

NATIONAL ACADEMY OF SCIENCES

H E R B E R T C H A R L E S B R O W N
1 9 1 2 — 2 0 0 4

A Biographical Memoir by
EI-ICHI NEGISHI

*Any opinions expressed in this memoir are those of the author
and do not necessarily reflect the views of the
National Academy of Sciences.*

Biographical Memoir

COPYRIGHT 2008
NATIONAL ACADEMY OF SCIENCES
WASHINGTON, D.C.



Photograph Credit Here.

Herbert C. Brown

HERBERT CHARLES BROWN

May 22, 1912–December 19, 2004

BY EI-ICHI NEGISHI

HERBERT CHARLES BROWN, R. B. Wetherill Research Professor Emeritus of Purdue University and one of the truly pioneering giants in the field of organic-organometallic chemistry, died of a heart attack on December 19, 2004, at age 92. As it so happened, this author visited him at his home to discuss with him an urgent chemistry-related matter only about 10 hours before his death. For his age he appeared well, showing no sign of his sudden death the next morning. His wife, Sarah Baylen Brown, 89, followed him on May 29, 2005. They were survived by their only child, Charles A. Brown of Hitachi Ltd. and his family.

H. C. Brown shared the Nobel Prize in Chemistry in 1979 with G. Wittig of Heidelberg, Germany. Their pioneering explorations of boron chemistry and phosphorus chemistry, respectively, were recognized. Aside from several biochemists, including V. du Vigneaud in 1955, H. C. Brown was only the second American organic chemist to win a Nobel Prize behind R. B. Woodward, in 1965. His several most significant contributions in the area of boron chemistry include (1) codiscovery of sodium borohydride (1972[1], pp. 39-49) with his Ph.D. and postdoctoral mentor, H. I. Schlesinger, which helped modernize organoboron chemistry; (2) systematic exploration and methodological development of the reduction of a

wide variety of organic compounds with sodium borohydride as well as other related borohydrides and aluminohydrides (1972[1], pp. 209-251); (3) discovery of hydroboration and subsequent developments of hydroboration-based organic synthetic methods (1972[1], pp. 255-446); and (4) development of asymmetric allylboration, crotylboration, and related reactions as a group of widely used methods for asymmetric carbon-carbon bond formation. Although Brown was not directly involved, his work on organoboron chemistry was instrumental in the discovery in 1978¹ by this author and the subsequent extensive development since 1979 by A. Suzuki, another former postdoctoral associate of H. C. Brown, of the Suzuki coupling (2003) as one of the most widely used methods for carbon-carbon bond formation. Notably, Brown was also actively involved in the industrial production of a wide range of organoboron reagents used in this reaction. Brown published nearly 1300 scientific publications, several books, and several dozen patents, averaging about 20 publications a year over nearly seven decades.

In addition to the Nobel Prize, H. C. Brown also received numerous other awards and recognitions. He was elected to the National Academy of Sciences in 1957 and the American Academy of Arts and Sciences in 1966. He received the American Chemical Society (ACS) Award for Creative Research in Synthetic Organic Chemistry in 1960, the National Medal of Science in 1969, the ACS Roger Adams Award in 1971, the ACS Priestley Medal in 1981, the Perkin Medal in 1982, the American Institute of Chemists Gold Medal in 1985, the National Academy of Sciences Award in Chemical Sciences in 1987, the Emperor's Decoration: Order of the Rising Sun, Gold and Silver Star (Japan) in 1989, and the inaugural ACS H. C. Brown Award for Creative Work in Synthetic Methodology in 1998. In 1998 *Chemical and Engineering News* named him one of the top 75 contributors to the chemical

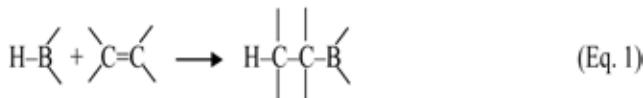
enterprise over the preceding 75 years. Brown also received 14 honorary doctorates, including one from the University of Chicago in 1968.

