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A Tribute to Herbert C. Brown

Herbert C. Brown

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Herbert C. Brown was born in London on May 22, 1912, but was brought to the U.S. at age two and grew up in Chicago. He enrolled in Crane Junior College in 1933, where he met Sarah Baylen, now his wife of more than 55 years. When Crane closed for lack of funds in June, 1933, they continued their training in the home laboratory of one of their teachers, Nicholas D. Cheronis. 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." They then entered the University of Chicago in 1935 as juniors. H. C. Brown completed two years of work in one year and graduated in 1936. A graduation gift from Sarah, Alfred Stock's Baker Lectures on "Hydrides of Boron and Silicon," was in part responsible for his choosing H. I. Schlesinger as his graduate research advisor 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 assistant to Schlesinger (with rank of instructor) and codiscovered sodium borohydride. He became assistant professor at Wayne (now Wayne State) University in 1943, exploring steric strains. He was promoted to associate professor in 1946. 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 has been R. B. Wetherill Research Professor Emeritus, supervising a research group of approximately 15 postdoctoral associates, a secretary, and visiting scholars. He has published five books and more than 1100 scientific publications. He has won the majority of major awards in his field, as indicated by the following list of awards, honors, and memberships. Both he and his wife enjoy good health and make frequent trips that typically combine lectures and other scientific commitments including manuscript preparation, sightseeing, and photography, as well as occasional visits to their grandchildren in California.

AWARDS, HONORS, AND MEMBERSHIPS

Herbert C. Brown

1953	*Harrison Howe Lectureship*
1955	*Centenary Lectureship and Medal; The Chemcial Society (London)*
1957	*National Academy of Sciences*
1959	*W. H. Nichols Medal, New York Section, American Chemical Society*
1960	*ACS Award for Creative Research in Synthetic Organic Chemistry*
	SOCMA Award, Society of Organic Chemistry Manufacturing Society

1042-7163/92/$3.50 + .25

1961 *Phi Lambda Upsilon Key for Honorary Membership*

1962 *American Academy of Arts and Sciences*

1968 *Linus Pauling Medal, Oregon and Puget Sound Section of the American Chemical Society*

Honorary Doctor of Science Degree, the University of Chicago

1969 *National Medal of Science, U.S. Government*

Baker Lectureship, Cornell University

1971 *Roger Adams Medal, American Chemical Society*

1972 *Phi Beta Kappa, Honorary Membership*

1973 *C. F. Chandler Medal, Columbia University*

1975 *M. Marshall Award*

1976 *City College of New York Alumni Award and Medal for Scientific Achievement*

1977 *Royal Society of Chemistry, Honorary Membership*

Indian National Science Academy, Elected Fellowship

1978 *C. K. Ingold Memorial Lectureship and Medal, The Chemical Society, London*

Allied Award, Allied Chemical Company

E. Cresson Medal, The Franklin Institute, Philadelphia

1979 *Nobel Prize for Chemistry*

1980 *Medal of Culture, Ministry of Education, Taiwan*

Chinese Chemical Society, Honorary Membership

Honorary Old Master, Purdue University

1981 *Priestley Medal, American Chemical Society*

1982 *Perkin Medal, American Section, Society of Chemical Industry*

C. S. Hamilton Award, University of Nebraska

Chemical Society of Japan, Honorary Membership

Pharmaceutical Society of Japan, Honorary Membership

Academy of Arts and Sciences of Puerto Rico, Honorary Membership

Indiana Academy of Sciences, Honorary Membership

1983 *National Honor Society, Honorary Membership*

A. J. Beckman Memorial Medal, Colorado School of Mines

1985 *A. I. C. Gold Medal, American Institute of Chemists*

1986 *60th Anniversary Commemorative Medal, Jewish Academy of Arts and Sciences*

Sesquicentennial Commemorative Medal, National Library of Medicine

1987 *National Academy of Sciences Award and Medal for the Chemical Sciences*

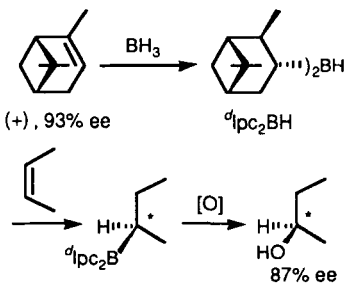
G. M. Kosolapoff Award, Auburn Section, American Chemical Society

