The 1979 Nobel Prize for Chemistry

The 1979 Nobel Prize for Chemistry has been awarded jointly to Georg Wittig of the University of Heidelberg and Herbert C. Brown of Purdue University for their separate work in organic synthesis. Wittig's major achievement was the development of a highly specific method for the synthesis of olefins. Brown found major new routes to add substituents to olefins selectively. Both employed elements that had found little previous use in organic synthesis, and both prospered by following up on unexpected observations.

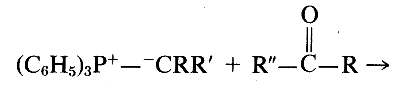
Wittig: Fortune Favors the Prepared Mind

Georg Wittig's share of this year's Nobel Prize in Chemistry was awarded for his discovery that phosphorus ylides react with ketones and aldehydes to form alkenes. The reaction is of unmatched importance for specific introduction of carbon-carbon double bonds in a known location and is used extensively in the synthesis of pharmaceuticals and other complex organic substances. Professor Wittig's achievement is another example of an eminently practical discovery made in the course of fundamental research lacking any preconceived practical objectives. In the present atmosphere of submarginal support for basic science, it is especially appropriate to review the events leading to the Wittig reaction. The discovery was due to a fortuitous combination of circumstances, foremost among which was Wittig's ability to recognize the significance of an unexpected result.

During the 1940's Wittig was interested in the possibility that group V elements (for example, nitrogen, phosphorus, and arsenic) might be capable of covalent bonding to five organic substituents. A logical approach to such structures was to react nucleophilic organometallic reagents with group V quaternary salts. Similar reactions had been investigated many years before by H. Staudinger, C. S. Marvel, and others, but stable pentavalent adducts had not been isolated. Eventually, Wittig's coworkers were successful in obtaining pentaphenyl derivatives of the common group V elements, with the exception of nitrogen. Most of these findings were published shortly after 1950.

During attempts to add phenyllithium to tetramethylammonium halides, Wittig found that deprotonation rather than addition occurred. A labile ammonium ylide $(CH_3)_3N^+CH_2^-$ was formed as its lithium halide adduct. This substance was trapped by benzophenone to give a stable, zwitterionic product which was isolated as a protonated β-hydroxyammonium salt, $(CH_3)_3N^+CH_2C(C_6H_5)_2OH$. It was no surprise when tetramethylphosphonium chloride reacted with phenyllithium to give a similar (although much more stable) ylide that also formed a stable adduct with benzophenone. These results were first described in 1949 (Wittig and M. Rieber).

Several years passed before the key discovery was made. A seemingly trivial change in substituents attached to the ylide phosphorus atom [from $(CH_3)_3P^+{-}CH_2^-$ to $(C_6H_5)_3P^+{-}CH_2^-$] altered the properties of the benzophenone adduct. The adduct was no longer stable and was observed to fragment to diphenylethylene and triphenylphosphine oxide (Wittig and G. Geissler, 1953). After this critical experiment came a series of exciting results demonstrating that several different alkyltriphenylphosphonium salts could be deprotonated in the same way, and that the derived ylides would condense readily with ketones and aldehydes (Wittig and Urich Schollkopf, 1954; Wittig and W. Haag, 1955). There followed an avalanche of related discoveries establishing the Wittig alkene synthesis as a process of great versatility and generality:



$$(C_6H_5)_3P^+{-}{}^-CRR' + R''{-}\overset{\overset{O}{\|}}{C}{-}R \rightarrow$$

$$RR'C{=}CR''R'' + (C_6H_5)_3P{=}O$$

(at least one substituent must be H)

For those interested in the history of science, the Wittig reaction offers a fascinating example of how elusive an important discovery can be, and how much depends on the ability of a scientist to recognize the full implications of an experiment that does not occur as planned. The first phosphorus ylide was described by Staudinger in 1919, 30 years before Wittig's work. The air-sensitive diphenylmethylenetriphenylphosphorane was prepared in crystalline form by pyrolysis of a phosphazine precursor, and was fully characterized by methods then available.

