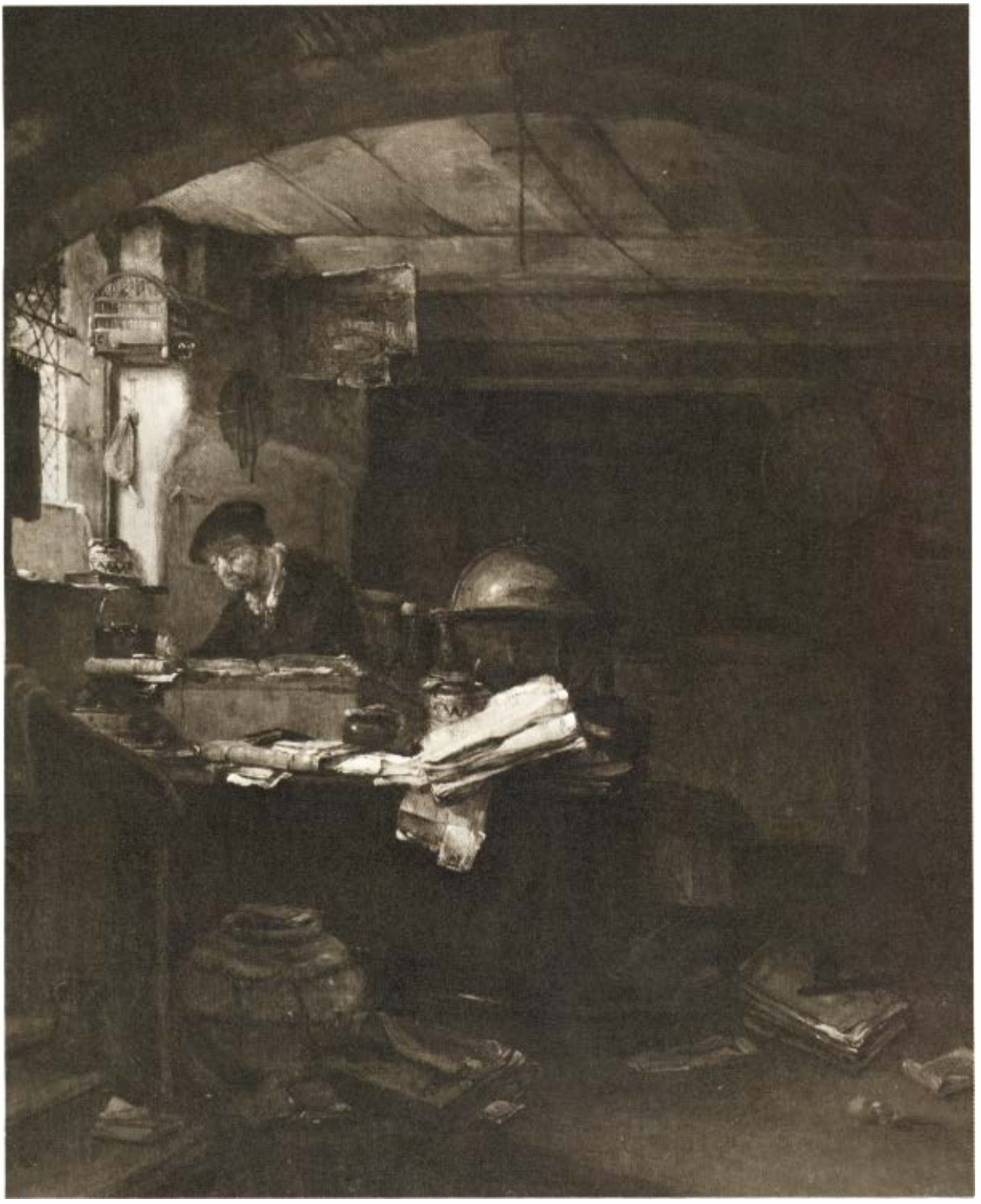
Aldrichimica Acta

Volume 20, Number 1, 1987



Dedicated to Professor Herbert C. Brown on his seventy-fifth birthday

chemists helping chemists in research & industry

aldrich chemical company, inc.

Aldrichimica Acta

Volume 20, Number 1, 1987
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About Our Cover:

Really fine 17th-century paintings of scholars are hard to find; and so our chemist-collector was happy to acquire this work by Thomas Wyck, a mid-17th-century Haarlem artist. The first painting on an *Acta* cover, in 1968, was by Thomas Wyck (Fig. 1) — a much more involved work, with an alchemist and his assistant in a magic circle practicing, not chemistry, but some form of black art.

Here, an impressive scholar, perhaps an alchemist, sits alone in his study deep in thought. What an appropriate cover for the *Acta* dedicated to Professor Herbert C. Brown.

Fig. 1

Rembrandt and the Bible - in Japan

We are offering a limited number of a 174-page catalog of an exhibition in Japan, the first of its kind there, on Rembrandt and the Bible. The scholarly essays in Dutch, English, German and Japanese deal with works by Rembrandt and his students — 38 paintings, 7 drawings and 44 etchings, all beautifully illustrated. Thirteen of the paintings, all in full color, have appeared on covers of the *Acta*. The works are fully described in English and Japanese. An unusual and wonderful buy for lovers of art and the Bible!

Pictures from the Age of Rembrandt

Twenty-five paintings that have been reproduced on our *Acta* covers, and six that have been on our catalog covers are among thirty-six paintings in an exhibition of Dutch paintings at Queen's University in Kingston, Ontario. The fully illustrated catalog written by Professor David McTavish contains a wealth of art-historical information — enough for several evenings of relaxed enjoyment — probably the best value in art-history anywhere.

Reprints of Aldrich Catalog Covers

Eight beautiful 14 x 11 inches, full-color reproductions of paintings on our catalog covers are available, ready for framing, to add beauty to your laboratory.

Selections from the Aldrichimica Acta, 1968-1982

Because of the ever-increasing demand for earlier issues of the *Acta*, we now offer a collection of articles from volumes 1-15. We chose those articles which we believe are still of interest to our readers — 354 pages of great review articles, in one beautiful hardbound volume.

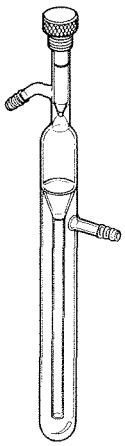
Lab Notes

The control and monitoring of gas flow present a recurring problem in synthetic laboratories. While various valves and meters are available for these purposes, we have found that an oil bubbler fitted with a Rotaflo® or similar valve is especially convenient as a one-piece unit for both controlling and monitoring gas flow at low (<2 psi) pressures. Using this bubbler, we have found it very easy to set up systems using polyethylene tubing and "T" valves to control the flow of N_2 or Ar independently from a single gas tank to many manifolds. We also use it when adding gaseous reagents (*e.g.*, acetylene and ammonia) to reactions.

®Registered trademark of Corning Glass Works

William D. Wombat
J. Michael Chong
The Guelph-Waterloo Centre for Graduate Work in Chemistry
University of Waterloo
Department of Chemistry
Waterloo, Ontario N2L 3G1

Editor's note: Aldrich now offers a mineral-oil bubbler fashioned after that described by the authors.



The value of K_2CO_3 as a base in two-phase systems often depends on its degree of division, even when a phase-transfer catalyst is employed. Hand grinding is exhausting, slow and only moderately effective, while laboratory mills can be very expensive. We have found that a blender-type coffee mill will reduce 50-g batches of granules to a fine dust in a few seconds, with minimal atmospheric contact. This powder is so well suspended, it permits magnetic stirring of mixtures even at high-solids loading, and reactivity is significantly enhanced.

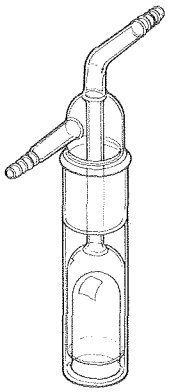
Alaric Naiman
Polaroid Corporation
750 Main Street -5C
Cambridge, MA 02139

Editor's note: Aldrich offers a blender-type mill for grinding small samples (~50g), as described above. Details of this **Lab Mill** are given in *Aldrichim. Acta* **1986,** *19*(3), 80. Aldrich Technical Information Bulletin No. AL-159 is also available.

Enclosed is a diagram of a double-surface cold trap which we find very useful for drying large amounts of nitrogen used in reactions requiring an inert atmosphere. It completely removes the necessity for cumbersome drying trains; applying a slight positive pressure of nitrogen when the trap is immersed in liquid N_2 causes some of the nitrogen gas to liquefy inside the trap. By ensuring that enough liquid is condensed to isolate the inlet side of the trap from the outlet - only nitrogen which evaporates at -196°C enters the reaction zone - no entrainment of water vapor in a moving stream of nitrogen gas is possible and the nitrogen "blanket" is thus completely dry. For less rigorously dry nitrogen requirements, the gas may be passed without condensation through two such traps in series; we regularly use this latter set-up for the handling of organolithium reagents.

Dr. A.G. Massey
University of Technology
Department of Chemistry
Loughborough
Leicestershire
England LE11 3TU

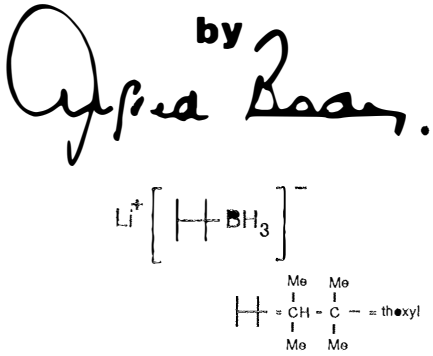
Editor's note: We have made and listed the cold trap following Dr. Massey's recommendations.



Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt.** *We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by



Professor Herbert C. Brown suggested that we offer lithium thexylborohydride,[1] a stable source of thexylborane, a versatile reagent for the preparation of unsymmetrical ketones.[2,3]

Naturally, we made lithium thexylborohydride.

1) Brown, H.C.; Singaram, B.; Mathew, C.P. *J. Org. Chem.* **1981,** *46,* 2712.
2) Brown, H.C. *Aldrichim. Acta* **1974,** *7*(3), 43.
3) Brown, H.C.; Mandal, A.K.; Kulkarni, S.U. *J. Org. Chem.* **1977,** *42,* 1392.

It was no bother at all, just a pleasure to be able to help.

To Live for Wisdom – An Appreciation of Herbert C. Brown[1]

James H. Brewster
Department of Chemistry
Purdue University
West Lafayette, IN 47907

Let us now praise famous men.[2]
(Eccl. 44:1)[3]

If wisdom is, as Webster says, "The ability to judge soundly and deal sagaciously with facts," then the pursuit of it is one of the highest callings of mankind, one on which our very survival may depend. But the rate at which factual knowledge is accumulating has made it necessary to fragment and specialize our wisdoms, especially in the sciences. There, wisdom is what makes good scientists great, for it guides their searches and is augmented by their findings. It is that which is honored with the palm boughs and laurels of a profession[4] and in the naming of buildings.[5] Herb Brown has devoted his life to the advancement of the special wisdom of organic chemistry with that single-minded passion that is necessary (but not always sufficient) to great achievement, and it is fitting that we heed the familiar injunction of the apocryphist (above) on the occasion of Herb's semisesquicentennial. And fitting, too, to follow one of Herb's frequent bits of advice to his students, "Read the whole reference," that we might discern what is ageless – and something of what may be ephemeral[6] – about humanity's long search for wisdom. Doing so, we find more than a lead; we find a text. Some of the more worldly portions are timeless and pertinent to the pursuit of any of the higher wisdoms; parts of it could have been written by – or about – Herb Brown.

Happy the man who fixes his thoughts on Wisdom
and uses his brains to think,
the man who contemplates her ways
and ponders her secrets.

(Eccl. 14:20-21)

We are not talking here of wistful daydreams but of the passions primeval:

Stalk her like a hunter
and lie in wait beside her path!

(Eccl. 14:22)

to which Wisdom will respond:

She will come out to meet him like a mother;
she will receive him like a young bride,
For food she will give him the bread of understanding
and for drink the water of knowledge.

(Eccl. 15:2-3)

The rewards of a life of the mind do not preclude those of the world.

She will promote him above his neighbors,
and find words for him when he speaks in the assembly.
He shall be crowned with joy and exultation;
lasting honor shall be his heritage.

(Eccl. 15:5-6)
(Fig. 1)

Fig. 1 - "He shall be crowned with joy and exultation."