Dedication of the H. C. Brown Laboratories of Chemistry

1989 *Emperor's Decoration (Japan), Order of the Rising Sun, Gold and Silver Star*

A SUMMARY OF STUDIES BY HERBERT C. BROWN ON ASYMMETRIC SYNTHESIS VIA ORGANOBORANES

The quantitative, practically instantaneous addition of borane to alkenes and acetylenes in ether solvents was first reported by Brown and Subba Rao in 1957, which made organoboranes readily available.[1] A few years later, Brown and Zweifel described, in a seminal paper, the asymmetric hydroboration of olefins with diisopinocampheylborane, which was synthesized readily from the commercially available α-pinene.[2]



In retrospect, this is a truly monumental achievement, as it is the first non-enzymatic asymmetric synthesis to provide products in such high optical purity. The chemical community had to wait nearly a decade before some additional examples of highly enantioselective organic reactions were reported. Frequent appearance of papers reporting high enantioselectivities lagged behind Brown's first paper by some 15–20 years.[3]

Brown's current research program on asymmetric synthesis via organoboranes began in 1977.[4] Since then, this research program has diversified and many outstanding contributions have been made.

His current research interests include:

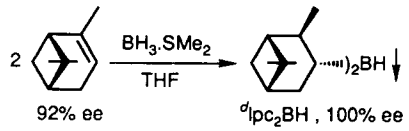
1. asymmetric hydroboration
2. general synthesis of enantiomerically pure organoboranes and organic compounds
3. asymmetric reduction, and
4. asymmetric allylboration.

In a great majority of investigations, organic chemists appropriately modify some well-established achiral chemistry to achieve the desired asymmetric synthesis. In contrast, Brown's program on asymmetric synthesis stems from the achiral organoborane chemistry that was developed almost entirely in his laboratories over the past four decades.[5]

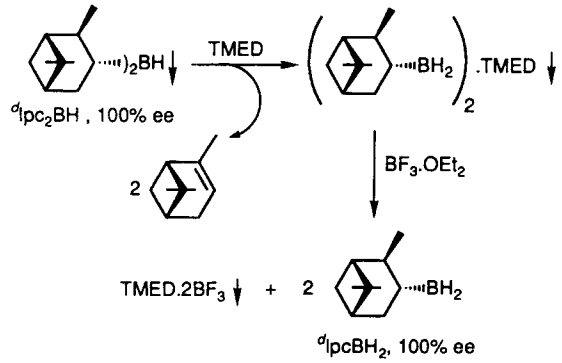
Asymmetric Hydroboration

Brown's synthesis of 100% enantiomerically pure diisopinocampheylborane (^{d}Ipc$_2$BH) and monoisopinocampheylborane (^{d}Ipc$_2$BH) is an ingeneous experimental achievement of great value in synthetic organic chemistry.

The hydroboration of (+)-α-pinene of 92% ee, with $BH_3.SMe_2$, affords a highly crystalline and enantiomerically pure ^{d}Ipc$_2$BH.



Treatment of ^{d}Ipc$_2$BH with one-half equivalent of N,N,N',N'-tetramethylethylenediamine (TMED) provides the 1:2 adduct, TMED. 2BH$_2$Ipc, with the liberation of (+)-α-pinene of 100% ee. The reagent, ^{d}IpcBH$_2$, also of 100% ee, is easily recovered from the adduct by treatment with boron trifluoride-etherate.

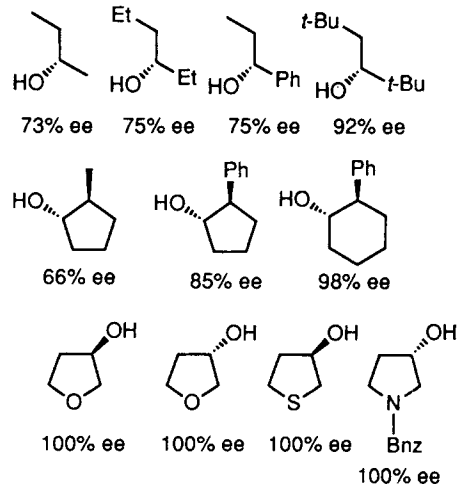


These two reagents complement each other. Thus, while ^{d}Ipc$_2$BH is excellent for the asymmetric hydroboration of (*Z*)-alkenes, ^{d}IpcBH$_2$ works well for (*E*)-alkenes and trisubstituted alkenes (Table 1).[6]