More remarkable still, Staudinger conceived the possibility of an olefin synthesis by condensation of his ylide with a carbonyl compound and drew a four-membered phosphorus, oxygen heterocycle (oxaphosphetane) as the intermediate. Staudinger's students demonstrated that carbonyl condensation did take place with phenylisocyanate or diphenylketene to give products containing a new C=C linkage, and also developed other ways to make ylides. However, many of these results were published only in thesis form and did not become widely known. Staudinger's work was so far ahead of its time that no one recognized its implications. This was an era when the Lewis theory of electronic structure was new, and the exact bonding of phosphonium salts was a controversial and somewhat esoteric question. The olefin synthesis was not pursued.

In the late 1920's, Marvel developed improved procedures for preparation and handling of alkyllithium reagents. With these versatile bases in hand, Marvel turned to the same problem that had stimulated Staudinger's work with phosphorus and would lead eventually to Wittig's discovery. Marvel attempted to prepare pentavalent nitrogen or phosphorus compounds by addition of alkyllithiums to the quaternary salts. These experiments did not give isolable adducts, nor did Marvel's co-workers intercept the nonstabilized ammonium ylides that Wittig would describe 20 years later. However, Marvel did obtain characteristically colored solutions of alkylidenetriphenylphosphoranes and deduced the correct structures on the basis of ylide cleavage with water to give alkyldiphenylphosphine oxides and benzene. Current practitioners will recognize the 1929 procedure as identical to the butyllithium method still in use today for generating nonstabilized phosphorus ylides. Although Marvel referred to Staudinger's work with the less reactive diphenylmethylene ylide, he reported no condensations with carbonyl compounds.

One additional historical predecessor of the Wittig reaction is of some interest. F. Kröhnke *et al.* had observed that phenacyl salts of various amines could be deprotonated to give stable betaines (nitrogen ylides), and had also extended these observations to arsenic ylides. While much of the relevant work with ammonium ylides was published in the general literature, a key experiment dealing with the arsenic analog $(C_6H_5)_3As^+CH^-COC_6H_5$ was described only in the Ph.D. dissertation of Kröhnke's student, W. Heffe (Berlin, 1937). The arsonium ylide was found to condense with benzaldehyde to give $C_6H_5COCH{=}CHC_6H_5$, an alkene synthesis that is the arsenic analog of the Wittig reaction. This result was apparently not pursued and did not become general knowledge until well after Wittig's 1953 publication.

The exact details of these earlier studies were not known in Wittig's laboratory when the experiments involving phosphonium salts and phenyllithium were initiated. Indeed, Wittig has stated emphatically that, had he known the details, the experiments leading to the olefin synthesis would not have been performed. From Marvel's results, one could conclude that alkylphosphonium salts were not suitable precursors of pentavalent phosphorus compounds. To avoid the undesired ylide formation, it would be logical to turn directly to the reaction of phenyllithium with tetraphenylphosphonium salts, substrates that are incapable of deprotonation. Since this combination does give a pentavalent phosphorus product, Wittig's objective would have been satisfied. The elusive alkene synthesis might not have been encountered.

Wittig's research efforts prior to the ylide era had focused more on questions of mechanism and theory than on preparative methods of synthetic chemistry. He had contributed extensively to studies of diradicals, carbanions, molecular rearrangements, autoxidations, and concepts of bonding and molecular structure. His early work was instrumental in the correct interpretation of reactions involving benzyne intermediates, and also uncovered a fundamentally new rearrangement of carbanions derived from benzylic ethers (the "other" Wittig reaction). These and related interests continued to develop during and after the period devoted to an intensive study of the preparative aspects of phosphorus ylide chemistry.

The most important work on the ylide synthesis of alkenes was published by Wittig in the decade after the initial discovery. The reaction was extended to include the conversion of ketones or aldehydes to simple methylene, alkylidene, or benzylidene derivatives. Vinyl ethers, sulfides, and halides were made with the corresponding heteroatom-substituted ylides. Carbonyl-stabilized ylides were shown to give α,β-unsaturated ketones or esters, and it was found that highly conjugated polyene esters could be made in this way. Work performed at BASF where Wittig was a consultant resulted in a successful synthesis of vitamin A, whose logical descendants are still in use on industrial scale (H. Pommer *et al.*).