Herb's parents, Charles Brovarnik and Pearl Gorinstein, came to London in 1908 as part of the large Jewish migration from Russia; they married there in 1909 and Herb was born in 1912. Two years later, his father decided to join his parents in Chicago where the family name had been anglicized to Brown (Fig. 2). Herb's father, finding that his skills as a cabinetmaker doing delicate inlay were not in great demand, opened a hardware store in an impoverished neighborhood. When his father died in 1926, Herb had to leave school to support his mother and three sisters; but a few years later, his mother took over the running of the store so that he could return to high school.

To the wise, education is a golden ornament
like a bracelet on the arm.

(Eccl. 21:21)

Fig. 2 - The Brown family. Chicago, 1925.

Jobs were scarce in 1930 so he enrolled in Crane Junior College, where he took a course in chemistry from which, like his first prize,[4] he never recovered. The Great Depression forced the college to close, but one of its instructors, Nicholas Cheronis, opened his private laboratory to a few students who wished to continue their studies. It was there that Herb met Sarah Baylen, beginning a love affair from which neither has recovered. They entered Wright Junior College and then the University of Chicago together; they were married in 1937. Julius Stieglitz advised Herb to enter graduate school and, employment still being scarce, he became a student of H.I. Schlesinger,

When you stand among your elders
decide who is wise and join him.

(Eccl. 6:34)

in part thanks to the effect of Alfred Stock's book on the hydrides of silicon and boron, which Sarah had given her "future Nobel laureate" on graduation. Those were times when they would sometimes subsist on a bowl of chili a day,

Bear every hardship that is sent you;
be patient under humiliation, whatever the cost.

(Eccl. 2:4)

but they endured.

In Schlesinger's labs Herb encountered the "Green Lady" (diborane burns green on contact with air) (Fig. 3) and developed the second great passion of his life. His thesis dealt with the reduction of carbonyl compounds by diborane, and reduction by means of boranes and borohydrides has been a major unifying theme of his

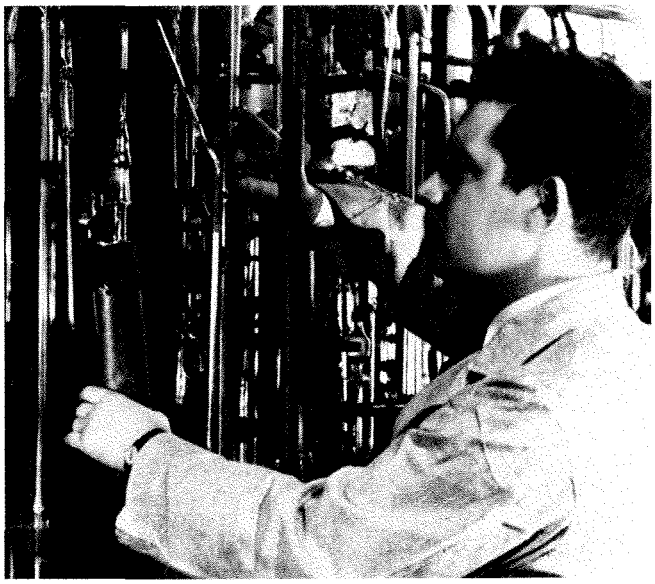


Fig. 3 - At the vacuum line. Chicago, 1940.

research[7] to this day.[8] He obtained a position at Wayne University in 1943 and began the work that made steric effects respectable again in physical organic chemistry, after their near eclipse by electronic effects. Results obtained using boron compounds as reference acids led him into carbonium-ion chemistry. He presented his findings with vigor,

Do not be over-modest in your own cause.

(Eccl. 4:20)

which brought him first into conflict with Ingold and then with the American solvolysis establishment, which was preoccupied with "nonclassical" structures for carbonium ions. As he saw it,

Many have been led astray by their speculations,
and false conjectures have impaired their judgement.

(Eccl. 3:24)

so he followed the injunction

Never remain silent when a word might set things right.

(Eccl. 4:23)

and did what he could to bring the discussion down to a solid basis of fact.

As the work of a potter is tested in the furnace,
so a man is tried in debate.

(Eccl. 27:5)

Sometimes his colleagues pressed him to abandon the fight and concentrate his whole effort on the chemistry of boranes.

Never take sides in a quarrel not your own
or become involved in the disputes of rascals.

(Eccl. 11:9)

He had troubles with referees who couldn't read and had to reply,

Do not find fault before examining the evidence;
think first, and criticize afterwards.

(Eccl. 11:7)

but he persevered.[7,9]

Trust your own judgement,
for it is your most reliable counsellor.
A man's own mind has sometimes a way of telling him more than seven watchmen posted high on a tower.

(Eccl. 37:13-14)

(Fig. 4)

Fig. 4 - "Trust your own judgement."

Rumbles of the "nonclassical carbonium-ion debate" are still heard,[10] though Michael Dewar may have provided closure with the conclusion that the norbornyl ion is a "nonclassical classical" carbocation.[11,12]

His concern with the importance of steric effects led him also into studies of aromatic substitution, where he showed how the effects of substituents on rates of nuclear substitution could be related to those for side-chain reactions.[13]

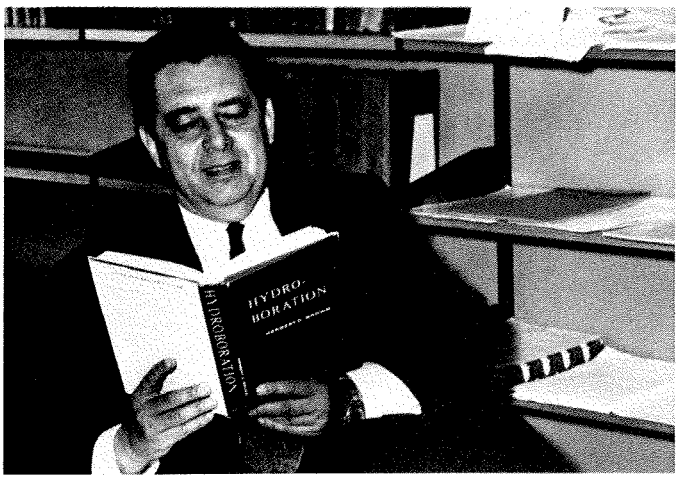


Fig. 5 - Relaxing with a good book, 1963.

Despite the distractions provided by these mechanistic excursions, work continued on the exploitation of the seminal discovery that diborane would add to olefins in ether solution.[14] The addition proved to be highly regio- and stereoselective and it was found that the boron atom could be replaced by hetero atoms and carbon atoms; a vast and rich field of synthetic chemistry opened up (Fig. 5). This was the work for which the Nobel Prize was awarded in 1979;[15] it continues.[16]

Stand by your contract and give your mind to it;
grow old at your work.

(Eccl. 11:20)

In the years of his "retirement", Herb has turned much of his attention to one of the prominent tasks of the times – developing methods for enantioselective synthesis with large ee's.[8,17] He has built on strength, putting his intimate and personally developed knowledge of the chemical attributes of the boranes to use, with the skill of an old master, in implementing a sure vision of how the major problems might be solved. His chief chiral adjuvant has been α-pinene, **1**, a terpene available in both enantiomeric forms,

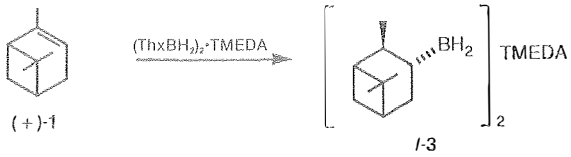
All things go in pairs, one the opposite of the other.

(Eccl. 42:24)

and inexpensive in a state of modest (but, in the event, adequate) optical purity (82-92% ee). Horeau's "principle of duplication"[18] was used to provide boranes of nearly complete optical purity. Thus, hydroboration of α-pinene, **1**, with $BH_3 \cdot SMe_2$ gives a mixture of the *l* ("like") and *u* ("unlike")[19] diastereomers of diisopinocampheylborane. The *l* isomer, **2**, is more abundant and crystallizes in near optical purity from solution in THF.[20]

(+)-1 *l*-2

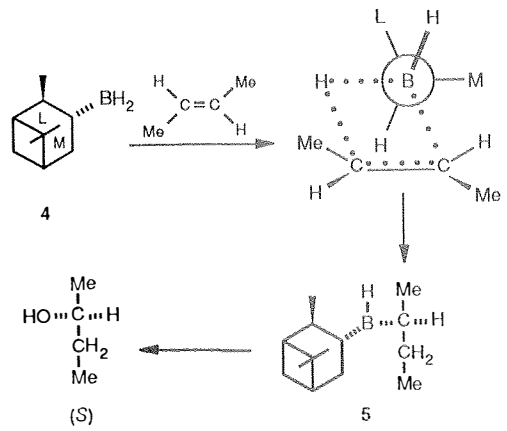
Similarly, hydroboration with the complex of tetramethylethylenediamine (TMEDA) with thexylborane gives diastereomeric complexes of TMEDA with monoisopinocampheylborane, from which an optically pure product **3** crystallizes.



(+)-1 *l*-3

Thx = thexyl = $-C(Me)_2-C(Me)_2-H$

It is seen that α-pinene serves as its own resolving agent. These products are versatile performers in the varied chemical games that boranes play and permit the preparation of almost any kind of chiral compound. Enantiomerically pure monoisopinocampheylborane (**4**) adds to a prochiral olefin to form a mixture of two diastereomeric dialkylboranes, one of which is generally in large excess and of predictable stereochemistry.[21] Separation of the two by crystallization gives an enantiomerically pure product **5**; once again the adjuvant has also served as a resolving agent.



4 5

In a bravura display of virtuosity in this use of boron chemistry, Herb and his group have recently devised methods for the preparation of primary amines in high optical purity.[22]

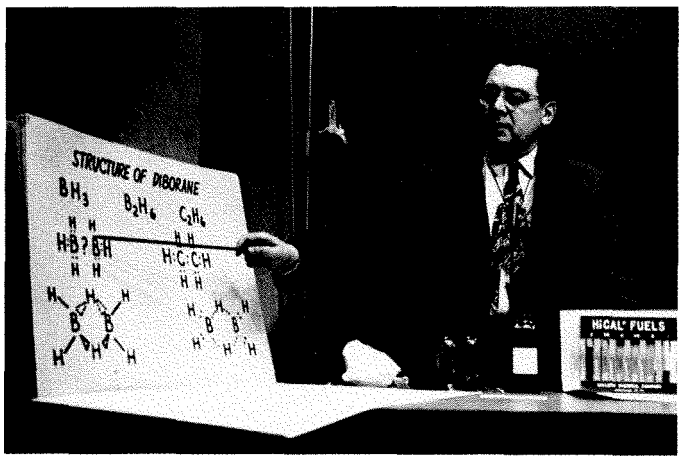


Fig. 6 - Star of television. "Continental Classroom," 1960.

Herb has always counted himself a teacher. Had he turned his hand to it, he would have made freshman chemistry a conversion experience for many young Hoosiers (Fig. 6). He has always excelled in the one-on-one teaching in the research lab (Fig. 7) and continues to this day in his "retirement" with a corps of able and enthusiastic postdocs from around the world. He remains an effective recruiter of students.

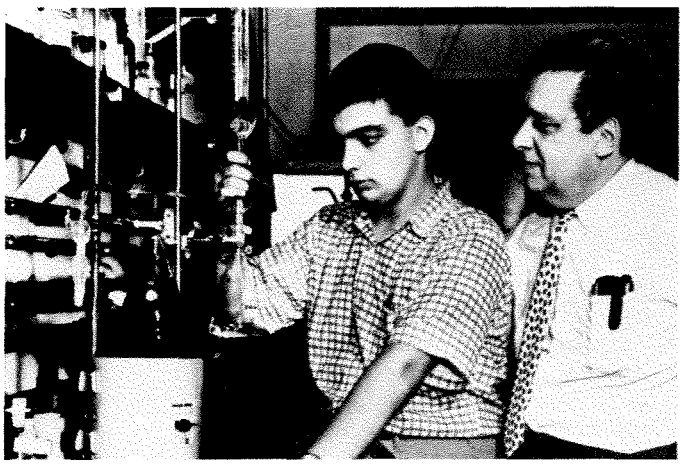


Fig. 7 - Development of the Brown Autogasimeter, with his son Charles.

Come to me, you who need instruction,
and lodge in my house of learning.
...bend your neck to the yoke,
be ready to accept discipline...
Your share of instruction may cost you a large sum of silver but it will bring you a large return in gold.
(excerpted, Eccl. 51, 23-28)

Every experiment in Herb's lab is meticulously planned. You can almost hear the rustle of that famous onion-skin paper.