TABLE 1 Asymmetric Hydroboration of Representative Olefins

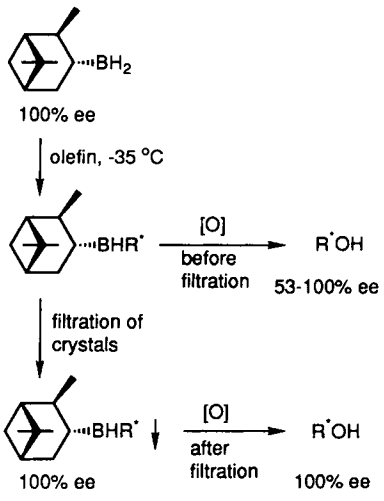
Olefin	%ee ^{d}Ipc$_2$BH	^{d}IpcBH$_2$
1,1-disubstituted alkenes	20	1
(*Z*)-alkenes	**100**	25
(*E*)-alkenes	20	**70-90**
trisubstituted alkenes	20	**60-100**

Thus, Brown's asymmetric hydroboration chemistry affords many alcohols in multi-gram quantities and exceptionally high enantioselectivities:



General Synthesis of Enantiomerically Pure Organoboranes and Organic Compounds

Brown made a significant observation that even in cases where the extent of asymmetric induction in hydroboration was less thatn 100%, enantiomerically pure products tended to crystallize for easy isolation.[7]



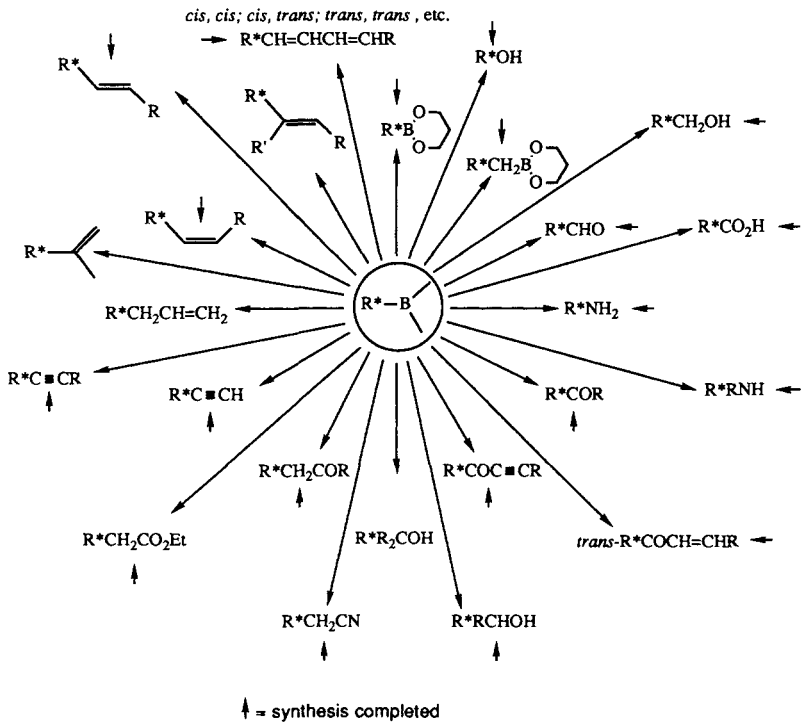


FIGURE 1 General Synthesis of Enantiomerically Pure Organic Compounds.

