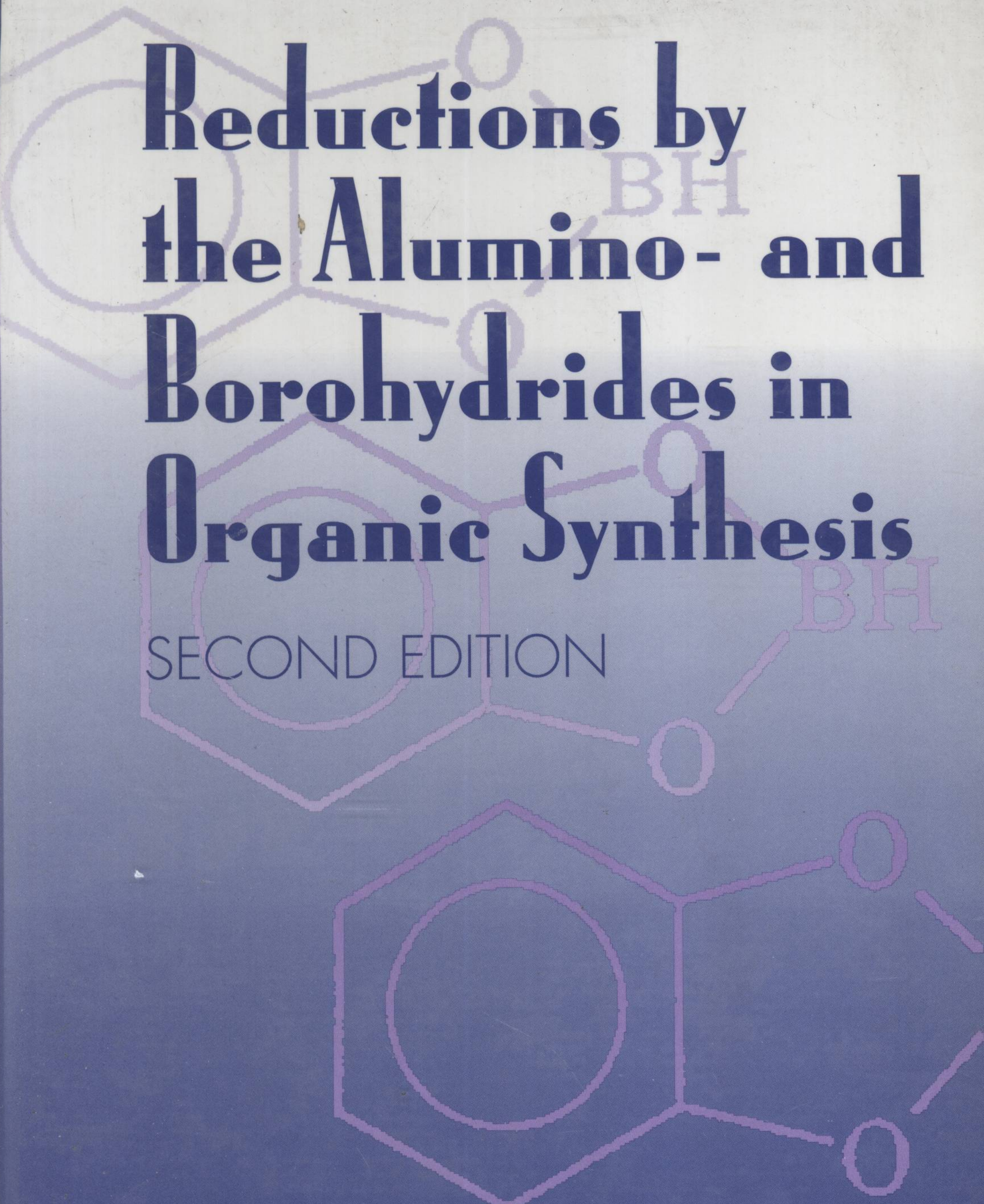
Reductions by the Alumino- and Borohydrides in Organic Synthesis

SECOND EDITION



Jacqueline Seyden-Penne

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Preface

Alumino- and borohydrides and, to a lesser extent, boranes form a part of the chemist's classic arsenal of reducing agents employed in organic synthesis. A number of these compounds are commercially available, but the study of their properties, the introduction of improved reagents, and the development of new reaction conditions continue to be important areas of research. Selectivity is imperative in modern organic synthesis, especially when multifunctional molecules are involved. The reagents chosen at each stage of a chemical transformation must not affect other functional groups in the molecule. Moreover, functional groups can influence a reaction process by altering regioselectivity or stereoselectivity.