Every undertaking begins in discussion
and consultation precedes every action.
(Eccl. 37:16)

Listen to him urge a first-year student to persevere as a teaching assistant,

Do your duty in good time,
and in his own time he will reward you.
(Eccl. 51:30)

counseling some who would rashly minor in math or physical chemistry,

Do not pry into things too hard for you
or examine what is beyond your reach.
(Eccl. 3:21)

reminding them to attend seminars and lectures,

Do not ignore the discourse of your elders...
they can teach you to understand
and to have an answer ready in time of need.
(Eccl. 8:9)

selling them on the merits of what some of his students called "the big B",

The bee is small among winged creatures
yet her produce takes first place for sweetness.
(Eccl. 11:3)

chivvying the fearful

Woe to faint hearts and nerveless hands!
(Eccl. 2:12)

and reassuring others,

do what I tell you, if you would be safe.
(Eccl. 3:1)

correcting faulty lab technique,

Stubbornness will come to a bad end,
and the man who flirts with danger will lose his life.
(Eccl. 3:26)

advising them before orals or job interviews.

Prepare what you have to say if you want a hearing;
marshal your learning and then give your answer.
(Eccl. 33:4)

He advised not only students, but young colleagues as well,

My son, do not engage in too many transactions;
if you attempt too much, you will come to grief.
(Eccl. 11:10)

or reproved them gently for their heckling of student seminar speakers,

Speak, if you are old - it is your privilege -
but come to the point and do not interrupt the music.
(Eccl. 32:3)

encouraging those who feel that organic chemistry is a mature science.

There remain many mysteries greater still.

(Eccl. 43:32)

(Fig. 8)

Fig. 8 - "There remain many mysteries still."

He was widely sought as a consultant and has received awards from the President of the United States and the King of Sweden.

The great avail themselves of his services,
and he is seen in the presence of rulers.

(Eccl. 39:4)

(Fig. 9)

Fig. 9 - Meeting the King and Queen of Sweden, with Sarah and Charles, at the Nobel Ceremony, 1979.

He has testified before committees of Congress and is the author of more than 1000 papers.[22]

He will have sound advice and knowledge to offer
and his thoughts dwell on the mysteries he has studied.
He will disclose what he has learnt
from his own education.

(Eccl. 39:7-8)

Ecclesiasticus speaks to Herb's personal life as well. Of his marriage of fifty years to Sarah Baylen:

A wife's charm is the delight of her husband,
and her womanly skill puts flesh on his bones.

(Eccl. 26:13)

On the matter of who should do the gardening, mow the lawn or take out the garbage (Fig. 10):

Fig. 10 - Editorial cartoon: Sattler, Lafayette (Indiana) Journal and Courier, October 20, 1979. (Republished with permission).

A scholar's wisdom comes of ample leisure;
if a man is to be wise he must be relieved of other tasks.

(Eccl. 38:24)

The Browns are world travelers. They have seen the midnight sun and the worship of the golden calf at Katmandu.

A man who travels grows in ability.
I have seen many things in my travels,
and understand more than I can tell.

(Eccl. 34:10-11)

Their life in recent years has not been as spartan as it was in Chicago or Detroit.

My son, if you can afford it, do yourself well...
Do not miss a day's enjoyment
or forgo your share of innocent pleasure.

(Eccl. 14:11,14)

But they have not been remiss in making donations to worthy causes.

Do good to your friend;
reach out as far as you can to help him.

(Eccl. 14:13)

He and Sarah have endowed a chair in Organic Chemistry at Purdue and also a lectureship that allows the department to hold annual symposia with three or four speakers.

In his epilog ben Sirach summarizes his own life of single-minded pursuit of wisdom and he summarizes Herb's life, too.

When I was young, before I set out on my travels,
I asked openly for wisdom in my prayers.
In the forecourt of the sanctuary I laid claim to her,
and I shall seek her to the end.
...She has been the delight of my heart.
From my youth my steps have followed her without swerving.
I had hardly begun to listen when I was rewarded,
And I gained for myself much instruction.
I made progress in my studies;
I determined to practice what I had learnt...
I strove for wisdom with all my might
and was scrupulous in whatever I did.
I set my heart on possessing wisdom...
with her I gained understanding from the first;
therefore I shall never be at a loss.
Because I passionately yearned to discover her,
I won a noble prize.

(Eccl. 51:13-21)

Footnotes and references:

1) An extension of remarks delivered at a symposium honoring Professor Brown at West Lafayette on October 10, 1980.
2) Issues of *Aldrichimica Acta* have also been dedicated to Robert Burns Woodward (Vol. 10, No. 1, 1977), Gilbert Stork (Vol. 15, No. 1, 1982), Alfred Bader (Vol. 17, No. 1, 1984) and Ralph Alexander Raphael (Vol. 19, No. 1, 1986).
3) *Ecclesiasticus, or the Wisdom of Jesus ben Sirach* is a part of the Apocrypha, which is to say, that part of the Old Testament that came to us in Greek, from Alexandria, but not in Hebrew, from Palestine. It is not to be confused with *Ecclesiastes,* which is canonical and is the source of the familiar passage: "To all things there is a time...". This quotation is from the King James Version; all others are from the New English Bible.
4) Young Herbie Brown wrote a humor column for his high school newspaper and won a national prize for it, starting a habit from which, he says, he has never recovered. He has been honored with lectureships - Harrison Howe Lecturer (1953), Centenary Lecturer (the Chemical Society) (1955), Baker Lecturer (Cornell) (1968) and Ingold Memorial Lecturer (1978). There have been medals and awards - the Nichols Medal (1959), the A.C.S. Award and S.O.C.M.A. Medal for Creative Research in Organic Chemistry (1960), the Linus Pauling Medal (1968), the Medal of Science (1969), the Roger Adams Award (1971), the Charles Frederich Chandler Medal (1973), the Madison Marshall Award (1975), the CCNY Alumni Scientific Achievement Award (1976), the Allied Award (1978), the Ingold Memorial Lecturer and Medal (1978) and the Elliott Cresson Medal (1978). The Nobel Prize came in 1979, to be followed by the "Triple Crown" of American chemistry: the Priestley Medal of the American Chemical Society (1981), the Perkin Medal of the Society of American Industrial Chemists (1982) and the American Institute of Chemists Gold Medal (1985). His uncomplicated enjoyment of such honors does not fade and is a continuing pleasure to his colleagues - he is a good winner. In addition, he has been elected a member of the National Academy of Science (1957), a fellow of the American Academy of Arts and Sciences (1957), a fellow of the Royal Institute of Chemistry (1978) and Foreign Fellow of the Indian National Science Academy (1978). He has received honorary degrees from the University of Chicago (his alma mater) (1968), Wayne State University (who first hired him) (1980), Purdue University (who kept him on the staff) (1981), the Hebrew University of Jerusalem (1980), the University of Wales (1981) and the Université de Paris Sud (1982). He is Richard Benbridge Wetherill Distinguished Professor (emeritus) at Purdue and is a Sagamore of the Wabash (1979).
5) His colleagues at Purdue are pleased that the edifice now known simply as "Chemistry II" will be named "Herbert C. Brown Laboratory of Chemistry" this spring.
6) Jesus ben Sirach flourished in Palestine about 200 B.C., a scribe, perhaps, who had acquired wisdom in the marketplace as well as in the temple. *Ecclesiasticus* is an instruction manual for his sons. As a part of the "wisdom literature" of the times, its counsel is one of prudence in the presence of great power rather than of piety, respect rather than love, good sense rather than morality. The patriarchal parts, dealing with the management of women, children, slaves, beasts of burden and other forms of property may be read for the picture they give of times long past, avoiding offense by looking through the verbiage and around the metaphors.
7) For a review, see Brown, H.C. *Boranes in Organic Chemistry;* Cornell University Press: Ithaca, 1972.
8) See, for example, Brown, H.C.; Chandrasekharan, J.; Ramachandran, P.V. *J. Org. Chem.* **1986,** *51,* 3394, and Brown H.C.; Cho, B.T.; Park, W.S. *ibid.* **1986,** *51,* 3396.
9) Brown, H.C. with Schleyer, P. von R. *The Nonclassical Ion Problem;* Plenum Press: New York, 1977; see, also, Bartlett, P.D. *Nonclassical Ions;* W.A. Benjamin, Inc.: New York, 1965.
10) Brown, H.C.; Vander Jagt, D.L.; Rothberg, I.; Hammar, W.J.; Kawakami, J.W. *J. Org. Chem.* **1985,** *50,* 2179.
11) Dewar, M.J.S.; Merz, K.M., Jr. *J. Am. Chem. Soc.* **1986,** *108,* 5634.
12) Perhaps a bit of Quaker wisdom is in order here - when good people disagree, the chances are high that both are right.
13) See Stock, L.M.; Brown, H.C. *Adv. Phys. Org. Chem.* **1963,** *1,* 35.
14) Brown, H.C.; Subba Rao, B.C. *J. Am. Chem. Soc.* **1956,** *78,* 2582.
15) Brown H.C. *Science* **1980,** *210,* 485.
16) See, most recently, Brown H.C.; Racherla, U.S. *J. Org. Chem.* **1986,** *51,* 427, 895. Jadhav, P.K.; Bhat, K.S.; Perumal, P.T.; Brown, H.C. *ibid.* **1986,** *51,* 432. Brown H.C.; Vara Prasad, J.V.N.; Zee, S.-H. *ibid.* **1986,** *51,* 439. Brown H.C.; Bhat, K.S. *ibid.* **1986,** *51,* 445. Brown H.C.; Bhat, N.G.; Campbell, J.B., Jr. *ibid.* **1986,** *51,* 3400.
17) Brown, H.C.; Jadhav, P.K. *Asymmetric Synthesis;* Morrison, J.D., Ed.; Academic Press: New York, 1983; Vol. 2; p 1.
18) Vigneron, J.P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973,** *29,* 1055.
19) Each Ipc residue can be treated as a single but complex chirogen existing in one of two enantiomeric configurations. See Brewster, J.H. *J. Org. Chem.* **1986,** *51,* 4751.
20) A statistical assembly of dialkyl boranes from (+)-pinene of 90% ee (95% +; 5% -) would contain: 90.25% + +, 0.25% - -, and 9.5% + -. The *l* diastereomer has an enantiomeric purity of 99.45% ee. It is not uncommon for substances of such high enantiomeric purity to give crystals of even higher ee: Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates and Resolutions;* Wiley-Interscience: New York, 1981; pp 424-428.
21) Houk, K.N. *et al. Science* **1986,** *231,* 1108. This model can be extended to $(Ipc)_2BH$ by assuming that one alkyl group acts simply as a very bulky group; thus, *cis*-2-butene gives *R*-2-butanol.
22) Brown, H.C.; Kim, K.W.; Cole T.E.; Singaram, B. *J. Am. Chem. Soc.* **1986,** *108,* 6761 (paper M).

About the Author

James H. Brewster obtained the B.A. from Cornell and worked as a chemist with Atlantic Refining Company. He was an ambulance driver with British forces in Italy, Germany and India during World War II. After graduate study with H.R. Snyder at Illinois and postdoctoral work with Frank Westheimer at Chicago, he joined the faculty at Purdue in 1949 and has been there ever since.

Tris(dimethylamino)borane

$B(NMe_2)_3$

Tris(dimethylamino)borane has been employed in the synthesis of macrocyclic spermidine alkaloids[1] and in the preparation of polycyclic aminoboranes.[2]

1) Yamamoto, H.; Maruoki, K. *J. Am. Chem. Soc.* **1981,** *103,* 6133.
2) Richman, J.E.; Yang, N.-C.; Anderson, L.L. *ibid.* **1980,** *102,* 5790.

The Utility of Chiral Organoboranes in the Preparation of Optically Active Compounds[1]

Morris Srebnik
Aldrich Chemical Co., Inc.
Route 3
Sheboygan Falls, WI 53085

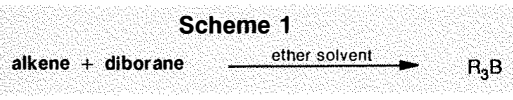
P. Veeraraghavan Ramachandran
Richard B. Wetherill Laboratory
Purdue University
West Lafayette, IN 47907

I. INTRODUCTION

Many biological molecules exist in nature as non-superimposable mirror images. Usually only one of these optical isomers is responsible for the particular biological activity, while the other isomer is, at best, essentially useless, or at worst capable of causing serious side effects.[2] The ability to prepare rationally either of the possible optical isomers in essentially pure form, without recourse to laborious or empirical separation techniques would certainly be desirable. Only recently have chemists realized this possibility.[3] To this end boron chemistry serves admirably.