Treatment of the hydroboration products, Ipc_2BR^* and IpcBHR*, with acetaldehyde liberates α-pinene and provides boronic acid esters.[8a] Therefore, it is now practical to obtain a variety of chiral boronic acids and esters in 100% optical purity.[8b]

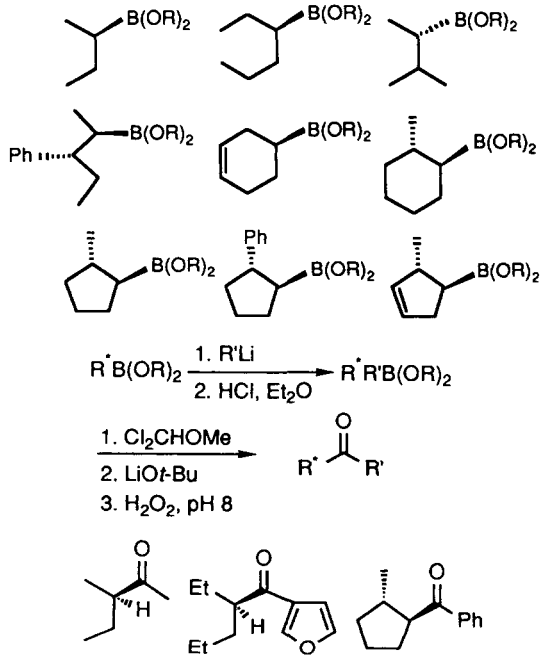
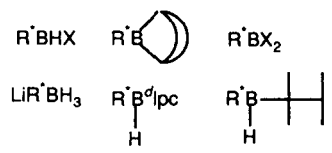


FIGURE 2 Synthesis of Optically Active Ketones of ≥99% ee.

Thus, Brown's pinanyl reagents enable a convenient synthesis of both enantiomers of $R^*B(OR)_2$ in 100% ee. This has further led to the development of simple and practical methods for the preparation of a wide variety of organoborane derivatives (such as shown below) of essentially 100% ee.



Brown and others have previously shown that most organoborane reactions proceed with complete retention of configuration. Over the last decade, Brown has developed efficient methods for the synthesis of many classes of organic compounds of essentially 100% optical purity, starting from the various organoborane intermediates outlined in Figure 1.[9] Some examples are shown in Figures 2–7.

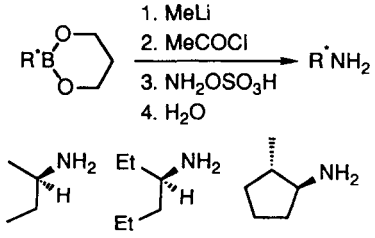


FIGURE 3 Synthesis of Optically Active Amines of ≥99% ee.

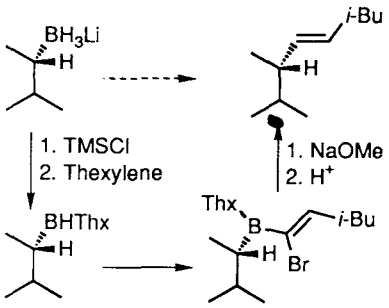


FIGURE 4 Synthesis of Optically Active *Trans*-Alkenes of ≥99% ee.

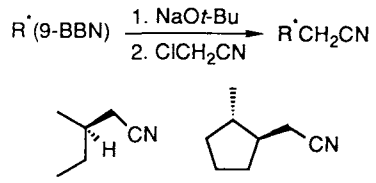
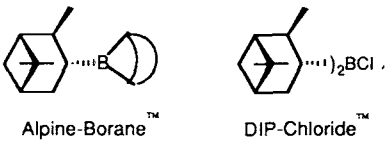


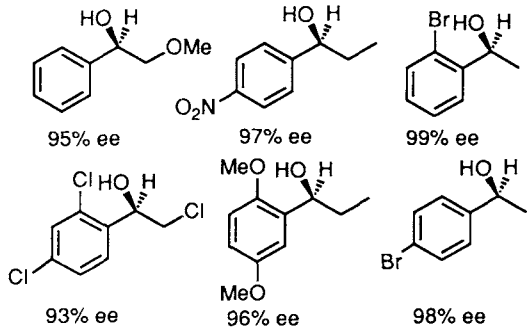
FIGURE 6 Synthesis of Optically Active Nitriles of ≥99% ee.

Asymmetric Reduction

Asymmetric reduction of carbonyl compounds is of major importance in organic synthesis. Today, many satisfactory asymmetric reducing agents are available. Among these, Alpine-Borane® (Midland's reagent) and DIP-Chloride® are two of the most readily available and highly selective reagents.[10]



In particular, the development of DIP-Chloride® is one of Brown's major achievements in the area of asymmetric reduction. This reagent permits, in a predictable manner, a reagent-controlled reduction of aralkyl ketones.