H. C. Brown was born in London, England, in 1912 to Jewish parents from Ukraine. Two years later his family moved to Chicago where he lived until he moved to Detroit in 1943. His childhood and early adulthood swung between school activities and hardship in the economic turmoil of the 1920s and 1930s. His father died when he was a teenager, which forced him to leave school to tend the hardware store his father started. He later returned to school and graduated in 1930. After a series of unsuccessful attempts to obtain a job, he entered Crane Junior College operated by the City of Chicago. It was at this college that he met Sarah Baylen, a 16-year-old chemical engineering major and his future wife. When Crane Junior College was closed shortly thereafter because of lack of funding, about 10 students, including Herb and Sarah, were invited by one of the professors, N. D. Cheronis, to conduct chemical experiments in a small laboratory at his home. When Wright Junior College was opened a year or so later, Herb and Sarah as well as Cheronis went there. On graduation day in 1935 Sarah prophetically inscribed in Herb's yearbook: "To a future Nobel Laureate." Herb won a scholarship to attend the University of Chicago in the same year. He took 10 courses per quarter and in 1936 obtained his B.S. degree in just three quarters. Sarah bought *Hydrides of Boron and Silicon*, a book by Alfred Stock, as a graduation gift for Herb. He learned from the book that hydrides of boron were prepared in only two laboratories in the world. One was Stock's laboratory in Karlsruhe, Germany, and the other was H. I. Schlesinger's laboratory at the University of Chicago. This was how Brown became associated with H. I. Schlesinger for his graduate research; he obtained his Ph.D. degree in 1939. In the meantime, Herb and Sarah got mar-

ried "secretly," as stated by them, in 1937. Their enviable marriage lasted more than 67 years. As a married man with a Ph.D. degree, Herb tried to secure an industrial job but once again failed. He was then offered a postdoctoral position in the group of M. S. Kharasch, where he investigated chlorination, chloroformylation, and other free-radical reactions (1972[1], pp. 24-39). A year later he rejoined H. I. Schlesinger's group as a research assistant carrying the rank of instructor. There he discovered or developed methods of preparation and reactions of lithium and sodium borohydrides and other related borohydrides (1972[1], pp. 39-49).

Brown finally obtained his first independent academic position as an assistant professor at Wayne University in Detroit in 1943. He was 32. The new head of the Chemistry Department, Neil Gordon, who started the Gordon Research Conferences, hoped to develop a Ph.D. program at Wayne, but the department was still ill equipped. In search of research projects not requiring elaborate and expensive laboratory equipment, Brown decided to develop empirical theories to explain poorly understood steric effects. His studies, first at Wayne and later at Purdue, led to a convenient and useful set of qualitative theories or explanations based on his notion about F-, B-, and I-strains, where F, B, and I stand for front, back, and internal, respectively (1972[1], pp. 53-128). Brown's research at Wayne University quickly established him as an active, prolific, and pioneering researcher, and he was promoted to associate professor in 1946. In 1947 the head of the Chemistry Department at Purdue University, F. Hass, hired him as a full professor. At Purdue he continued his work on steric effects and electrophilic aromatic substitution and he resumed his research on the chemistry of borohydrides and aluminohydrides, which led to his discoveries of hydroboration with B. C. Subba Rao (1956) and its asymmetric version

with N. R. Ayyangar and G. Zweifel (1964). Many consider the former to be the single most important discovery made by H. C. Brown. He often jokingly mentioned his parents' foresight in giving him the initials H, C, and B, which correspond to the three elements involved in hydroboration (Eq. 1).