In 1956, Brown and Subba Rao discovered the ether solvent-catalyzed hydroboration reaction (Scheme 1) which made trialkylboranes readily available.[4]

Scheme 1



A systematic study of the reactions of organoboranes revealed their exceptional versatility.[5] The typical transformations are indicated in Scheme 2.[5]

These studies revealed that the substitution reactions of organoboranes proceed with essentially complete retention of configuration (Scheme 3). Only a few exceptions are known.[6]

It was soon recognized by Brown and co-workers that a successful asymmetric hydroboration of alkenes would provide optically active organic groups attached to boron (R*B<). Such groups might then be converted into pure enantiomers. In 1961, Brown and Zweifel reported the preparation of alcohols of high optical purity.[7] This landmark paper heralded the age of non-enzymatic preparation of optically active compounds.

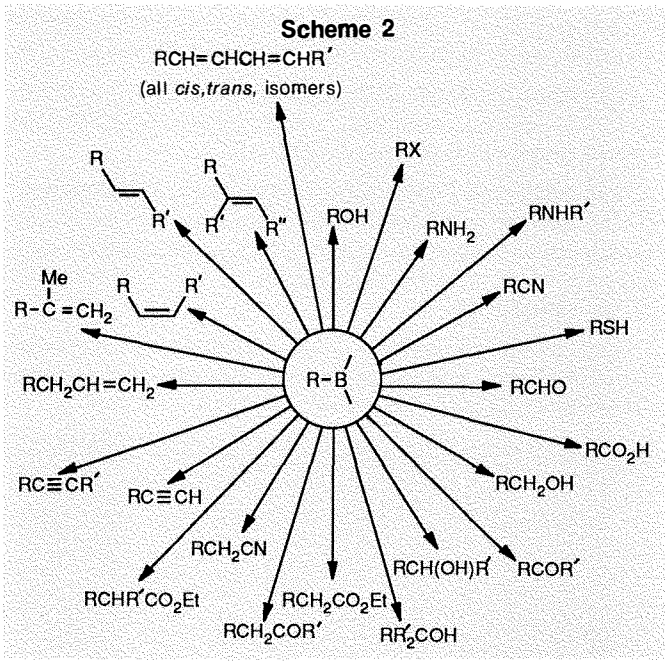
In this article, we propose to review the main contributions of Brown and his co-workers in the field of asymmetric synthesis — developments which promise a general and rational synthesis of enantiomers of high optical purity.

II. ASYMMETRIC HYDROBORATION

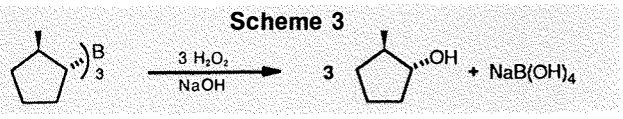
A. Diisopinocampheylborane (Ipc_2BH)

The hydroboration reaction[4] led to the first practical asymmetric synthesis. Brown and Zweifel found that the reaction of *cis* alkenes with (-)-diisopinocampheylborane, (-)-Ipc_2BH, readily obtainable from (+)-α-pinene, led, after oxidation with alkaline hydrogen peroxide, to optically active *secondary* alcohols.[7] Indeed, the hydroboration of *cis*-2-butene in diglyme (DG) with Ipc_2BH (from α-pinene of 93% ee) provided 2-butanol in 87% enantiomeric excess (ee) (Scheme 4).

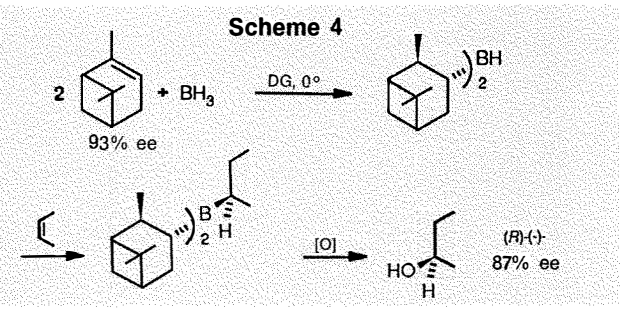
Scheme 2



Scheme 3



Scheme 4



Subsequent developments showed Ipc_2BH to be generally applicable to the hydroboration of *cis* alkenes[8,9] (Scheme 5). Since (+)- and (-)-α-pinenes are readily available from natural sources, both optical isomers of Ipc_2BH can be synthesized at will.

The potential of Ipc_2BH to transfer chirality effectively to *cis* alkenes initiated a vigorous search for an efficient method of preparing this chiral borane. Brown and Moerikofer observed a significant dissociation of Ipc_2BH into $IpcBH_2$ and α-pinene in solution[10] (Scheme 6).

A systematic study by Brown and Yoon revealed that the above dissociation reaction could be suppressed by the addition of 15% excess of α-pinene.[11] They obtained optically pure Ipc_2BH from the reaction of α-pinene (of 97.4% ee) and borane-tetrahydrofuran (BH_3•THF) at 0°C for 3 days. The major isomer of α-pinene is incorporated into the reagent leaving the minor isomer in solution (Scheme 7).

The formation of optically pure Ipc_2BH is rationalized as in Scheme 8.

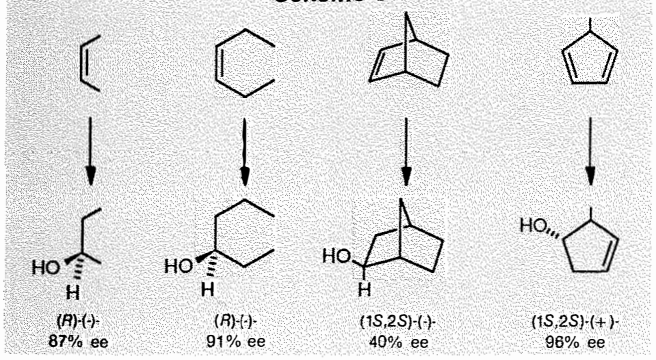
The preparation of Ipc_2BH in optically pure form could also be achieved from commercially available α-pinene of 92% ee by reaction with borane-methyl sulfide complex (BMS).[12] The methyl sulfide was removed prior to the equilibration. An alternate method of preparing optically pure Ipc_2BH was recently reported by Brown and Singaram.[13] It was discovered that Ipc_2BH, either (+) or (-), separated out in crystalline form from THF and could be purified simply by filtration and washing with THF (Scheme 9).

By utilizing Ipc_2BH of 100% ee and conducting the reactions at -25°C, improved asymmetric inductions were realized in the hydroboration of *cis* alkenes (Scheme 10).[13]

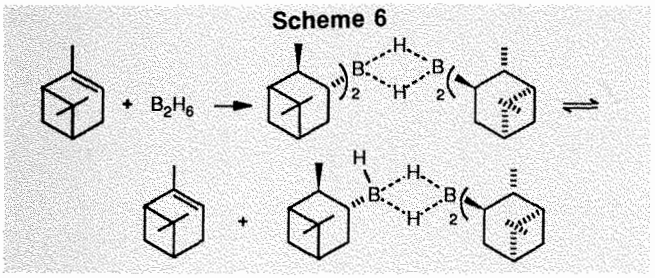
These results could be extended to heterocyclic alkenes as well. The hydroboration of heterocyclic alkenes is both regio- and stereoselective.[14] Thus, the following heterocyclic alcohols were prepared by hydroboration-oxidation of the corresponding alkenes (Scheme 11).

When Ipc_2BH was used for asymmetric hydroboration of other classes of alkenes such as *trans* alkenes, 2-methyl-1-alkenes and trisubstituted alkenes, the optical inductions were poor.[8]

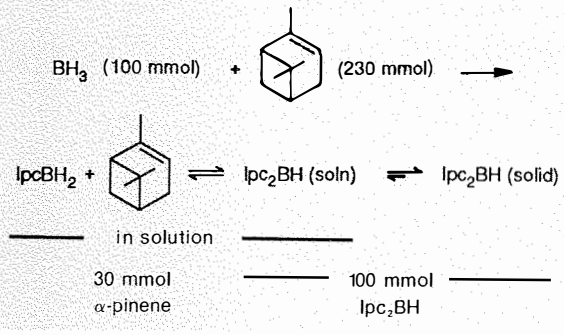
Scheme 5



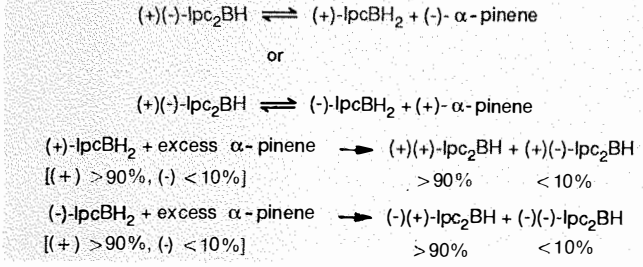
Scheme 6



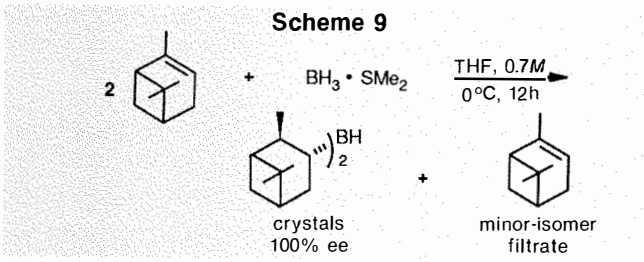
Scheme 7



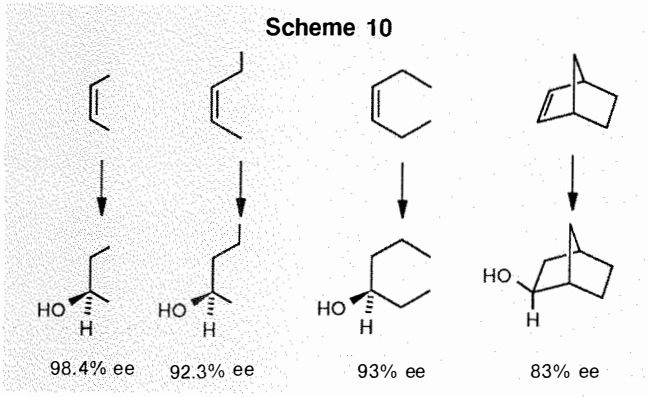
Scheme 8



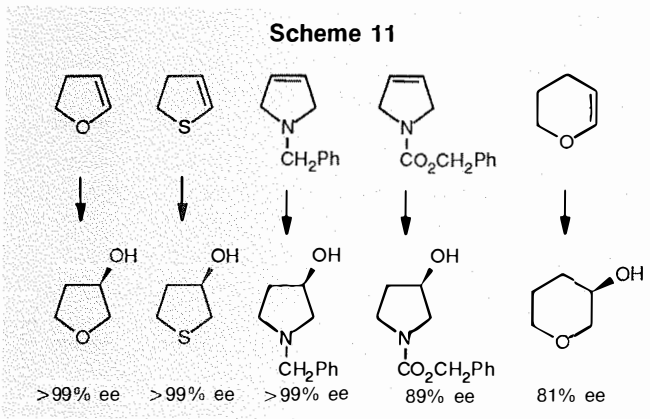
Scheme 9



Scheme 10



Scheme 11



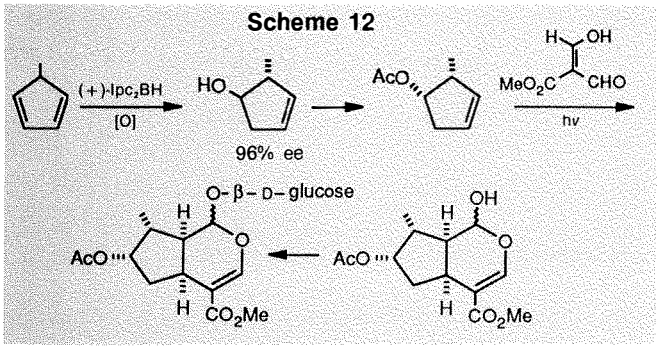
The exceptional ability of Ipc_2BH to hydroborate *cis* alkenes has been used on various occasions in organic synthesis. Using Ipc_2BH, Uskokovic and co-workers achieved an elegant synthesis of loganin[15] (Scheme 12) and Corey's lactone intermediate for prostaglandin synthesis[16] (Scheme 13).

Further examples of the utility of asymmetric hydroboration using Ipc_2BH are the synthesis of $PGF_{2\alpha}$ by Corey and Noyori[17] (Scheme 14) and the synthesis of the carotenoids (3*R*,3′*R*)-zeaxanthin, (3*S*,3′*S*)-zeaxanthin and *meso*-zeaxanthin by Ruttimann and Mayer[18] (Scheme 15).