This reagent also permits reduction of hindered α,β-acetylenic ketones in a highly enantioselective manner. The results shown below are far superior to those obtained by any of the presently available chiral reducing agents.

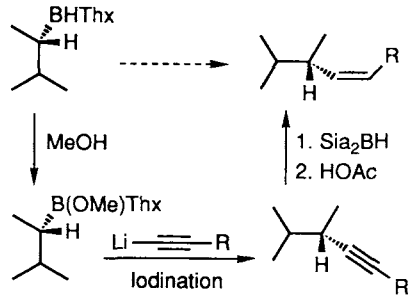


FIGURE 5 Synthesis of Optically Active *Cis*-Alkenes of ≥99% ee.

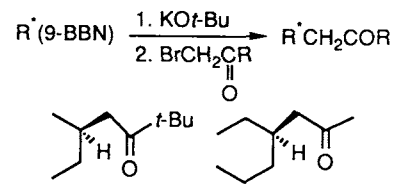
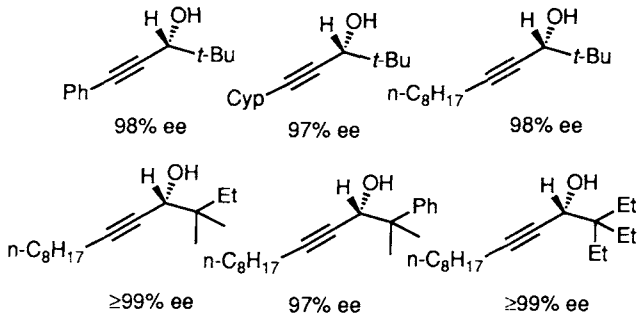
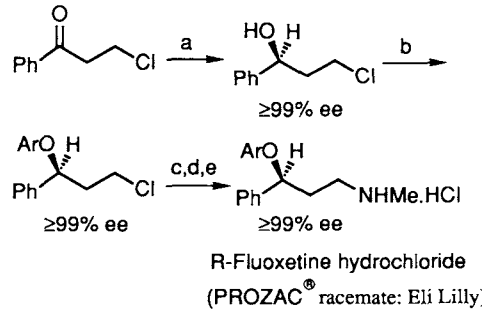


FIGURE 7 Synthesis of Optically Active Homologated Ketones of ≥99% ee.



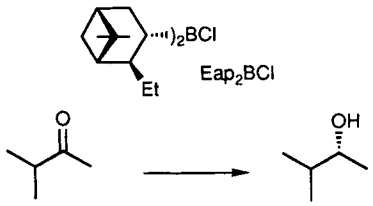
DIP-Chloride® is finding an increasing number of synthetic applications involving aralkyl ketones. Brown's synthesis of either enantiomer of the currently widely used anti-depressant drug, Fluoxetine Hydrochloride (Eli Lilly: Prozac®), elegantly demonstrates the synthetic potential of this powerful reagent (Scheme 1).[11]



(a) $^{d}Ipc_2BCl$; recrystallization; (b) *p*-CF_3PhOH, Mitsunobu reaction (c) $MeNH_2$, water, 130 °C; (d) HCl in Et_2O; (e) recrystallization.

SCHEME 1

Recently, Brown developed an even better chiral reducing agent, β-chlorodiiso-2-ethylapopinocampheylborane (Eap_2BCl), which effectively handles not only all those classes of ketones handled by DIP-Chloride®, but also aliphatic ketones, such as 3-methyl-2-butanone.[12]

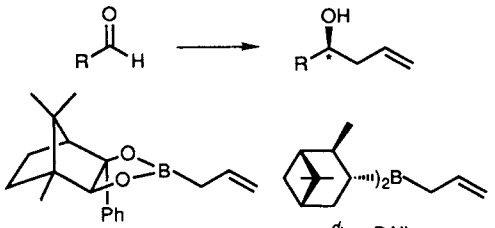


Ipc_2BCl	32% ee
Eap_2BCl	95% ee

Thus, Brown's chiral reducing agents, for example, $^{d}Ipc_2BCl$, handle most classes of ketones. The ready availability of these reagents offers a major advantage over many other stoichiometric chiral reducing reagents.