In this book, we compare the synthetic potential of the most important commercial hydrides and their readily available derivatives. All these hydrides are easy to use, and the book is organized so that the reader can match the appropriate reagent to a given transformation. The book emphasizes:

- Compatibility between the reduction of the target group and the other functional groups present in the molecule;
- The possibilities for partial reduction;
- The regio- and stereoselectivity of reductions that are altered or controlled by other neighboring groups;
- Asymmetric reductions. These reactions have rapidly developed since the First Edition. In addition to chiral hydrides, other strategies for asymmetric reduction include the use of reagents such as chiral chloroboranes or hydrogenation in the presence of catalysts bearing chiral ligands [S3].

This second edition has been broadly updated, but it is no longer exhaustive. As in the previous edition, the examples are selected in order to cover problems that are frequently encountered in synthesis.

The present book is organized in the following fashion:

- Chapter 1 introduces the most useful reagents and indicates their stability and solubility characteristics and their main applications;
- Chapters 2–5 present the reduction of the main functional groups by these reagents, with reference to features of selectivity (chimio-, regio-, stereo-, and enantioselectivity) and compatibility;
- At the end of the book, synoptic tables indicate how to obtain the main functional groups by hydride reduction.

I am particularly grateful to Mr. Fenouil (Lavoisier-Tec-Doc), who allowed me to publish this Second Edition with a free hand, and to the staff of the library of the University of Aix-Marseille-St-Jérôme, who allowed me to work there as often as I wanted. I am also grateful to the members of the Orsay laboratory, who supplied all the documents that I needed, namely, Robert Bloch, Yves Langlois, and above all Tekla Strzalko. My husband, Bob, handled the production aspects of the work, typing the manuscript and drawing the figures on the computer. I also thank Suzanne Curran and Valerie Wadyko for correcting the files according to the proposals of Dennis Curran, who revised my text and my English. Again, I greatly appreciated the improvements he brought to this book.

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Foreword

Although it may be difficult to imagine now, it was not that long ago that the basic reduction of one organic functional group to another was a demanding proposition. Choices of reagents were very limited, and reaction conditions were harsh. Enter the alumino- and borohydrides. Lithium aluminohydride and sodium borohydride were introduced by Schlesinger and Brown in 1953. Lithium aluminohydride was useful because it reduced so many things, while the milder sodium borohydride effected certain kinds of selective reductions in organic molecules. Soon the complexity of molecules grew, and along with this complexity came the need for more reducing agents with different properties and selectivities. So a few new alumino- and borohydrides were introduced. But the spiral did not stop there. The complexity of molecules grew rapidly, reductions became more and more demanding, and even better and more selective reducing agents were introduced in response to this demand. The response to the need for chiral reducing agents has recently sent this spiral to new heights.

So it would appear that synthetic organic chemists should be happy, because for a given kind a reduction—even a very demanding one—there is probably already an alumino- or borohydride reducing agent and a set of reaction conditions that is up to the task. But there is still unhappiness because finding the right combination from the maze of catalogs, papers, and experimental procedures can itself be a daunting task.

From out of this maze springs this book. Professor Jacqueline Seyden-Penne is an acknowledged expert in the area. The book is a major update of the First Edition, which was published in 1991 by VCH Publishers (a translation from the popular first French edition). It includes the important developments that have occurred in the intervening half-dozen years (notably in the area of asymmetric reductions). Professor Seyden-Penne first describes the features of more than two dozen of the most powerful and commonly used alumino- and borohydrides, and then goes on to detail in individual chapters their reactions with important classes of organic molecules. There is a strong emphasis on selectivity at every level (chemo-, regio-, diastereo-, and enantioselection), and experimental practicality is also directly addressed. Synoptic tables present much information at a glance, and extensive references (about 1000) lead the reader back to the original papers and experimental procedures.