The asymmetric version of hydroboration, exemplified by the facile synthesis of diisopinocampheylborane, abbreviated as HBIpc_2 , from inexpensive (+)- or (-)-pinene, is no less significant. As such, this represents one of the earliest examples of a highly enantioselective reaction under nonenzymatic conditions. Furthermore, the product HBIpc_2 and its derivatives are relatively inexpensive and widely useful reagents not only for asymmetric hydroboration but also for asymmetric reduction² as well as for allyl- and crotylboration.³

According to H. C. Brown, his investigation of steric effects led to his explanation of the surprisingly high *exo/endo* solvolysis rate ratios of norbornyl derivatives in terms of steric hindrance to ionization (1972[1], pp. 181-205). This, in turn, led him to doubt the validity of the growing tendency to represent a wide range of carbocationic species with "nonclassical" structures (1972[1], pp. 131-180). At the time this author joined his group in 1966, roughly half of his group members were engaged in the project on the classical versus nonclassical structures of carbocations. However, this author avoided the project despite his intense curiosity. Now that the dust appears to have settled, only the following brief personal view is presented here.

Fundamentally, any electron-deficient species that can participate in three or higher multicentered bonding may be considered to be nonclassical to varying degrees. From this viewpoint there seems no room for doubting the widely accepted conclusion that diborane and the parent norbornyl cation may be best represented by symmetrically electron-distributed nonclassical structures. There are however at least two factors to be carefully dealt with. One is structural perturbation, the other is the extent of ionization or electron deficiency. In most of Brown's solvolytic studies, structurally perturbed tertiary carbocationic species were investigated. Many of them were even benzylic or homobenzylic derivatives. In such cases more conventional electron delocalization effects, such as resonance and hyperconjugation effects, may become dominant, and the nonclassical framework, which is appropriate for the parent norbornyl cation, may not be the best representation. It is this author's view that Brown was primarily cautioning the overuse of nonclassical structure involving sigma carbon-carbon bond participation in cases where such structures may not be the most representative or significant. This issue is further complicated by the fact that unlike neutral and electron-deficient metal compounds, carbocations are associated with counteranions. This must always be taken into consideration in discussing carbocation structures.

Brown embarked on a major new area of the development of organoborane-based carbon-carbon bond formation in the mid-1960s. Ironically, some of his most creative and original investigations, such as those of carbonylation reactions (1972[1], pp. 255-446), have not yet been widely used by the synthetic community, perhaps in part because of their radically novel patterns of reactions that cannot be readily assimilated into the conventional organometallic carbon-

carbon bond-formation methodology. In the meantime, the Pd-catalyzed cross-coupling of organometals containing boron, zinc, aluminum, and so on that this author¹ and A. Suzuki (2003) have discovered and developed as well as the asymmetric allyl- and crotylboration most extensively developed by Brown's group,³ all of which can readily fit into the patterns of conventional organometallic methods for carbon-carbon bond formation, have become widely accepted and used.

At Purdue, H. C. Brown was promoted to R. B. Wetherill Professor in 1959 and R. B. Wetherill Research Professor in 1960. After his formal retirement in 1978, he was R. B. Wetherill Professor Emeritus. All of the awards and recognitions mentioned earlier were received by him while he was a Purdue faculty member. In recognition of his great accomplishments and contributions to Purdue University, one of the two main chemistry buildings was named the Brown Building, and the entire chemistry department has been renamed the Herbert C. Brown Laboratories of Chemistry.

Besides being a premier scientist, H. C. Brown was a superb mentor to those who were sufficiently self-motivated and fundamentally well equipped to pursue research in a logical and rational manner. He himself possessed the kind of logical and rational mind reserved only for the very best scientists. One of the early projects suggested by Brown to this author dealt with the cyclic hydroboration of dienes and trienes (1972 [2]), which had been previously investigated by other well-known workers in the field. Primarily on rational grounds, Brown questioned several previous structural assignments. Detailed investigations eventually led us to correct them all (1972 [2]). Another lesson he instilled was to not only do research but also to live with eternal optimism, of course not in a quixotic manner but with well-calculated rationalism. This has easily been the single most important lesson this author has learned from him.