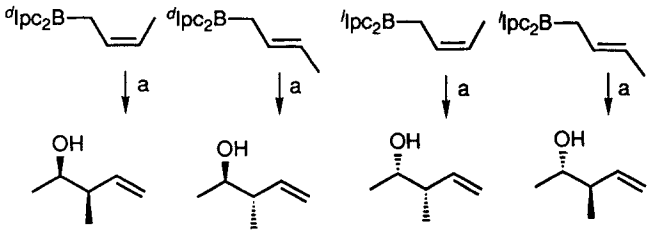
Asymmetric Allylboration

In 1981, Hoffmann reported the first asymmetric allylboration. However, he achieved somewhat modest enantioselectivities.[13] Brown later reported the allylboration of representative aldehydes with *B*-allyldiisopinocampheylborane, $^{d}Ipc_2BAll$.[14] This reagent is considerably more selective than Hoffmann's reagent.



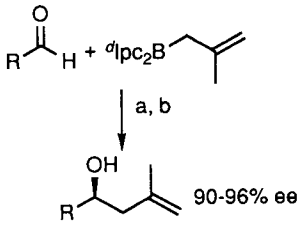
Hoffmann's reagent	$^{d}Ipc_2BAll$
R = Me, Et, *i*-Pr, *t*-Bu	R = Me, Et, *i*-Pr, *t*-Bu, Ph and vinyl
45-86% ee	84-94% ee

Subsequently, Roush, Masamune, Reetz and Corey, among others, have made significant contributions to this area of research.[15] The simplicity and versatility of asymmetric allylboration may be illustrated by the synthesis of all possible stereoisomers of 3-methyl-4-penten-2-ols (≥ 99% de, 90-94% ee).[16] Some additional examples are shown in Figures 9-12. It is noteworthy that crotylboration of a-chiral aldehydes does not seriously suffer from any significant mismatch problems (≥ 99% de; 90–96% ee).[16]



(a) acetaldehyde, -78 °C; OH^-, H_2O_2

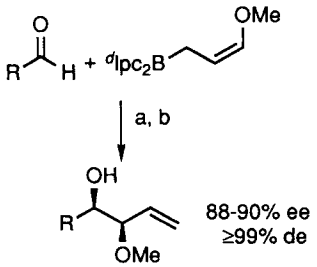
FIGURE 8 Asymmetric Crotylboration of Representative Aldehydes.



R = Me, Et,*n*-Pr, *t*-Bu and vinyl

(a) -78 °C, Et_2O; (b) OH^-, H_2O_2

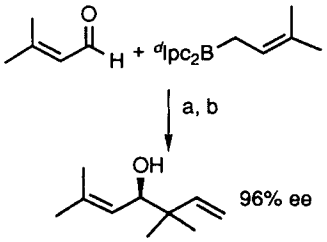
FIGURE 9 Asymmetric Methallylation of Aldehydes.



R = Me, Et,*i*-Pr, Ph and vinyl

(a) -78 °C, Et_2O; (b) OH^-, H_2O_2

FIGURE 10 Asymmetric Methoxyallylation of Aldehydes.



(a) -78 °C, Et_2O; (b) OH^-, H_2O_2

FIGURE 11 Asymmetric Synthesis of Artemesia Alcohol.

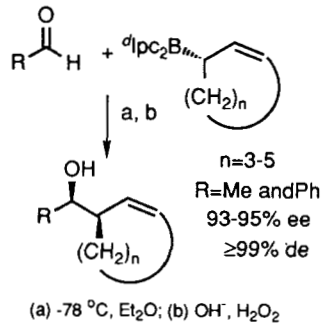


FIGURE 12 Asymmetric Cycloalkenylation of Aldehydes.

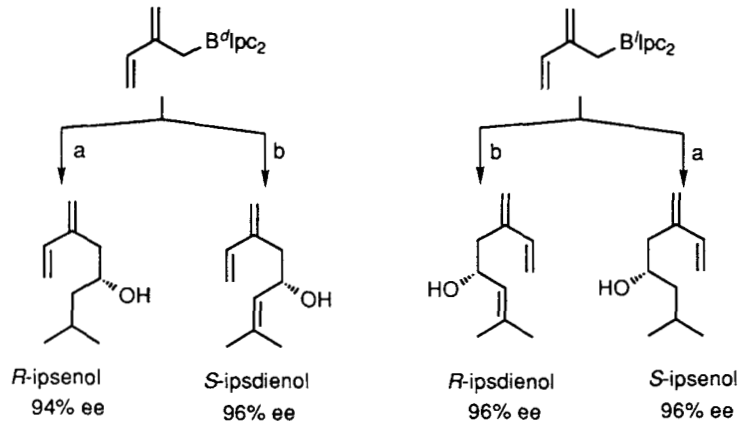


FIGURE 13 Asymmetric Synthesis of Ipsenol and Ipsdienol.