By the early 1960's, more than 100 papers on applications of the Wittig reaction for alkene synthesis had appeared from laboratories around the world. Important early contributions were made by L. D. Bergelson and M. N. Shemyakin, H. J. Bestmann, F. Bohlmann, E. J. Corey, H. H. Inhoffen, C. F. Hauser, H. O. House, B. Lythgoe, H. Schmidbaur, D. Seyferth, and S. Trippett. At present, the number of applications is surely in the thousands, but there is no easy way to be more specific. Wittig's synthesis has become accepted into that body of knowledge that everyone takes for granted without referring to the original work. To appreciate the impact of this discovery, one need only to consult the textbooks of the 1950's on organic chemistry. Nearly all alkene syntheses available prior to the Wittig reaction (such as alkyl halides plus base; alcohols plus strong acid; pyrolysis of acetates, xanthates, quaternary ammonium hydroxides) give mixtures of olefin isomers. Among these techniques, none is as predictable as we like students of elementary organic chemistry to believe. In contrast, Wittig's alkene synthesis always guarantees that the double bond will be formed between the carbonyl carbon and the ylide carbon.

L. Horner *et al.* had independently encountered a phosphorus-based alkene synthesis somewhat after Wittig's first experiments (1958). Anions of alkyldiphenylphosphine oxides were found to condense with ketones or aldehydes to give alkenes in an overall reaction that resembles the Wittig process. These important results did not acquire the early acceptance that would have been assured if Wittig's method had not been found. However, Horner's work did serve as a stimulus for the eventual development of alkene syntheses with the use of carbonyl-stabilized phosphonate anions (W. S. Wadsworth, Jr., and W. D. Emmons, 1961). These convenient reagents fill a need where the Wittig synthesis is not always successful (carbonyl-conjugated ylides are rather unreactive).


Georg Wittig

None of the numerous variations has seriously challenged the original Wittig synthesis for preparation of isolated carbon-carbon double bonds or conjugated polyenes. In recent years, the method has proved invaluable for synthesis of complex pharmaceuticals. Applications in vitamin A synthesis have already been mentioned. Other important uses include the attachment of side chains to steroid hormones, vitamin D derivatives, and prostaglandin precursors. The Wittig reaction is also important for synthesis of insect pheromones, substances that are promising agents for species-specific pest control.

Numerous other applications of industrial and academic relevance have been described. The method is compatible with diverse functional groups (including esters, nitriles, ethers, unactivated halides, aromatics, heterocycles, and carbohydrates) if experimental conditions are chosen with care. Disubstituted alkenes can be made selectively as the *cis* or *trans* isomers under controlled conditions. Intramolecular Wittig reactions are useful for the synthesis of heterocycles, cyclohexadienes, and a variety of unusual carbocycles. Many techniques are now available for ylide generation, and the oxaphosphetane intermediates of the Wittig reaction can be prepared by alternative techniques.

Wittig remained an active contributor to the preparative aspects of alkene synthesis for more than 10 years. However, his efforts were by no means restricted to reactions of phosphorus ylides. Much of the work on ammonium ylides as intermediates in molecular rearrangements and fragmentations was published during the 1950's. During that same time line, his research efforts were largely responsible for clarifying the chemistry of benzyne. Methods for benzyne generation were developed, and trapping with dienes or various heteroatom electron donors was studied in detail. During the 1960's Wittig's emphasis turned increasingly to the chemistry of highly strained cyclic alkynes and alkadienes. Among his newer interests, the concept of directed aldol condensation with the use of imine anions is especially important in preparative chemistry as a route to obtaining conjugated, unsaturated aldehydes. In 1967, when Wittig reached emeritus status, his active research interests also included an investigation of organozinc cyclopropanating reagents. There is no way, in a brief account, to do justice to the quality of Wittig's contributions, which span nearly 60 years of active science. As for volume, it is sufficient to note that Wittig was author of more than 50 publications in the decade after he became emeritus professor at Heidelberg.

Georg Wittig was born in Berlin on 16 June 1897. His education began in Kassel (Wilhelms-Gymnasium) and was completed at the Philipps-Universität, Marburg, after an interruption for military service in World War I. At Marburg came the first faculty appointment as dozent, 1926-1932. Another Marburg dozent at this time was Karl Ziegler, who was to share the Nobel Prize for Chemistry in 1963. Although Ziegler left in 1927, he and Wittig enjoyed a long professional and personal friendship, and shared such active interests as mountaineering. From Marburg, Wittig moved first to Braunschweig where he became the equivalent of associate professor ("Extraordinarius"), 1932-1937, and then to Freiburg as special professor, 1937-1944. By coincidence, this appointment at Freiburg happened to overlap with the tenure of Staudinger as Institute Director. However, Staudinger had long since become preoccupied with macromolecular chemistry for which he won the Nobel Prize in 1953 and no longer worked with phosphorus.