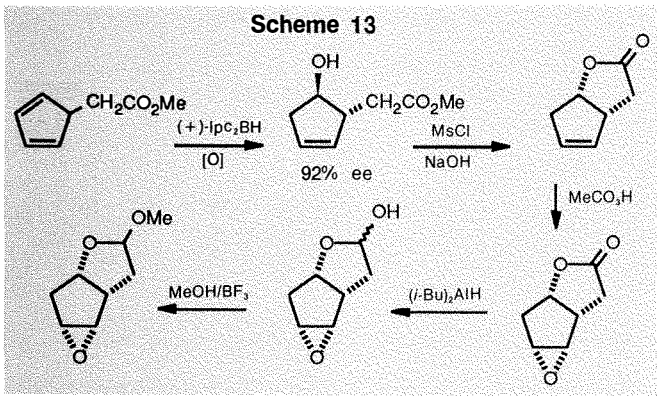
Optically active acetylenes are readily available *via* asymmetric hydroboration[19] (Scheme 16).

An application of this carbon-carbon bond-forming reaction is the synthesis of the sex pheromone of the tea tortrix moth[20] (Scheme 17).

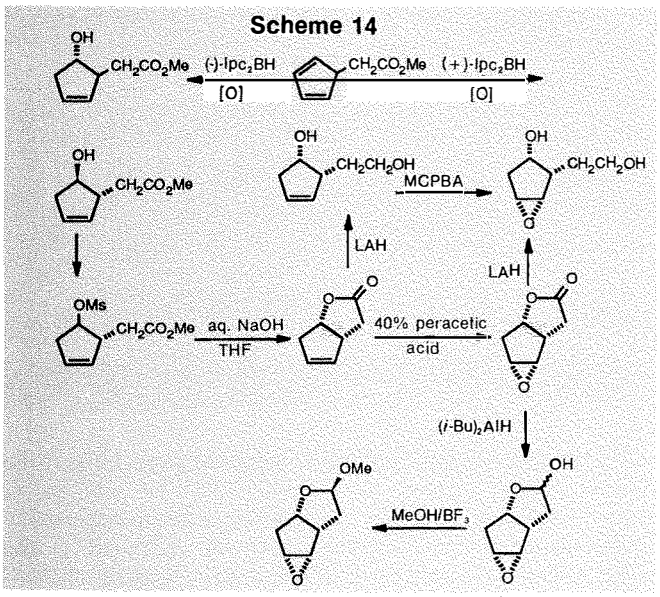
Scheme 12



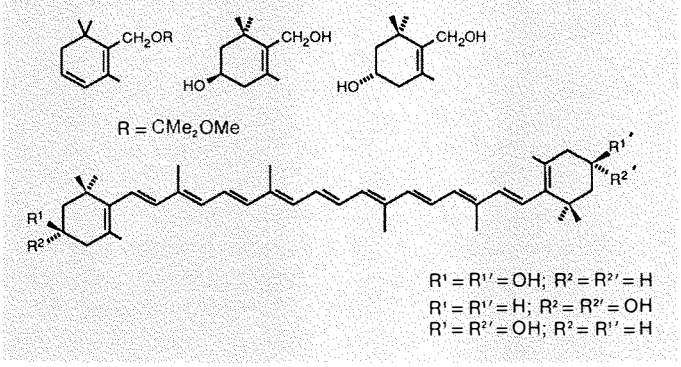
Scheme 13



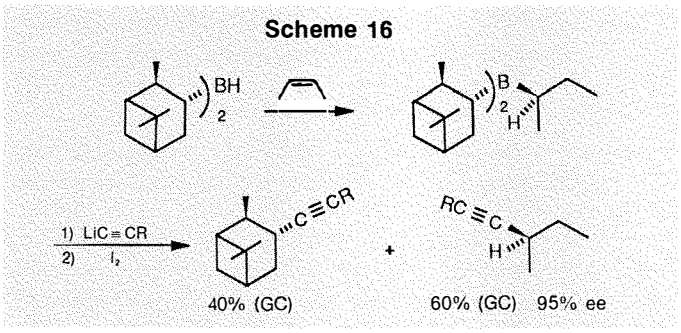
Scheme 14



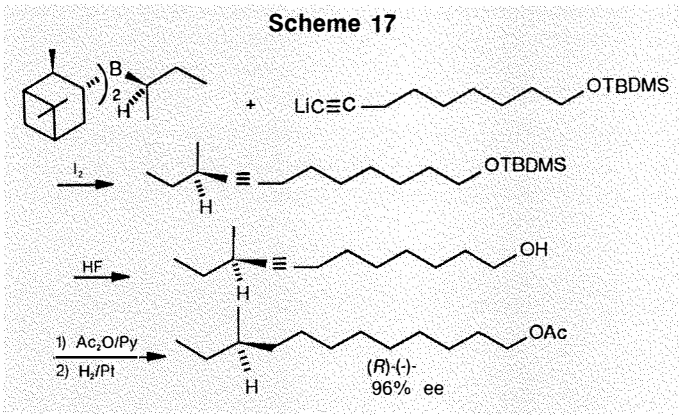
Scheme 15



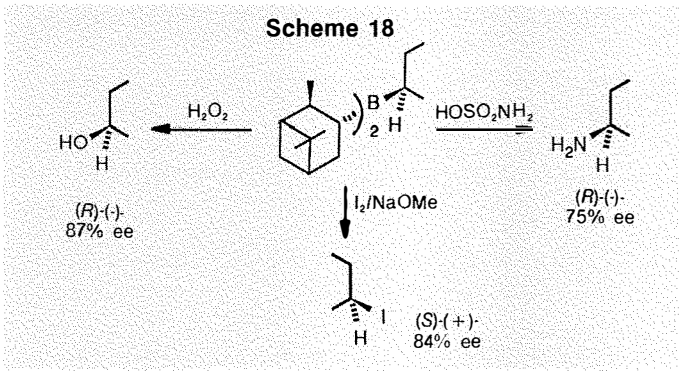
Scheme 16



Scheme 17



Scheme 18



The chiral alkyl groups obtained from the asymmetric hydroboration of *cis* alkenes with Ipc_2BH can be readily transferred to various other functionalities. For example, the chiral intermediate 2-butyldiisopinocampheylborane is readily converted into optically active 2-aminobutane with complete retention of configuration[21] or to 2-iodobutane with complete inversion of configuration[6] (Scheme 18). However, retention is by far the more common process.

B. α-Pinene of high optical purity

The preparation of Ipc_2BH of high enantiomeric excess has enabled the upgrading of commercially available (+)- and (-)-α-pinene to essentially pure material. Thus, essentially optically pure α-pinene [(+) or (-)] can be easily obtained from optically pure Ipc_2BH [(-) or (+)] either by reaction with benzaldehyde at 100°C for 20 hours or by conversion to the trialkylborane followed by reaction with acetaldehyde at room temperature[22] (Scheme 19).

C. Preparation of other chiral boron reagents

Ipc_2BH serves as the primary chiral reagent from which various other chiral reagents have been prepared (Scheme 20). Preparation of these reagents and their uses are discussed in subsequent sections.

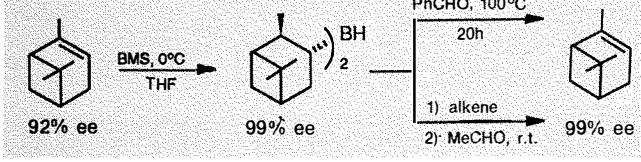
D. Monoisopinocampheylborane ($IpcBH_2$)

Considering the steric requirements of different classes of alkenes, it was envisaged that $IpcBH_2$ would handle classes of alkenes that were more hindered than the *cis* derivatives (Table 1). Ipc_2BH handles only one class effectively.

Hydroboration of α-pinene cannot be stopped at the monoalkylborane stage. Hence $IpcBH_2$ had to be synthesized *via* an indirect route. As in the case of Ipc_2BH, Brown and co-workers developed, over the past decade, various methods of preparing optically pure $IpcBH_2$.[23] The most successful of these is the treatment of Ipc_2BH with one-half equivalent of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) to provide the crystalline $IpcBH_2$•TMEDA complex (Alpine-Boramine™). $IpcBH_2$ can then be conveniently liberated with boron trifluoride etherate (BF_3•Et_2O)[24] (Scheme 21). As with Ipc_2BH, either optical isomer of $IpcBH_2$ is readily available from either (+)- or (-)-α-pinene.

$IpcBH_2$ has been found to be a useful reagent for the asymmetric hydroboration of *trans* alkenes[25] (Scheme 22) and trisubstituted alkenes[26] (Scheme 23). The reactions were carried out at -25°C in THF.

Scheme 19



Scheme 20

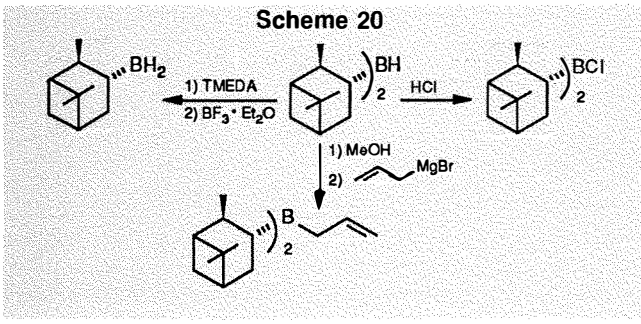
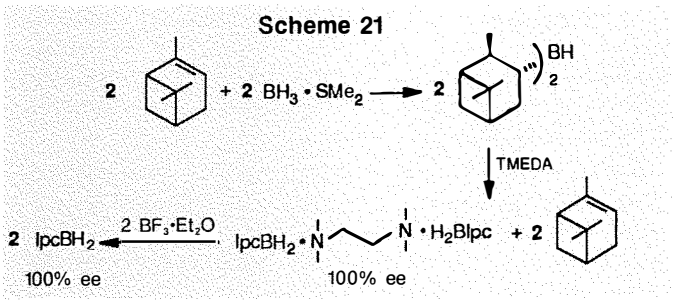


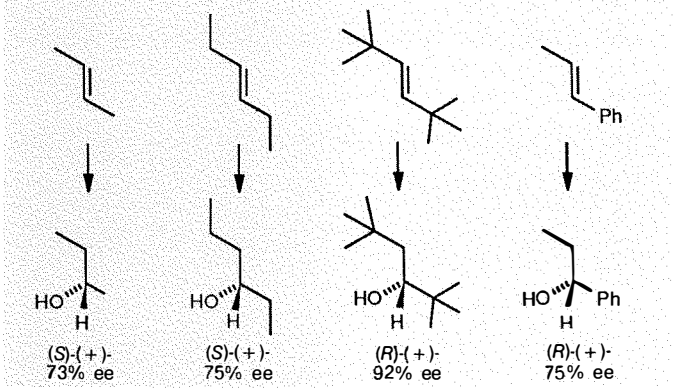
Table 1

	Class	% ee
Increasing steric requirements ↓	2-Methyl-1-alkenes	~20
	cis-Alkenes	~100
	trans-Alkenes	~20
	Trisubstituted alkenes	~20

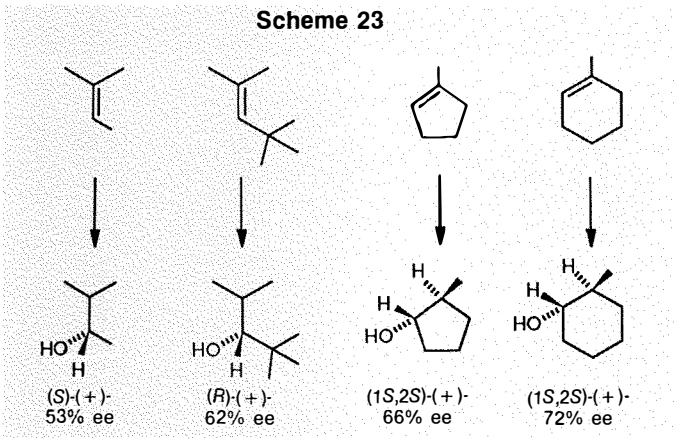
Scheme 21



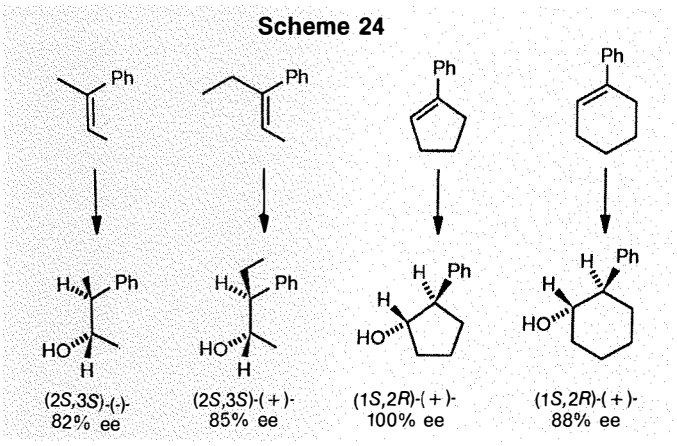
Scheme 22



Scheme 23



Scheme 24



These results suggested that increasing the steric bulk of the alkenes might improve the optical induction realized in hydroborations with $IpcBH_2$. Accordingly, a match between the alkene and the hydroborating agent was achieved in the hydroboration of phenyl trisubstituted alkenes (Scheme 24).[27]

However, superior results have now been obtained by the technique of recrystallization of the dialkylboranes (*vide infra*). Thus, Ipc_2BH and $IpcBH_2$ are complementary to each other and together handle three of the four classes of alkenes with good to excellent asymmetric induction (Table 2). A reagent for the fourth class of alkenes, 2-methyl-1-alkenes, has yet to be synthesized.