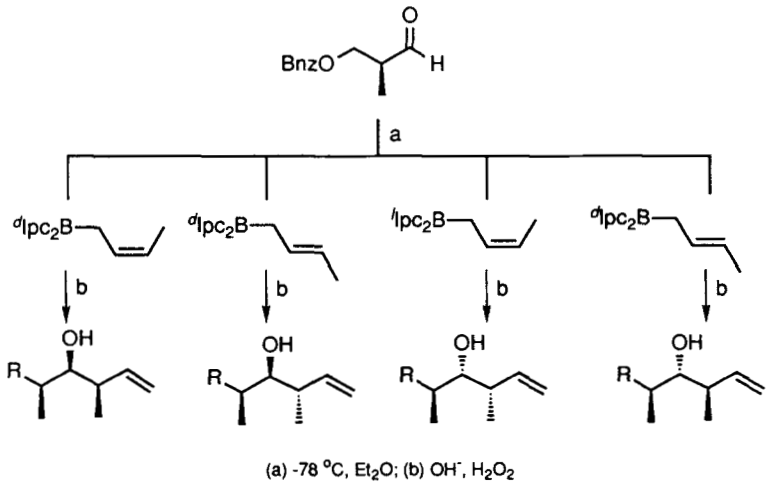
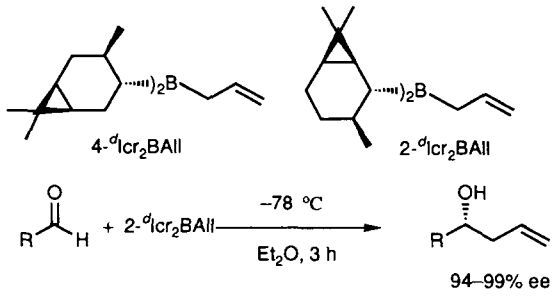


FIGURE 14 Asymmetric Crotylboration of α-Chiral Aldehydes.

TABLE 2 Asymmetric Allylboration of Aldehydes at –100°C

	%ee					
RCHO,	$^{d}Ipc_2BAll$		4-$^{d}Icr_2BAll$		2-$^{d}Icr_2BAll$	
R =	–78°C	–100°C	–78°C	–100°C	–78°C	–100°C
Me	92	≥99	94	≥99	98	≥99
n-Pr	86	96	88	98	94	≥99
i-Pr	88	96	95	98	94	≥99
t-Bu	83	≥99	88	≥99	99	≥99
vinyl	92	96	93	98	95	≥99
Ph	94	96	87	98	95	≥99

Brown has recently developed additional asymmetric allylborane reagents derived from Δ^3-carene and Δ^2-carene, 4-$^{d}Icr_2BAll$ and 2-$^{d}Icr_2BAll$, which are even better than $^{d}Ipc_2BAll$.[18]



R = Me, Et, *i*-Pr, *t*-Bu, Ph and vinyl

With these new reagents it is now possible to achieve an essentially 100% enantioselective allylboration of various aldehydes (Table 2).[19]

Brown's asymmetric allylboration has found numerous applications in natural product synthesis. Some examples are shown below.[20]

(a) Milbemycins and Avermectins: (E. J. Thomas); (b) Calcimycin: (R. K. Boeckmann); (c) Histrionicotoxin 235A: (G. Stork); (d) Nikkomycin B: (A. G. Barrett); (e) FK-506: (R. E. Ireland); (f) Calicheamycin: (K. C. Nicolaou).

Brown's research on asymmetric synthesis is multi-faceted, and it represents a truly remarkable post-retirement and post-Nobel contribution of exceptional quality and significance.

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[1] H. C. Brown, B. C. Subba Rao, *J. Org. Chem., 22,* 1957, 1136.

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