In 1944, Wittig accepted an offer to become Institute Director at Tübingen University. It was at Tübingen that the Wittig reaction was discovered, and where the pioneering studies were performed with Rieber, Geissler, and Schollkopf. In 1956 came the final move to Heidelberg University where a good share of the developmental work on substituted phosphorus ylides was completed.

Former students invariably mention music as Wittig's next strongest interest, and that his mastery of the piano might well have resulted in the choice of an entirely different career. As the son of a professor in fine arts, Wittig cultivated musical interests throughout. This is apparent in his 1964 review on phosphorus ylides (*Pure and Applied Chemistry*) entitled "Variations on a theme of Staudinger." That particular composition is well worth reading for a candid, personal account of events leading to discovery of the alkene synthesis, and also for a brief discourse on analogous historical occurrences involving Haydn, Brahms, Wagner, and others. As noted earlier, Wittig's own theme and its many variations have become part of the classical repertoire of synthetic chemists and are performed frequently.

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Brown: Passes Through the Mountains (*1*)

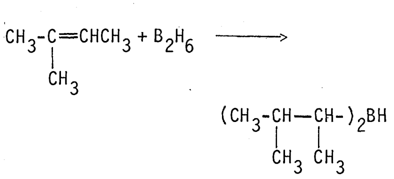
Herbert C. Brown's approach to research is unusually logical and systematic. Of course, any scientific study should be carried out in a logical manner, but, in fact, the literature of science is sprinkled with erroneous or premature conclusions based on untenable assumptions and intuitive feelings. Brown has been almost religious in resisting facile conclusions and has thereby succeeded in avoiding erroneous ones. Some of his most significant discoveries and developments have resulted from a dogged, logical pursuit of the kind of everyday chemical puzzle that many would dismiss with a glib rationalization.

"The main thing," Brown is fond of saying, "is to find out exactly what is going on."

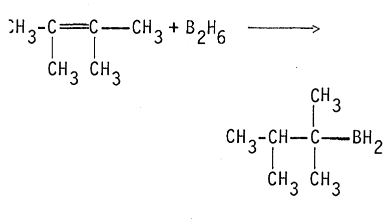
According to Brown (*2*), the hydroboration reaction for which he received his share of this year's Nobel Prize in Chemistry was an accidental discovery. In a systematic study of many and various esters with diborane (B_2H_6) generated in situ from $NaBH_4$ and $AlCl_3$, B. C. Subba Rao had observed that most of the reactions showed the clean 1:2 stoichiometry of ester to hydride required for reduction to the alcohol. But there was one exception, ethyl oleate ($CH_3(CH_2)_7CH{=}CH(CH_2)_2CO_2C_2H_5$), each mole of which consumed 2.4 mole of hydride. Pressed by Brown to account for this, Subba Rao suggested that it might be due to an impurity; perhaps this experiment should be dropped since they had such a nice selection of concordant results. But that is not Brown's way. Brown and his co-workers pursued the puzzle and soon discovered that the olefinic group was also being reduced.

This discovery, known as the hydroboration reaction, has made the organoboranes readily available as chemical intermediates. The boron atom adds to the less substituted carbon atom. Depending upon steric factors, mono-, di-, or trialkylboranes may be formed (Eqs. 1 to 3):

