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SPECIAL FEATURE SECTION: HYDRIDE REDUCTIONS

Editorial

Hydride reduction is quintessential to organic synthetic transformations. Reductions that were once deemed very difficult, such as the reduction of ketones using sodium in alcohol, are now carried out routinely using hydride reducing agents. Recent advances in "Hydride Reductions" permit very high-level regio-, stereo-, and chemoselective tranformations. The goal of this special feature section is two-fold. First, we want to honor Professor Herbert C. Brown and his contributions to this field. Without a doubt H. C. Brown was one of the most prolific and influential chemists of all time, and we will greatly miss him. Second, we hope to provide useful information on hydride reductions to organic chemists in academia and industry, as well as to graduate students. We invited the leaders of the Hydride Reduction community, irrespective of their backgrounds, to join us to create a snapshot of how the field stands in 2006. We hope that this special feature will further strengthen the field of Hydride Reductions and increase its visibility. We are most grateful to all the authors who made this special feature possible. Many of the papers in the feature section are reviews and, as such, provide a broad overview of the recent literature. The laboratories from which these papers originate represent many countries, including South Korea, the United Kingdom, Puerto Rico, and the United States of America. This special feature section of *Organic Process Research & Development* (OPRD) on Hydride Reductions in honor of the late Professor H. C. Brown prompts us to take the opportunity to briefly summarize his contributions to this field over the last six decades.

Herbert C. Brown was born in London, England, on May 22, 1912, and moved to Chicago, Illinois, U.S.A., in 1914. Fortunately, Dr. Nicholas D. Cheronis, one of his teachers, invited several students to continue their laboratory studies in his commercial laboratory in the backyard of his home. There Herbert met a fellow student, Sarah Baylen, who became his wife of more than 60 years. When new colleges were opened in 1934, they attended Wright Junior College, where Sarah autographed his yearbook with the inscription, "To a future Nobel Laureate." Forty-five years later she accompanied him to Stockholm to see her prediction come true. They then entered the University of Chicago in 1935 as juniors. H. C. Brown completed 2 years of work in 1 year and graduated in 1936. A graduation gift from Sarah, Alfred Stock's Baker Lectures on "Hydrides of Boron and Silicon," was in large part responsible for his choosing H. I. Schlesinger as his graduate mentor at Chicago. His Ph.D. thesis (1938) dealt with the reduction of carbonyl compounds with diborane. After a year of postdoctoral work with M. S. Kharasch, he became a research assistant to Schlesinger and with him co-discovered sodium borohydride.

H. C. Brown became an assistant professor at Wayne University in 1943, exploring steric strains. In 1947 he moved to Purdue University as Professor. He was promoted to R. B. Wetherill Professor in 1959 and R. B. Wetherill research professor in 1960. Since his "retirement" in 1978, he had been R. B. Wetherill Professor Emeritus, supervising a research group of approximately 15 postdoctoral associates. He was the author of five books and over 1180 scientific publications. He won the majority of the major awards in his field, including the Nobel Prize for Chemistry in 1979, the ACS Award for Creative Research in Organic Chemistry (1960), the National Medal of Science (1969), the Roger Adams Award (1971), the Preistly Medal (1981), the Perkin Medal (1982), the American Institute of Chemists Gold Medal Award (1985), the National Academy of Sciences Award in Chemical Sciences (1987), the Emperor's Decoration (Japan): Order of the Rising Sun, Gold and Silver Star (1989), the Oesper Award, Cincinnati ACS Section (1990), Honorary Scholar of the University of Wales, Swansea (1994), and Honorary Professor of the Institute of Organometallic Chemistry, Chinese Academy of Science (1994).

H. C. Brown's thesis work was published in 1939 in a paper entitled "Hydrides of Boron XI. The Reaction of Diboranes with Organic Compounds Containing a Carbonyl Group" (*J. Am. Chem. Soc.* **1939**, *61*, 673). This work on the reduction of aldehydes and ketones did not attract much attention, since diborane was a rare chemical at that time, made in milligram quantities in only two laboratories in the world. Research initiated by the onset of World War II led to the synthesis of sodium borohydride (SBH) and the large-scale production of diborane. During the purification of SBH, Brown and Schelsinger discovered that SBH reduces acetone rapidly to isopropyl alcohol and opened up a huge field of organic chemistry: "Hydride Reductions."

The discovery of sodium borohydride (SBH) in 1942 and lithium aluminum hydride (LAH) in 1945 brought about a revolutionary change in procedures for the reduction of functional groups in organic molecules. Today, to reduce functional groups such as ketones, esters or nitriles the choice of the chemists will be hydride reducing agents rather than classical reducing methods, such as dissolving metal reaction, transfer hydrogenation, or catalytic hydrogenation. Both SBH and LAH provide a convenient and a simple route for the reduction of such functional groups.