In his research group Brown expected us to actively and vigorously pursue our research projects and be successful and productive. However, he was far from being a “slave driver.” One of his unmistakably clear policies was “time is your own.” He would openly and repeatedly tell his group members that he did not believe in the value of spending much more than eight hours a day in the laboratories. Instead, he emphasized the significance of good thinking, planning, preparation, execution of laboratory experiments in a highly efficient manner, and timely interpretation of the results. In short, he expected each of us to be a successful entrepreneur, working jointly with him. He would even tell us before his departure on frequent trips, “Do not work too hard.” And yet, many of the group members in the mid- to late-1960s were somehow motivated to work harder during his absences, perhaps to show what they were capable of doing in his long absence.

Outside the research arena H. C. Brown was a truly caring person. As one of the frequent beneficiaries of his kind and continual mentoring, it is very easy for the author to say what is stated above. This author still truly believes that many, if not all, of his former associates will echo the above statement. Herb and Sarah also were very generous donors. In addition to the ACS Herbert C. Brown Award for Creative Work in Synthetic Methodology, which was predominantly endowed by the Browns, they provided a series of endowments for funding the Herbert C. Brown Lectures in 1983, the Herbert C. Brown Distinguished Professorship in 1998, and the Herbert C. Brown Center for Borane Research in 1998.

Herb Brown, together with Sarah, indeed lived a very enviable life. They vividly demonstrated that with raw capability, dedication, and eternal optimism, a man and a woman together can make some remarkable achievements,

become happier with time well into their 80s and beyond, and become rich enough to return part of their wealth to the community.

NOTES

1. E. Negishi. Selective Carbon-Carbon Bond Formation via Transition Metal Catalysis: Is Nickel or Palladium Better than Copper?. In *Aspects of Mechanism and Organometallic Chemistry*, ed. J. H. Brewster, pp. 285-317. New York: Plenum, 1978.
2. A. F. Abdel-Magid, ed. *Reductions in Organic Synthesis*. ACS Symposium Series 641. Washington, D.C.: American Chemical Society, 1996.
3. P. V. Ramachandran. Pinane-Based Versatile “Allyl” boranes. *Aldrichimica Acta* 35(2002):23-35.

SELECTED BIBLIOGRAPHY

1939

With H. I. Schlesinger and A. B. Burg. Hydrides of boron. XI. The reaction of diborane with organic compounds containing a carbonyl group. *J. Am. Chem. Soc.* 61:673-680.

1944

With M. D. Taylor and M. Gerstein. Acid-base studies in gaseous systems. I. Precise dissociation measurements. *J. Am. Chem. Soc.* 66:431-435.

1953

With H. I. Schlesinger and A. E. Finholt. New developments in the chemistry of diborane and of the borohydrides. 6. The preparation of sodium borohydride by the high temperature reaction of sodium hydride with borate esters. *J. Am. Chem. Soc.* 75:205-209.

1956

With B. C. Subba Rao. A new technique for the conversion of olefins into organoboranes and related alcohols. *J. Am. Chem. Soc.* 78:5694-5695.

1959

With G. Zweifel. The hydroboration of acetylenes—a convenient conversion of internal acetylenes to *cis* olefins of high purity and of terminal acetylenes to aldehydes. *J. Am. Chem. Soc.* 81:1512.

1960

With B. C. Subba Rao. Hydroboration. 3. The reduction of organic compounds by diborane, an acid-type reducing agent. *J. Am. Chem. Soc.* 82:681-686.

1964

With N. R. Ayyangar and G. Zweifel. Hydroboration. 18. Reaction of diisopinocamphenylborane with representative *cis*-acyclic, cyclic, and bicyclic olefins. Convenient synthesis of optically active alcohols and olefins of high optical purity and established configuration. *J. Am. Chem. Soc.* 86:397-403.

1967

With M. W. Rathke. Reaction of carbon monoxide at atmospheric pressure with trialkylboranes in presence of sodium or lithium borohydride. A convenient procedure for oxymethylation of olefins via hydroboration. *J. Am. Chem. Soc.* 89:2740-2741.