$$RCH{=}CH_2 + B_2H_6 \longrightarrow (RCH_2CH_2{-})_3B \quad (1)$$

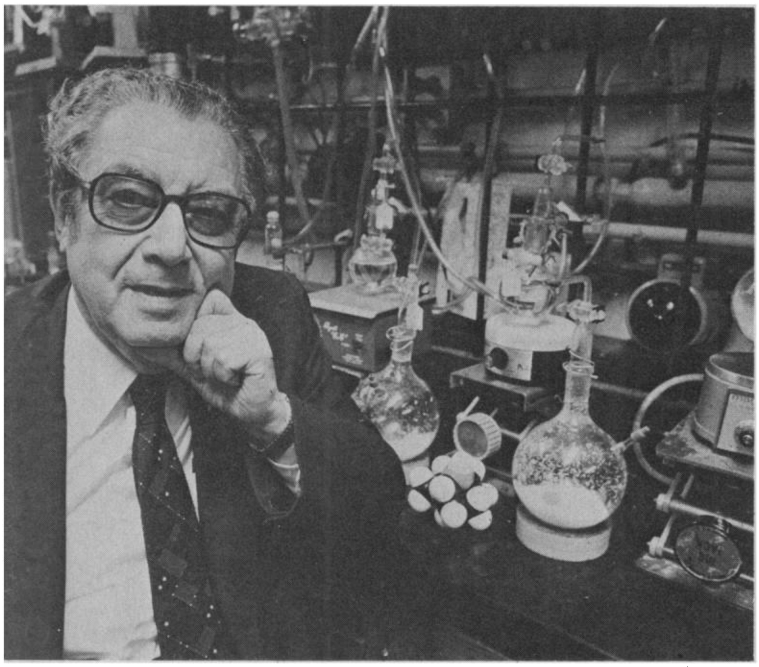


$$CH_3{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CHCH_3 + B_2H_6 \longrightarrow (CH_3{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-})_2BH \quad (2)$$



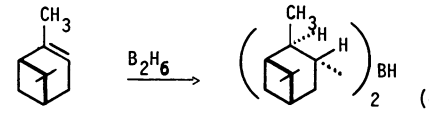
$$CH_3{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}CH_3 + B_2H_6 \longrightarrow CH_3{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}\overset{\displaystyle CH_3}{\overset{|}{\underset{\displaystyle CH_3}{\underset{|}{C}}}}{-}BH_2 \quad (3)$$

All these products give the synthetically useful reactions whereby the boron atom is replaced (below), but the mono- and



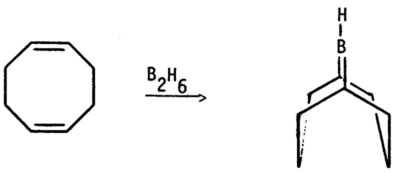
Herbert C. Brown

dialkylboranes are also useful as reducing or hydroborating agents, most notable being the adducts from α-pinene (diisopinocampheylborane) (Eq. 4)



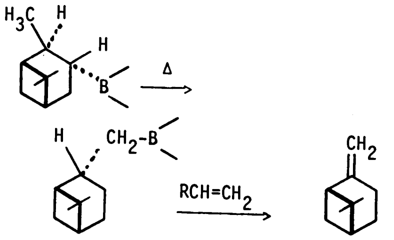
(4)

and 1,3-cyclooctadiene (9-borabicyclononane, or 9-BBN) (Eq. 5).



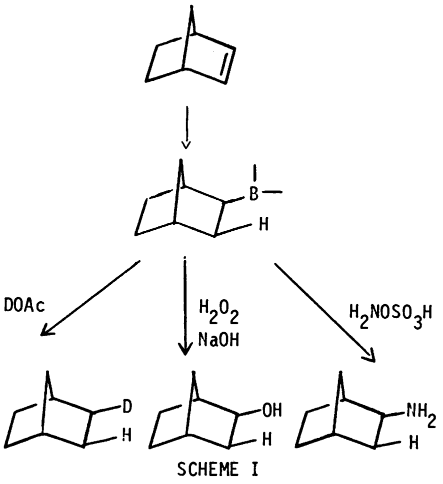
(5)

The Brown hydroboration reaction occurs without skeletal rearrangement and gives clean *cis-* addition to the less hindered side of the double bond. Boranes do rearrange when they are heated in polyether solvents, but only in the sense that the boron migrates to the least crowded position on the carbon chain. This provides organoboranes that would otherwise have to be made from terminal olefins. The fact that the hydroboration reaction is reversible makes these sometimes unstable or less accessible olefins available from internal or endocyclic olefins (Eq. 6).



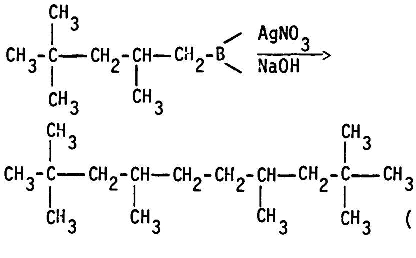
(6)

The boron atom can be replaced with complete retention of configuration by hydrogen, deuterium, hydroxyl, and amino groups (scheme 1). The use of chiral boranes, such as diisopinocampheylborane, leads to chiral products, often in high enantiomeric purity.



SCHEME I

Valuable as these reactions are, those that lead to carbon-carbon bond formation seem likely to prove even more so. The alkyl groups of organoboranes are coupled with silver nitrate (Eq. 7); mixed boranes give mixed products (Eq. 8).