E. Dilongifolylborane (Lgf_2BH)

Ipc_2BH and $IpcBH_2$ were the only two chiral hydroborating agents known prior to 1981. Brown and Jadhav studied the synthesis and utility of various other chiral hydroborating agents using terpenes like longifolene and limonene as the chiral auxiliary. The results of hydroboration-oxidation of representative alkenes with Lgf_2BH indicated that it behaved similarly to $IpcBH_2$[28] (Tables 3 and 4). Recently, in a procedure similar to the preparation of Ipc_2BH, Lgf_2BH was crystallized from THF in optically pure form[29] (Scheme 25).

F. Limonylborane (LimBH)

This was the first boraheterocydane to be studied as a chiral hydroborating agent. The reagent was synthesized by hydroborating limonene with chloroborane etherate followed by hydridation using lithium aluminum hydride[30] (Scheme 26).

Hydroboration-oxidation of representative alkenes with limonylborane gave inferior results[30] (Table 5).

Table 2
Scope of Applicability of Ipc_2BH and $IpcBH_2$

	Class	Ipc_2BH (% ee)	$IpcBH_2$ (% ee)
Increasing steric requirements ↓	2-Methyl-1-alkenes	~20	~1
	cis-Alkenes	~100	~25
	trans-Alkenes	~20	70-90
	Trisubstituted alkenes	~20	60-100

Table 3
Asymmetric Hydroboration of Representative Examples Selected from Four Major Classes of Alkenes with Lgf_2BH

Alkene	Alcohol	% ee	Configuration
2-Methyl-1-butene[a]	2-Methyl-1-butanol	1	*S*
cis-2-Butene[a]	2-Butanol	78	*R*
trans-2-Butene[a]	2-Butanol	25	*S*
2-Methyl-2-butene[b]	3-Methyl-2-butanol	70	*R*

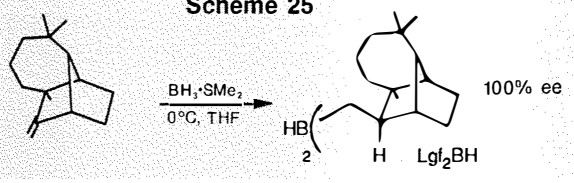
[a]Reactions were carried out at 20°C in THF.
[b]Reaction was carried out at 30°C in THF.

Table 4
Asymmetric Hydroboration of cis-Alkenes with Lgf_2BH

Alkene	Alcohol	% ee	Configuration
cis-2-Butene[a]	2-Butanol	78	*R*
cis-3-Hexene[a]	3-Hexanol	71	*R*
cis-4,4-Dimethyl-2-pentene[b]	4,4-Dimethyl-2-pentanol (99%) 2,2-Dimethyl-3-pentanol (1%)	59	*R*
cis-1-Phenyl-1-propene[b]	1-Phenyl-1-propanol	61	*S*

[a]Reactions were carried out at 20°C in THF.
[b]Reactions were carried out at 35°C in THF.

Scheme 25



Scheme 26

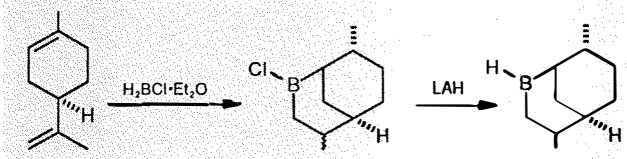


Table 5
Asymmetric Hydroboration of Representative Examples Selected from Four Classes of Alkenes with LimBH

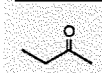
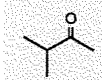
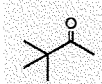
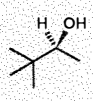
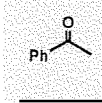
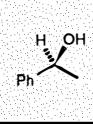
Alkene	Alcohol	% ee	Configuration
2-Methyl-1-butene[a]	2-Methyl-1-butanol	5.2	*R*
cis-2-Butene[a]	2-Butanol	55.0	*R*
trans-2-Butene[a]	2-Butanol	58.6	*R*
2-Methyl-2-butene[a]	3-Methyl-2-butanol	66.5	*R*
1-Methylcyclopentene[b]	*trans*-2-Methylcyclopentanol	45.0	*1R,2R*

[a]Reactions were carried out at -25°C in Et_2O.
[b]Reaction was carried out at 0°C in Et_2O and also in THF.

III. ASYMMETRIC REDUCTIONS

Although Ipc_2BH and $IpcBH_2$ are good chiral hydroborating reagents, they are poorly suited for use as chiral reducing agents for prochiral ketones[31,32] (Table 6).

Table 6
Asymmetric Reduction of Representative Ketones with (-)-Ipc_2BH and (-)-$IpcBH_2$

		(-)-Ipc_2BH		(-)-$IpcBH_2$	
Ketone	Alcohol	% ee	Config.	% ee	Config.
		13.4	*S*	22	*S*
		37	*S*	46	*S*
		20	*S*	21	*S*
		9	*R*	15	*S*

(-)-Ipc_2BH and (-)-$IpcBH_2$ of ~100% ee are prepared from (+)-α-pinene, $[\alpha]_D$ +48.1°, 94% ee

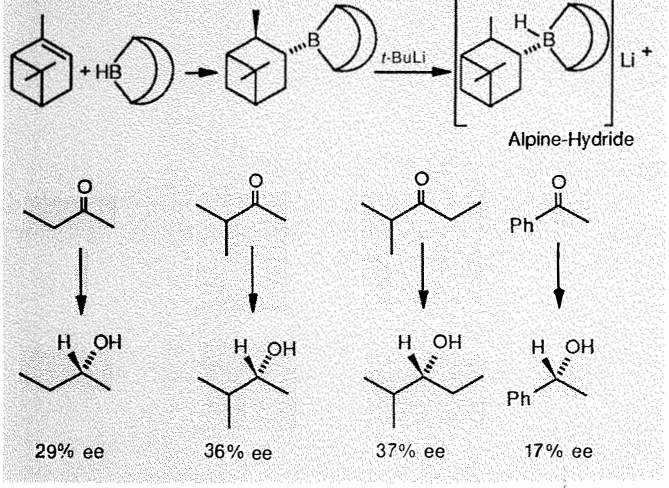
Another chiral reducing agent derived from α-pinene, lithium *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane hydride (Alpine-Hydride®), also proved ineffective in transferring chirality to the product alcohols[33] (Scheme 27).

In 1978, Midland and co-workers discovered that *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (*R*-Alpine-Borane®) reduced deuteroaldehydes and acetylenic ketones to alcohols of exceptionally high optical purity[34] (Scheme 28).

Unfortunately, Alpine-Borane proved to be unsatisfactory for the reduction of aliphatic or aralkyl ketones under the conditions originally developed by Midland. As was diagnosed much later, the poor optical induction achieved in the reduction of less reactive ketones by Alpine-Borane is due to a side reaction caused by an achiral reduction of the substrate by 9-BBN formed *via* a slow unimolecular dissociation of Alpine-Borane.[35] With reactive carbonyl compounds such as aldehydes and α,β-acetylenic ketones, Alpine-Borane reacts directly presumably *via* a six-membered cyclic transition state (Table 7), to give the chiral alcohol products. With less reactive ketones such as acetophenone, the dissociative side reaction predominates (Scheme 29).

However, Brown and Pai discovered that conducting the reactions under neat conditions not only increased the rate of the reaction but improved the optical purity of the alcohols considerably by suppressing the dehydroboration[36] (Scheme 30).

Scheme 27



Scheme 28

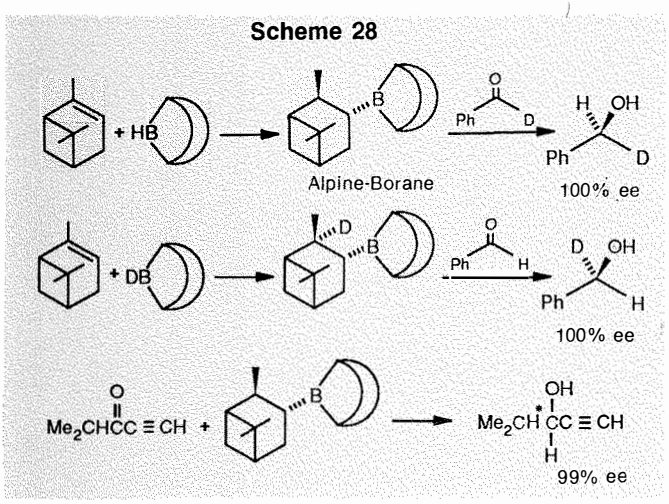
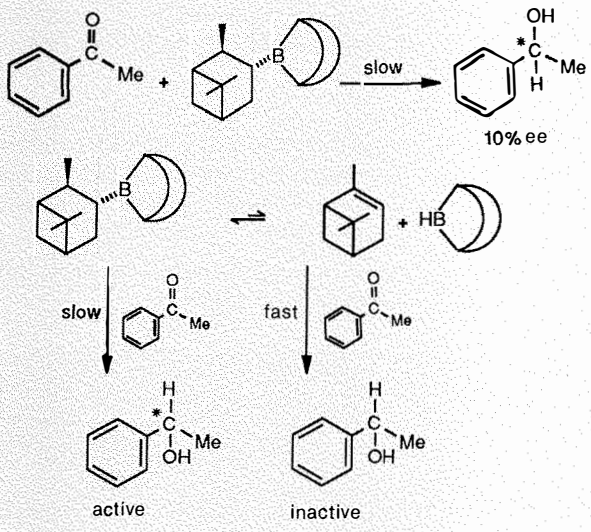
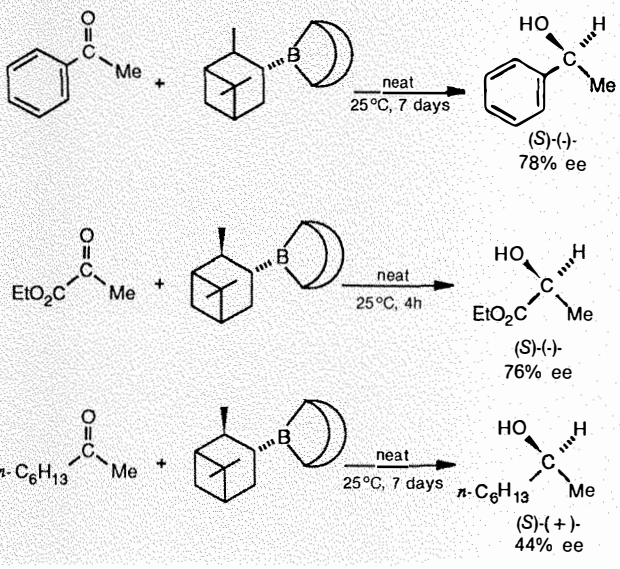


Table 7
Proposed Cyclic Boat-Like Transition State for Reductions with *R*-Alpine-Borane

Scheme 29



Scheme 30

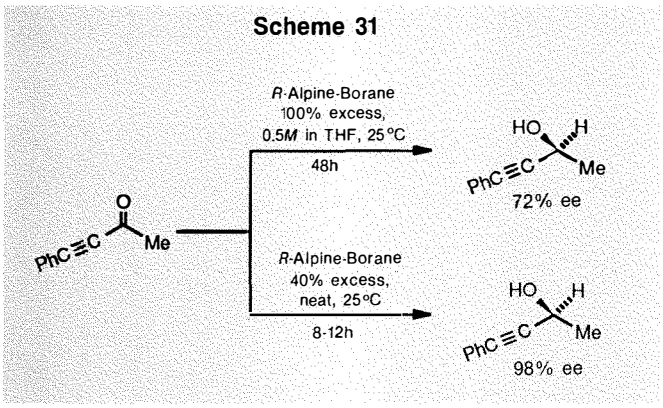


Utilizing these new neat conditions, various classes of ketones were reduced using Alpine-Borane. The reagent has proven particularly efficient for the chiral reduction of acetylenic ketones (Scheme 31), α-keto esters (Scheme 32) and halo-ketones[36] (Scheme 33).