With E. Negishi. Carbonylation of thexyldialkylboranes. A new general synthesis of ketones. *J. Am. Chem. Soc.* 89:5285-5287.

1968

With M. W. Rathke and M. M. Rogic. A fast reaction of organo-boranes with iodine under the influence of base. A convenient procedure for the conversion of terminal olefins into primary iodides via hydroboration-iodination. *J. Am. Chem. Soc.* 90:5038-5040.

With M. M. Rogic, M. W. Rathke, and G. W. Kabalka. Reaction of organoboranes with ethyl bromoacetate under influence of potassium *t*-butoxide. A convenient procedure for conversion of olefins into esters via hydroboration. *J. Am. Chem. Soc.* 90:818-820.

1971

With C. F. Lane. Light-induced reaction of bromine with trialkylboranes in presence of water—remarkably simple procedure for union of 2 or 3 alkyl groups to produce highly substituted alcohols. *J. Am. Chem. Soc.* 93:1025-1027.

1972

- [1] *Boranes in Organic Chemistry*. Ithaca: Cornell University Press.
- [2] With E. Negishi. The cyclic hydroboration of dienes—simple convenient route to heterocyclic organoboranes. *Pure Appl. Chem.* 29:527-545.
- [3] With S. Krishnamurthy. Lithium tri-*sec*-butylborohydride—new reagent for reduction of cyclic and bicyclic ketones with super stereoselectivity—remarkably simple and practical procedure for conversion of ketones to alcohols in exceptionally high stereochemical purity. *J. Am. Chem. Soc.* 94:7159-7161.

1975

Organic Syntheses: Via Boranes, vol. 1. Milwaukee: Aldrich Chemical Co.

1977

The Nonclassical Ion Problem (with comments by P. von Schleyer). New York: Plenum Press.

1979

With S. Krishnamurthy. 40 years of hydride reductions. *Tetrahedron* 35:567-607.

1983

With P. K. Jadhav. Asymmetric carbon-carbon bond formation via *B*-allyldiisopinocampheylborane. A simple synthesis of secondary homoallylic alcohols with excellent enantiomeric purities. *J. Am. Chem. Soc.* 105:2092-2093.

1985

With T. Imai, M. C. Desai, and B. Singaram. Chiral synthesis via organoboranes. 3. Conversion of boronic esters of essentially 100-percent optical purity to aldehydes, acids, and homologated alcohols of very high enantiomeric purities. *J. Am. Chem. Soc.* 107:4980-4983.

1986

With K. S. Bhat. Enantiomeric (*Z*)- and (*E*)-crotyldiisopinocamphenylboranes. Synthesis in high optical purity of all four possible stereoisomers of β -methylhomoallyl alcohols. *J. Am. Chem. Soc.* 108:293-294.

With K. W. Kim, T. E. Cole, and B. Singaram. Chiral synthesis via organoboranes. 8. Synthetic utility of boronic esters of essentially 100-percent optical purity—synthesis of primary amines of very high enantiomeric purities. *J. Am. Chem. Soc.* 108:6761-6764.

1988

With J. Chandrasekharan and P. V. Ramachandran. Chiral synthesis via organoboranes. 14. Selective reductions. 41. Diisopinocampheylchloroborane. An exceptionally efficient chiral reducing agent. *J. Am. Chem. Soc.* 110:1539-1546.

With B. Singaram. Development of a simple general procedure for synthesis of pure enantiomers via chiral organoboranes. *Accounts Chem. Res.* 21:287-293.

1992

With P. V. Ramachandran. Asymmetric reduction with chiral organoboranes based on alpha-pinene. *Accts. Chem. Res.* 25:16-24.

2001

With M. Zidlewicz. *Recent Developments*, vol. 2, *Organic Syntheses: Via Boranes*. Milwaukee: Aldrich Chemical Co.

2003

With A. Suzuki. *Suzuki Coupling*, vol. 3, *Organic Syntheses: Via Boranes*. Milwaukee: Aldrich Chemical Co.