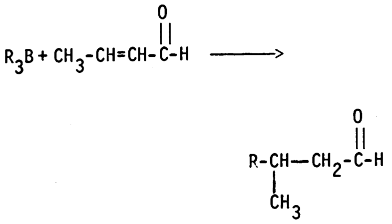


$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-\underset{CH_3}{CH}-CH_2-B\langle \xrightarrow[NaOH]{AgNO_3}$$

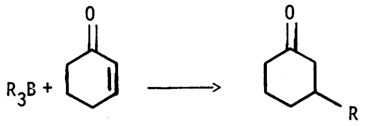
$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-\underset{CH_3}{CH}-CH_2-CH_2-\underset{CH_3}{CH}-CH_2-\underset{CH_3}{\overset{CH_3}{C}}-CH_3 \qquad (7)$$

$$R_3B + R_3'B \longrightarrow RR + 2R'R + R'R' \qquad (8)$$

Alkyl groups can be added to α,β-unsaturated aldehydes and ketones under free radical catalysis (Eqs. 9 and 10) while α-bromoesters and α-bromoketones can be alkylated in the presence of strong bases (Eqs. 11 and 12).

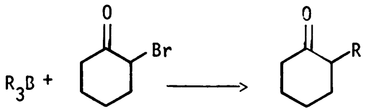


$$R_3B + CH_3-CH=CH-\overset{O}{\overset{\|}{C}}-H \longrightarrow R-\underset{CH_3}{CH}-CH_2-\overset{O}{\overset{\|}{C}}-H \qquad (9)$$



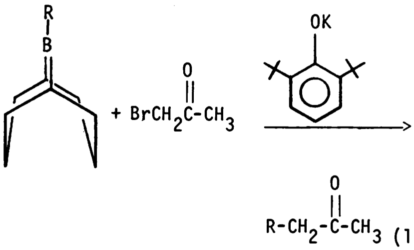
(10)

$$R_3B + BrCH_2CO_2Et \xrightarrow{KOtBu} RCH_2CO_2Et \qquad (11)$$



(12)

The use of 9-BBN derivatives is especially noteworthy because methyl and phenyl compounds can also be employed (Eq. 13).

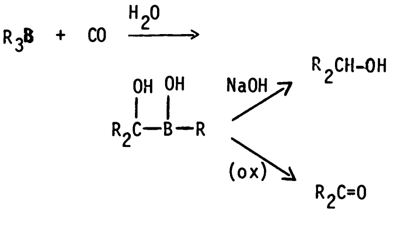


(13)

R = $-CH_3$, $-C_6H_5$, or alkyl from an olefin

New routes to alcohols (Eqs. 14 to 16), aldehydes (Eq. 15), and ketones (Eq. 16) are provided by the reaction of organoboranes with carbon monoxide.

$$R_3B + CO \longrightarrow R_3C\text{-}BO \xrightarrow{(ox)} R_3C\text{-}OH \qquad (14)$$



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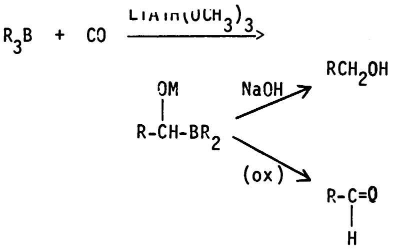
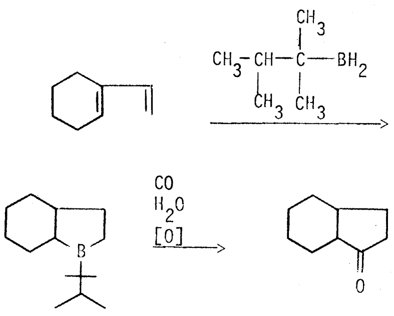


(16)

Annulation reactions based on this kind of process have been developed (Eq. 17).



(17)

The introduction of such versatile reagents produces an exponential increase in the number of pathways available to a synthetic goal and suggests whole new areas of organometallic chemistry to explore. It leaves a legacy of mechanistic and theoretical problems to the coming generation. For this, the Nobel Prize is richly deserved.