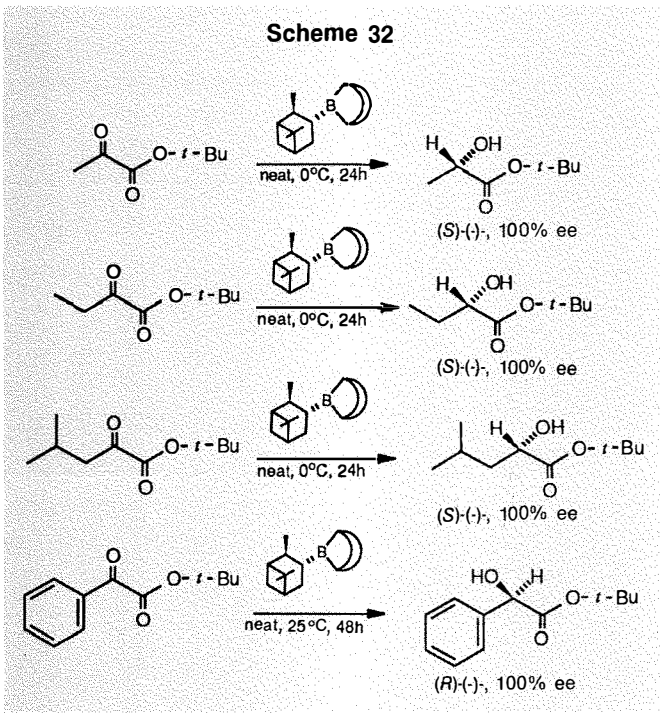
The use of Alpine-Borane has increased in organic synthesis. Representative examples are the syntheses of Japanulore[37] (Scheme 34) and a corticosteroid intermediate[38] (Scheme 35).

Recently, Brown and co-workers synthesized a modified borohydride reagent, potassium 9-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane (K-9-*O*-DIPGF-9-BBNH) derived from α-D-glucofuranose, as the chiral auxiliary[39] (Scheme 36).

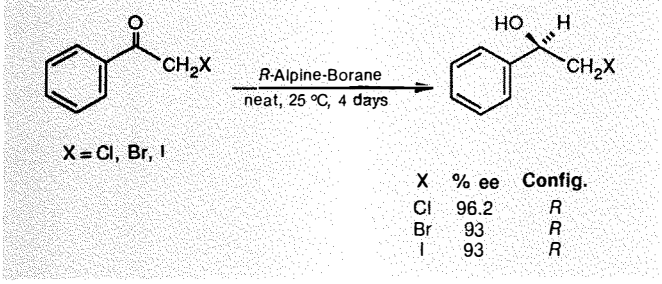
Scheme 31



Scheme 32

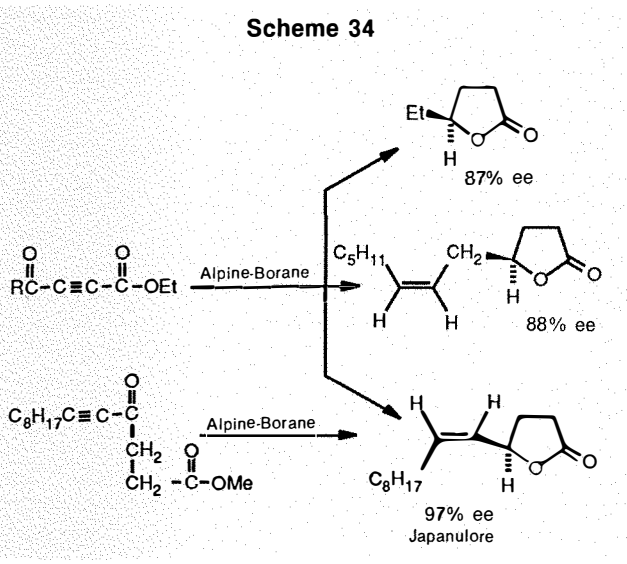


Scheme 33

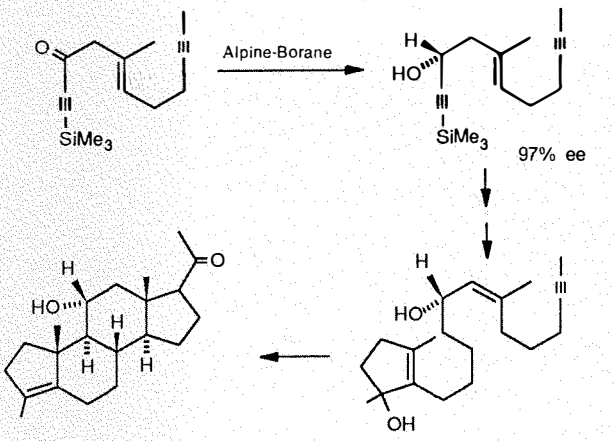


X	% ee	Config.
Cl	96.2	*R*
Br	93	*R*
I	93	*R*

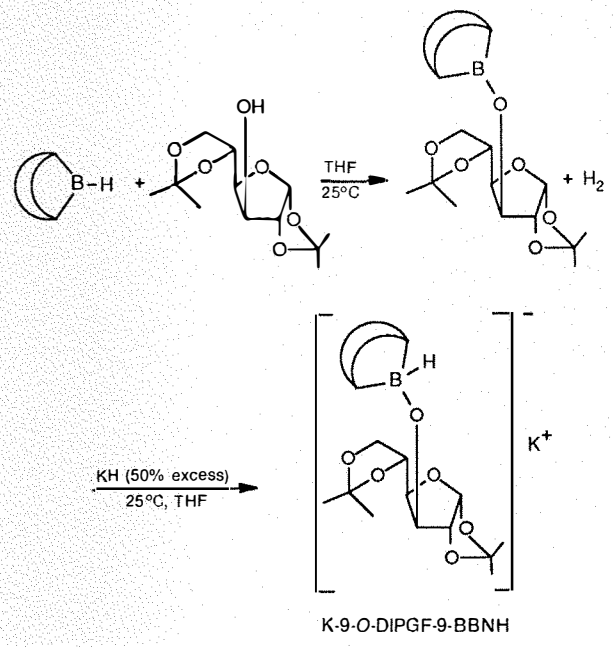
Scheme 34



Scheme 35



Scheme 36



This reagent reduces aralkyl ketones (Table 8) and aliphatic ketones (Table 9) with good to excellent optical inductions.[39] α-Keto esters (Table 10) are reduced to the corresponding alcohols with excellent optical purity.[40]

In an entirely different approach, the effect of changing the electronic environment of the reducing agent by placing a chlorine atom on boron was investigated. This reagent, Ipc_2BCl (patent applied for), has proven to be an excellent chiral reducing agent, exhibiting a much superior rate of reduction and optical induction for aralkyl ketones[41] (Table 11) and α-tertiary alkyl ketones[42] (Table 12). The easy method of preparation, mild reaction conditions and simple workup procedure make Ipc_2BCl the most practical chiral reducing agent for these types of ketones[41,42] (Scheme 37).

In addition, Ipc_2BCl reduces aryl ω-chloroalkyl ketones to the corresponding chloroalcohols in exceptionally high ee. These chloroalcohols can be readily converted to epoxides and cyclic ethers with complete retention of optical purity.[43a] These cyclic ethers are of potential importance in the synthesis of biologically active compounds and pharmaceuticals[43b] (Scheme 38).

Table 8
Aralkyl Ketones Reduced with K-9-*O*-DIPGF-9-BBNH at -78°C

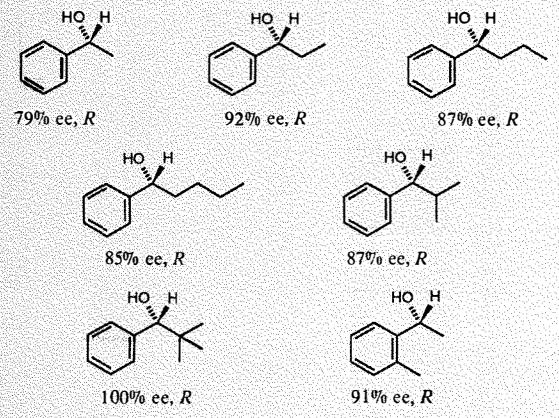


Table 9
Aliphatic Ketones Reduced with K-9-*O*-DIPGF-9-BBNH in THF at -78°C

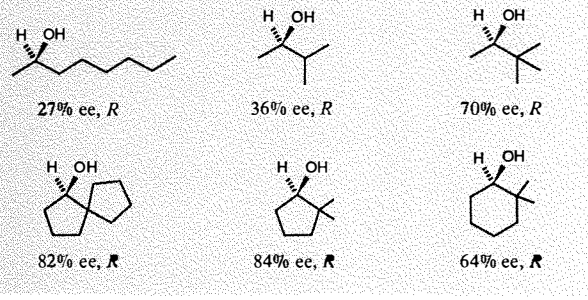


Table 10
α- Keto Esters Reduced with K-9-*O*-DIPGF-9-BBNH in THF at -78°C

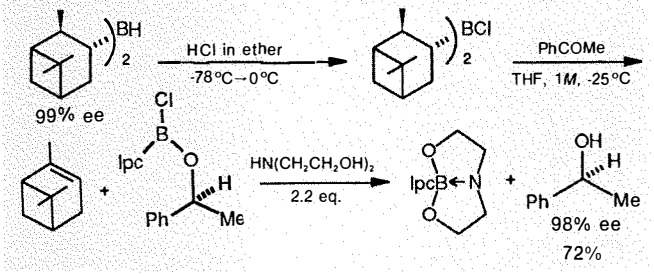
α-Keto ester	Time (h)	Yield (%)	% ee	Absolute configuration
Ethyl pyruvate	6	75	86	*S*
Ethyl 2-oxobutanoate	6	80	92	*S*
Ethyl 2-oxopentanoate	6	81	94	*S*
Methyl 3-methyl-2-oxobutanoate	8	83	98	*S*
Ethyl 3-methyl-2-oxobutanoate	8	85	97	*S*
Methyl 3,3-dimethyl-2-oxobutanoate	10	85	97	*S*
Ethyl 3,3-dimethyl-2-oxobutanoate	10	87	98	*S*
Ethyl 4-methyl-2-oxopentanoate	6	83	93	*S*
Methyl benzoylformate	10	85	92	*S*
Ethyl benzoylformate	10	80	94	*S*
Isopropyl benzoylformate	10	83	93	*S*
Ethyl α-oxo-1-naphthaleneacetate	10	78	96	*S*

Table 11
Aralkyl Ketones Reduced with (-)-Ipc_2BCl in THF at -25°C

Ketone	% ee	Product configuration
Acetophenone	98	*S*
2'-Acetonaphthone	98	*S*
3-Acetylpyridine	92	*S*
2-Acetylthiophene	91	*S*
Indanone	97	*S*
Propiophenone	98	*S*
Butyrophenone	98	*S*
Isobutyrophenone	78	*S*
Phenyl *t*-butyl ketone[a]	79	*R*

[a] Reaction was carried out at 25°C.

