:3
3-Me-4-$MeOC_6H_4$	Bz	20	70	>97:3
2-Thienyl	Bz	20	76	>97:3
5-Me-2-Thienyl	2-Furylmethyl	20	60	97:3
Ph	(S)-1'-phenylethyl	2-5	80	97:3
Ph	(+)-1'-phenylethyl	2-5	76	>97:3
4-$MeOC_6H_4$	(S)-1'-phenylethyl	2-5	63	97:3
4-$MeOC_6H_4$	(+)-1'-phenylethyl	2-5	75	>97:3
3-Me-4-$MeOC_6H_4$	(S)-1'-phenylethyl	2-5	80	>97:3
3-Me-4-$MeOC_6H_4$	(+)-1'-phenylethyl	2-5	78	97:3

CONCLUSION

Borohydride chemistry has developed far beyond simple aldehyde and ketone reductions. The above examples demonstrate that modified borohydride reagents can reduce not only ester functions but also selectively reduce hydroxy esters in the presence of non-substituted esters. Other surprising chemoselective and stereoselective reductions can be obtained using Sodium Borohydride and its derivatives. Finally, through the *in situ* generation of boranes, electrophilic reduction chemistry is possible using Sodium Borohydride.

Rohm and Haas Company is the world's largest and most experienced supplier of Sodium Borohydride. We support the synthesis community with Mor-Care technical and safety support services to help you select the appropriate reduction technology.

We invite you to contact Rohm and Haas (www.hydridesolutions.com) to learn more about how this versatile reducing agent can solve your reduction chemistry challenges.

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