The book is in effect a road atlas that allows the organic chemist to maneuver rapidly through the maze of information on reductions of organic compounds by alumino- and borohydrides to locate the desired goal. For anyone trying to navigate in this area, this road atlas is indispensable.

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Abbreviations

Ac	acetyl
AcOEt	ethyl acetate
Ar	aryl
BOC	*t*-butyloxycarbonyl
Bz	benzoyl
DMA	dimethylacetamide
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
Et_2O	diethyl ether
HMPA	hexamethylphosphorotriamide
i-Pr	isopropyl
Me	methyl
MeCN	acetonitrile
MEM	methoxymethyl
Ph	phenyl
s-Bu	*sec*-butyl
Sia	*iso*-amyl
TBDMS	*t*-butyldimethylsilyl

t-Bu	*tert*-butyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
Tol	*p*-methylphenyl

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Contents

Chapter 1

Description and Characteristics of the Main Reagents

This chapter lists and describes the characteristics of the main reagents. Cross references are made to the corresponding sections of the other chapters for more complete details.

1.1 LITHIUM AND SODIUM ALUMINOHYDRIDES: $LiAlH_4$ (LAH), $NaAlH_4$ (SAH)

Lithium aluminohydride ($LiAlH_4$, LAH) is soluble in ethers. In diethylether and dioxane it forms tight ion pairs, but in THF and in DME it forms loose ion pairs [AD1, WS1]. LAH is used either in solution, as a suspension, or in a solid–liquid phase transfer medium (benzene, 15-crown-5) [DC1, GL4]. It is also used adsorbed onto silica gel [KH2, KH3]; however, its reducing power is so diminished under the latter conditions that it can selectively reduce ketoesters to hydroxyesters or amide esters into amide alcohols [KS5].

LAH reacts violently with water and must be handled away from moisture. Decomposition of an excess of LAH can be carried out either by careful treatment with water-saturated diethylether or by addition of ethyl acetate, which is reduced to ethanol, before treatment with water. Crude reaction mixtures can be treated either in acidic or basic media, by complexation with tartaric acid, or even by the addition of a stoichiometric quantity of water to form LiOH and $Al(OH)_3$, which precipitate and are coated by solid $MgSO_4$ and Na_2SO_4, through which they are filtered [H3]. If the reaction leads to aminoalcohols, which are good ligands for aluminum, it is sometimes difficult to recover the product of the reduction, but treatment with $(HOCH_2CH_2)_3N$ before the addition of water allows isolation of the product in good yield [PJ1].

LAH shows very high reducing power and consequently does not appear to be very selective, even when the conditions of medium and temperature are varied. Alcohols and phenols react with LAH in controlled amounts to produce alkoxyaluminum hydrides, whose reducing power can be modulated (see the following). Reaction with secondary amines forms aminoaluminohydrides. Some of these have been characterized by X-ray crystallography [HS5]. With tertiary amines, complexes can be formed. For example, N-methylpyrrolidine gives an air-stable complex [FS1] whose reducing properties are similar to those of LAH. The use of this complex does not require special procedures for exclusion of moisture and air and after reduction, workup is done by addition of water. Treatment of LAH with pyridine produces a special reagent, lithium tetrakis N-dihydropyridinoaluminohydride [LL1]. There is a review devoted to the rearrangements of various carbon skeletons observed during reduction by LAH [C2].

Sodium aluminohydride ($NaAlH_4$, SAH) in THF is somewhat less reactive than LAH toward carboxylic acids, anhydrides, epoxides, amides, and nitro compounds [CB5], and it can be used for selective reductions. However, it is as sensitive to moisture as LAH; so similar precautions must be taken.

1.2 LITHIUM AND SODIUM ALKOXY- AND AMINOALUMINOHYDRIDES

The reaction of stoichiometric quantities of alcohols with LAH leads to the formation of alkoxyaluminohydrides. The problem most often encountered in this reaction is disproportionation according to the following equilibria [HM3]:

$$\begin{aligned}
LiAlH_4 + ROH &\rightleftharpoons Li(RO)AlH_3 + H_2\\
Li(RO)AlH_3 + ROH &\rightleftharpoons Li(RO)_2AlH_2 + H_2\\
Li(RO)_2AlH_2 + ROH &\rightleftharpoons Li(RO)AlH_3 + H_2\\
Li(RO)AlH_3 + ROH &\rightleftharpoons ROLi + (RO)_3Al + H_2
\end{aligned}$$

Because of this disproportionation, some solutions of alkoxyaluminohydrides contain essentially the alcoholates and LAH, and thus they present the same characteristics as LAH itself. This is especially the case when R = Et or *i*-Pr [WS1].