LAH and SBH represent two extremes of a possible broad spectrum of reducing power. Both Professors H. I. Schlesinger and W. G. Brown reported the exceptionally powerful reducing property of LAH. On the other hand, SBH is a very mild reducing agent capable of reducing only activated

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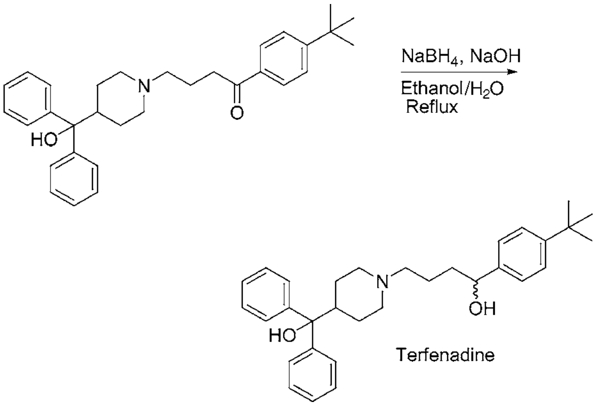
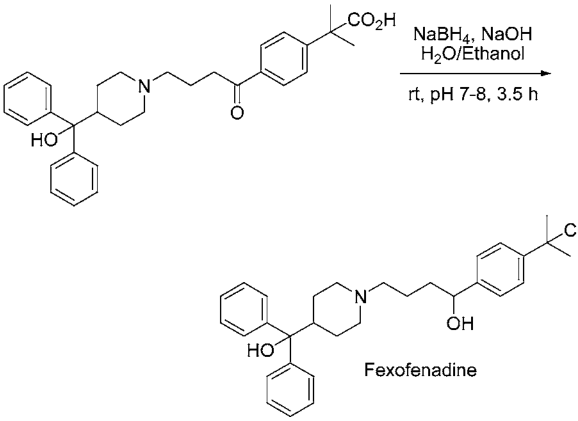
carbonyl compounds. Either by decreasing the reducing power of LAH or by increasing that of SBH, or both, chemists would have available a more complete spectrum of reagents for selective reductions. Professor H. C. Brown undertook to develop a family of hydride reducing agents with capabilities between SBH and LAH. He started a new area, “Selective Reducing Agents,” at Purdue which produced a variety of acidic hydride reducing agents, such as BH_3:L, BH_2Cl:L, $BHCl_2$:L, BH_2R, BHR_2, AlH_3:L, $AlHCl_2$, $AlHR_2$, and basic reducing agents, such as MBH_4, $MBH(OR)_3$, $MBHR_3$, $MAlH_4$, $MAlH(OR)_3$, and $MAlHR_3$. Synthetic chemists can now do many selective reductions of one group in the presence of another group or vice versa. It is now possible to do partial reductions of acid chlorides, nitriles, and tertiary amides to the corresponding aldehydes using LiAlH(O-*t*-Bu)$_3$. The search for catalysts to enhance the reducing power of SBH led to the discovery of hydroboration and the syntheses of organoboranes under ambient conditions. This development led to the discovery of the alkylborohydrides, such as Super Hydrides, as selective reducing agents and later to the discovery of asymmetric hydroborating/reducing agents, such as $IpcBH_2$, Ipc_2BH, and Ipc_2BCl. Professor H. C. Brown’s 60 years of Hydride Research produced a variety of reducing agents and versatile reduction procedures for the reduction of organic functional groups. His systematic work in the area of Hydride Reductions is helping chemists now in finding the most favorable reducing agents and conditions when faced with the challenge of doing selective reductions.

In organic synthesis the utilization of hydride reagents for reduction has become very common in the past 60 years. Professor H. C. Brown’s efforts have made the once exotic reagent SBH now readily available in multi-ton quantities and the economical source of hydride. SBH has found applications in many industries, including paper industries where it solved a major environmental problem. SBH has also been utilized in the pharmaceutical industry. It was employed in the last step of the process to manufacture the non-sedating antihistamine terfenadine to reduce a carbonyl group to the corresponding alcohol (eq 1).[1]



(1)

It has subsequently been used to carry out the same transformation in the process to manufacture fexofenadine (eq 2).[2]



(2)

Both of these processes were operated on a multi-ton scale. Currently, in the pursuit of a nonpolluting source of energy, SBH is being used as the source of hydrogen in fuel cells.

Many other reducing agents, such as 9-BBN, are now readily available commercially, in bulk quantities, for use in process chemistry. The asymmetric reducing agent Ipc_2BCl (DIP-Cl) is now routinely used in process development to carry out the asymmetric reduction of aromatic ketones. Aldrich Chemical and BASF Corporation supply bulk quantities of BH_3•THF and BMS for large-scale use in process chemistry. Any new applications that open up a large market for these hydrides will bring their costs down and expand enormously their utilization in academia and in the chemical industry. There is little doubt in our minds that both the development of new hydride reagents and their application in organic synthesis will continue to grow.

A few more thanks and apologies are in order. We acknowledge our error of omission to any leaders in the field of Hydride Reductions that we failed to invite. We hope that the people not represented in this special feature will continue to build the field of Hydride Reductions so that it will continue to benefit the chemical community. We would like to again thank all the contributors to this special feature section of OPRD for providing excellent articles for publication, and also to thank all of the reviewers for their valuable contributions. Last, but not least, we would like to thank Trevor Laird for the opportunity to serve as guest editors for this special feature section.

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