Brown has often compared his researches to the exploration and settlement of a new continent. One cannot follow all of the trails. Some lead to passes through the mountains and some only to pleasant pastures in box canyons or to inspiring views from isolated mountaintops. Sensing the synthetic potential in the hydroboration reaction, he has explored that dimension of the problem with skill and vigor and unparalleled success, and has resisted the urgings of many to pause a bit to study the mechanistic dimension. Time has shown the rightness of that choice.

Herbert C. Brown was born in London on 22 May 1912. His father was a cabinet-maker and the family lived in an apartment project that the Rothschilds had built to house refugees from the pogroms of the Czar. The Browns emigrated to Chicago in 1914 to join other members of the family. His father ran a hardware store but died when Herb was 14, making it necessary for him to leave school and go to work to support his mother and three sisters. In 1929 he was able to return to Englewood High School while continuing to work in the hardware store on evenings and weekends. He completed 2 years of schooling in 1 year and wrote for the school publications as well. After the family business failed and the store was sold, Herb worked as a shoe salesman and held jobs packing notebook paper and men's belts. This experience persuaded him to resume his education.

He enrolled in Crane Junior College in February of 1933 and there took a freshman chemistry course that kindled a flame of enthusiasm that still burns strong. It was at Crane that he met Sarah Baylen, now his wife of more than 40 years. She was his classmate in the slide-rule course and graded his papers in the freshman chemistry course; she has described her ambivalent response to his performance in both classes (*3*). When the city colleges closed for lack of funds at the depth of the depression, Herb and Sarah were allowed to continue their training in the home laboratory of Dr. Nicholas D. Cheronis. At this time Herb also took evening courses at Armour Institute (now Illinois Institute of Technology) and a home-study course in quantitative analysis from the University of Chicago.

The colleges opened again in the fall of 1934; the two attended Wright Junior College and then entered the University of Chicago on scholarship as juniors majoring in chemistry. Again, Herb completed 2 years of work in one. He graduated in 1935, and Julius Stieglitz encouraged him to go to graduate school. A graduation gift from Sarah—Alfred Stock's Baker lectures on "Hydrides of Boron and Silicon" (inscribed by her "to the future Nobel Prize winner")—helped persuade him to choose H. I. Schlesinger as his research adviser. His Ph.D thesis (1938) dealt with the reduction of carbonyl compounds with diborane.

After a year in postdoctoral work with M. S. Kharasch, he was made instructor and assistant to Schlesinger, who was then investigating the metal borohydrides. This work was supported as a defense project during the early years of World War II and produced new ways of generating diborane in quantity as well as methods for making sodium borohydride by reaction of sodium hydride with boron halides or esters of boric acid. The experience gained during these years formed the basis for his later work with boron compounds as Lewis acids, as selective reducing agents, and as versatile reagents for synthesis in organic chemistry. Beyond this, it probably influenced the style of his later research operation which, like Schlesinger's, featured close integration of the efforts of many persons under the immediate supervision of seasoned postdoctoral research assistants.

In 1943 he accepted a position at Wayne (now Wayne State) University in Detroit. Here, under most difficult circumstances, he began the work on steric strains which brought him into national prominence and an offer of a position at Purdue University in 1947. These studies, important for their own sake, led, in steps, to his classical studies on the mechanism of aromatic substitution reactions, to the Selectivity Principle, to a major extension and refinement of the Hammett Relationship, and to the great and divisive debate on the structure of carbonium ions. Here, in the words of one of the standard undergraduate textbooks, he "played a role familiar to him: that of gadfly—the organic chemist's conscience—forcing careful examination of ideas that had been accepted perhaps too readily because of their neatness" (*4*). He has reviewed his own work, and revealed much of his own philosophy of research, in several books (*2*, *5*).

He has remained at Purdue despite several temptations to stray, finding the relative quiet of the Purdue campus and the West Lafayette community conducive to thought and work. His son, Charles, now a chemist with IBM in California, was raised here and attended Purdue, where in collaboration with his father he developed the Brown-square apparatus and method of hydrogenation. Herb is a devoted family man, as fond of world travel, perhaps, as of chemistry. His former students constitute a large second family, many of whom came back to West Lafayette in May of 1978 for a reunion and to honor him on his formal retirement. The university continues to provide him space and some general support for the research of a number of postdoctoral associates. His research program is as vigorous as ever, and he is now turning his attention to the application of some of his synthetic methods to the preparation of such substances as insect pheromones. He has been a kind and supportive colleague and those of us who have been associated with him over the years took the particular delight that comes when a good friend receives well-deserved recognition.

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