The following reagents are nevertheless stable:

- $Li(MeO)_3AlH$ is a dimer in THF [BK5, M1, M3]: Its interest resides in the 1,2 attack of α-enones (Section 3.2.9).
- $Li(t\text{-}BuO)_3AlH$ (LTBA) is a monomer in THF, and its reductive properties have been well studied [BK5, M1, M3, W3]. Its principal applications are the reduction of acid chlorides and imidazolides to aldehydes at low temperature. Because of its bulkiness, a high stereoselectivity during the reduction of carbonyl compounds often makes the reaction more selective than with LAH. At low temperature, aldehydes can be reduced in the presence of ketones, and only slightly hindered ketones can even be reduced in the presence of more hindered ones (Section 3.2.1). Likewise, LTBA attacks saturated ketones more rapidly than α-enones (Section 3.2.9). LTBA leaves ethers, acetals, epoxides, chlorides

and bromides, and nitro derivatives intact. Aliphatic esters are reduced only slowly; in contrast, phenyl esters are converted into aldehydes (Section 3.2.5). $Na(t\text{-}BuO)_3AlH$ can be prepared in a similar way. Sparingly soluble in THF, it may be used in DME–THF mixtures and is recommended for reductions of acid chlorides to aldehydes [CB6].

- $Li(t\text{-}BuEt_2O)_3AlH$ is a bulky reagent that has been used in stereoselective reductions of prochiral ketones [BD2], and it reduces aldehydes selectively in the presence of ketones [K4].
- $Li(EtO)_3AlH$ (LTEA) and $Li(EtO)_2AlH_2$ can be produced in situ and have some interesting properties, but because they rapidly undergo disproportionation, they must be used very soon after their formation to reduce sufficiently reactive substrates. They reduce nitriles into imines, which can then be hydrolyzed to aldehydes (Section 4.3), and they also convert tertiary amides into aldehydes (Section 3.2.8).
- Reducing agents having special properties are obtained by the reaction of alkoxyaluminohydrides with CuBr [CA1, SS1]. These reduce the double and triple bonds of α,β-unsaturated carbonyl compounds (Sections 3.2.9, 4.2, 4.4) and allow one to obtain N-acyldihydro-1,4-pyridines (Section 3.3.3.3).

Various sodium aminoaluminohydrides have been proposed for selective reduction of esters and aromatic nitriles to the corresponding aldehydes [CK3, CK5, CJ1, YA2]. Chiral alkoxy- and aminoaluminohydrides have been used in asymmetric reductions of ketones and imines, and these will be described in the corresponding chapters (Sections 3.2.3 and 3.3.1).

1.3 SODIUM BIS(METHOXYETHOXY)ALUMINOHYDRIDE: $Na(OCH_2CH_2OCH_3)_2AlH_2$ (Red-Al)

An interesting feature of sodium bis(methoxyethoxy)aluminohydride is its solubility in aromatic hydrocarbons [M1, MC1, W3]. It is also soluble in ethers. Most frequently, reductions are carried out in a benzene or toluene solution to which are added various cosolvents. The reaction of Red-Al with water is less violent than that of LAH, which facilitates workup. As with LAH, hydrolysis can be carried out in acidic or basic media or with a minimal amount of water. In the last case, the addition of a small amount of acid to neutralize the NaOH that forms is recommended.

The features of Red-Al are the following: It easily reduces halogenated derivatives even if acetylenic (Section 2.1); tertiary amides lead to aldehydes (Section 3.2.8); and propargylic alcohols and amines are reduced to corresponding allylic alcohols and amines (Section 4.1). Epoxides remain intact unless they carry an alcohol functional group at the α position: The reduction is then regioselective (Section 2.3). Aromatic nitriles are reduced, but aliphatic nitriles are not affected (Section 4.3).

In the presence of CuBr in THF, Red-Al gives rise to an interesting reagent [SS1] that is especially good for selective reduction of the carbon–carbon double and