Scheme 37



Scheme 38

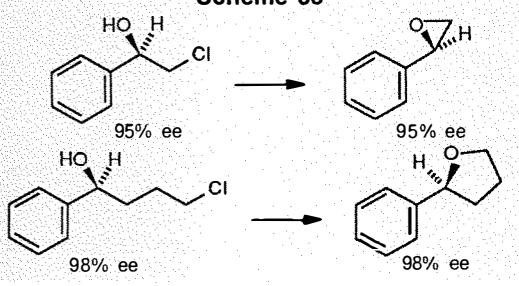
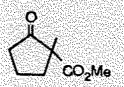
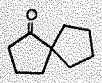


Table 12
Asymmetric Reduction of Hindered Aliphatic Ketones with (-)-Ipc_2BCl at 25°C

Ketone	% ee	Ketone	% ee
	95 (*S*)		91 (*S*)
	82 (*S*)		93[a]
	98 (*S*)[b]		89 (1*S*,2*S*)
	95 (*S*)		

[a] 96% ee for reaction at -25°C
[b] Based on analogy with reduction of spiro[4.4]nonan-1-one

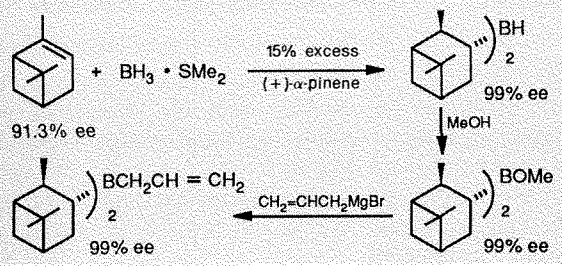
It is reasonable to assume that further modification, both electronic and steric, of these reagents will produce new chiral reducing reagents for the efficient chiral reduction of hitherto inaccessible ketones.[44]

IV. ALLYLBORATION

The allylboration of aldehydes with allyldiorganylboranes is a powerful and convenient method for the preparation of homoallylic alcohols.[45-56] The work of Hoffmann and co-workers,[46] and modifications by Roush,[47] have led to the development of a number of methodologies for the asymmetric version of this reaction based on allylboronic esters. Midland has prepared α-chiral allylborinic esters and found them to undergo typical allylborane reactions with aldehydes.[48] Brown and co-workers have prepared a series of chiral allyldiisopinocampheylboranes for use in asymmetric allylboration reactions. For example, *B*-allyldiisopinocampheylborane[49] was readily prepared from *B*-methoxydiisopinocampheylborane by treatment with allylmagnesium bromide (Scheme 39). *B*-Allyldiisopinocampheylborane reacts rapidly with aldehydes, even at -78 °C. Accordingly, the treatment of an appropriate aldehyde at -78 °C followed by workup provides the homoallylic alcohols in high ee (Table 13).

The allylboration reaction has been postulated to proceed *via* a cyclic six-membered transition state. In an attempt to gain further insight into the subtleties of this reaction, additional chiral allyldialkylboranes were prepared from (+)-limonene, (-)-β-pinene, (+)-longifolene, (-)-10-methyl-α-pinene and (+)-Δ^3-carene (Table 14) in a manner analogous to the preparation of *B*-allyldiisopinocampheylborane.[50]

Scheme 39



These chiral allyldialkylboranes were condensed with acetaldehyde and the product of the reaction, 4-penten-2-ol, analyzed for the optical activity[50] (Table 15).

Table 13
Chiral Allylboration Applicable to Various Aldehydes

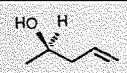
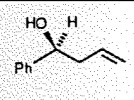
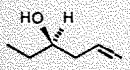
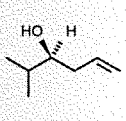
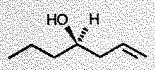
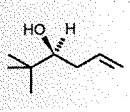
% ee		% ee
	93	 96
	86	 90
	87	 83

Table 14


(+)-limonene


(-)-β-pinene


(+)-longifolene


(+)-α-pinene


(-)-10-methyl-α-pinene


(+)-3-carene

Table 15
Allylboration of Acetaldehyde with Chiral *B*-Allyldialkylboranes

	4-Penten-2-ol		
$R_2BCH_2CH=CH_2$ (±; terpene rotation)	% Yield (isolated)	% ee	Configuration
B-Allyllimonylborane (+)	72	7	*R*
B-Allyldi-10-pinanylborane (-)	65	11	*S*
B-Allyldilongifolylborane (+)	67	34	*S*
B-Allyldiisopinocampheylborane (+)	74	93	*R*
B-Allyldi(10-methylisopinocampheyl)borane (-)	72	93 (99)[a]	*S*
B-Allyldicaranylborane (+)	72	99	*R*

[a] Corrected for optical purity of the chiral auxiliary

Allyldicaranylborane proved to be particularly promising. Accordingly, this reagent was explored with a representative selection of aldehydes[49] (Table 16).

Clearly, allylboration of these aldehydes with allyldicaranylborane, as can be seen from Table 16, is highly effective, furnishing the corresponding homoallylic alcohols in high enantiomeric excess.

Allylboration with substituted allyldialkylboranes should similarly furnish appropriately substituted homoallylic alcohols. Thus, methallyldiisopinocampheylborane, prepared from methallyllithium and Ipc_2BOMe (Scheme 40), reacted with acetaldehyde to give 4-methyl-4-penten-2-ol in 90% ee.[51] Additional examples reveal that methallylboration is an efficient process for obtaining the corresponding homoallylic alcohols in high ee (Table 17).

Success with methallylboration prompted Brown and coworkers to apply the reaction sequence to other substituted derivatives, $H_2C=C(R)CH_2Blpc_2$. For example, 3,3-dimethylallyldiisopinocampheylborane, readily obtained by hydroboration of 3-methyl-1,2-butadiene, has proven to be a very versatile reagent for the asymmetric isoprenylation of various aldehydes.[52] Condensation of 3,3-dimethylallyldiisopinocampheylborane with 3-methyl-2-butenal followed by oxidative workup provided (+)-artemisia alcohol in 95% ee[52] (Scheme 41). Additional examples of this useful isoprenylation sequence are listed in Table 18. This isoprenylation appears to be broadly applicable, with high ee achieved for a broad range of aldehydes, except in the case of pivaldehyde.

Table 16
Chiral Allylboration with Allyldicaranyborane

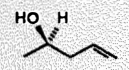
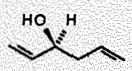
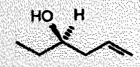
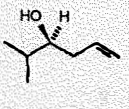
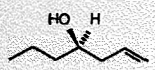
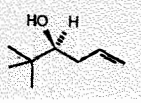
% ee		% ee
	99	 86
	91	 97
	89	 88

Table 17
Chiral Methallylboration Applicable to Various Aldehydes

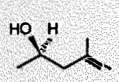
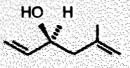
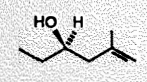
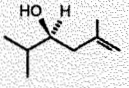
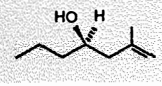
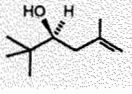
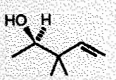
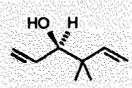
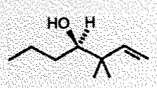
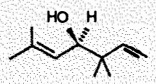
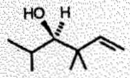
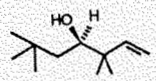
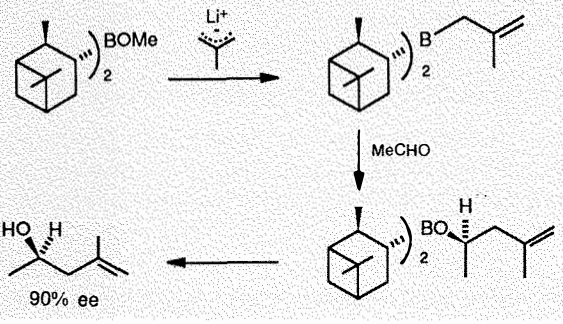
% ee		% ee
	90	 92
	85	 96
	91	 91

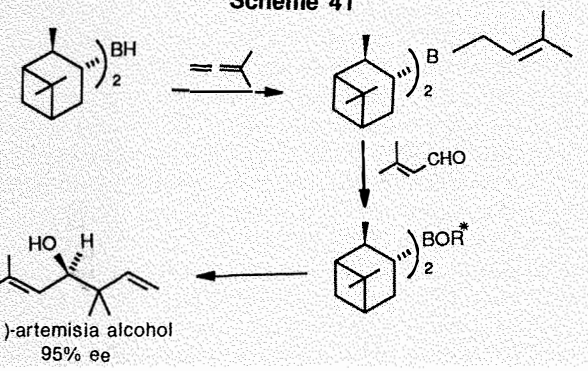
Table 18
Condensation of Aldehydes with 3,3-Dimethylallyldiisopinocampheylborane

% ee		% ee
	91	 95
	92	 96
	89	 67

Scheme 40



Scheme 41



In addition to excellent optical induction, high diastereoselectivity has been achieved in the allylboration of *B*-2-cyclohexene-1-yl-diisopinocampheylborane [derived from either (+)- or (-)-α-pinene and 1,3-cyclohexadiene] with acetaldehyde.[53] Removal of the Ipc_2B-O moiety with ethanolamine provides 1-(2-cyclohexen-1-yl)ethanol in 100% erythro selectivity and 94% ee (Scheme 42). In a similar manner, high diastereoselectivity is realized in the condensation of (*Z*)-(3-methoxyallyl)diisopinocampheylborane with acetaldehyde[54] (Scheme 43).

Other acyclic 1,2-diol derivatives can also be obtained with excellent diastereoselectivities.

The synthesis of all four possible stereoisomers of β-methylhomoallylic alcohols has been recently reported by Brown and co-workers. Starting from geometrically defined (*E*)- and (*Z*)-crotylpotassium, the corresponding (*E*)- and (*Z*)-*B*-crotyldiisopinocampheylborane derivatives [(+)- and (-)-] were prepared[55] (Scheme 44).

Condensation of these four reagents with acetaldehyde furnishes the four stereoisomers of 3-methyl-4-penten-2-ol (Scheme 45). The addition of the crotyl groups proceeds with 100% diastereoselectivity.

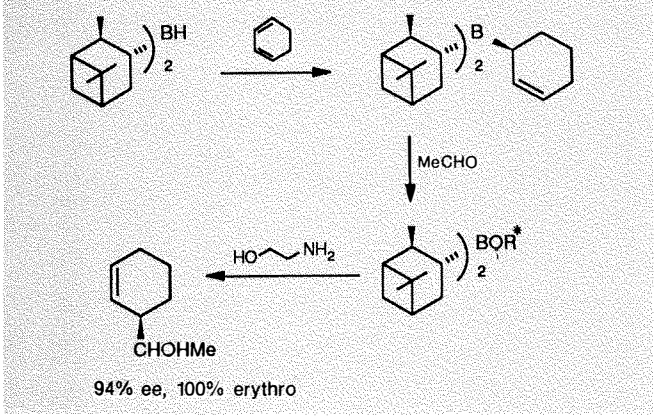
More recently, (+)- and (-)-*B*-allyldiisopinocampheylborane have been reacted with α-substituted chiral aldehydes to yield the enantiomeric *syn* and *anti* homoallylic alcohols in high optical activities[56] (Scheme 46).

The stereochemistry of the newly formed chiral center is controlled by selecting the appropriate enantiomeric reagent, (+)- or (-)-*B*-allyldiisopinocampheylborane. The chirality of the reagent dictates the overall diastereofacial selectivity of the reaction. These results indicate that *B*-allyldiisopinocampheylborane derivatives are not only the most enantioselective, but also the most diastereoselective agents available for allylboration.

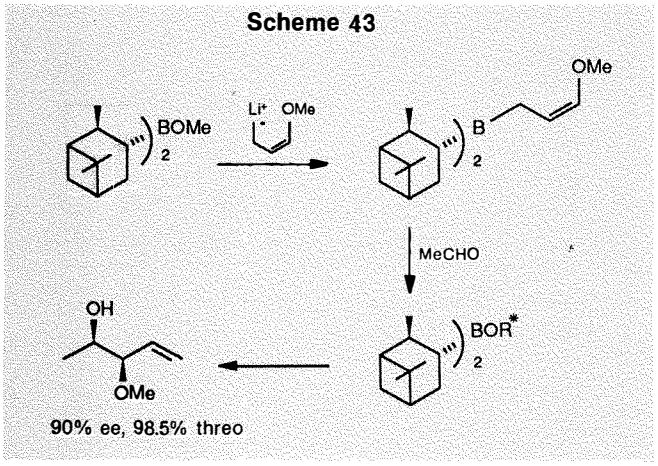
V. BORONIC ESTERS

Since the alkyl group on boron is most efficiently utilized in transformations with boronic esters, these esters have emerged as important organoborane intermediates in asymmetric synthesis. Of particular importance is the facile formation of carbon-carbon bonds. Accordingly, much effort has been devoted to developing new methodologies for preparing optically pure boronic esters.[57] Previously, it had been observed that the products of hydroboration of alkenes with Ipc_2BH and $IpcBH_2$ were often solids. It was then discovered that simple crystallization provides products of essentially 100% optical purity[58] (Scheme 47).

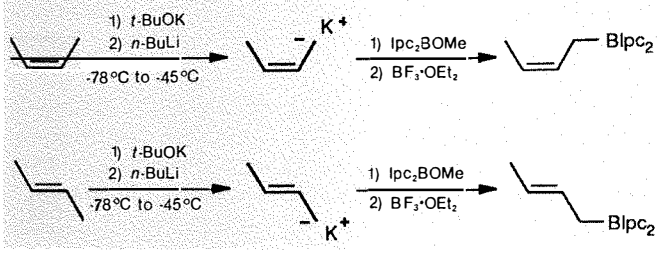
Scheme 42



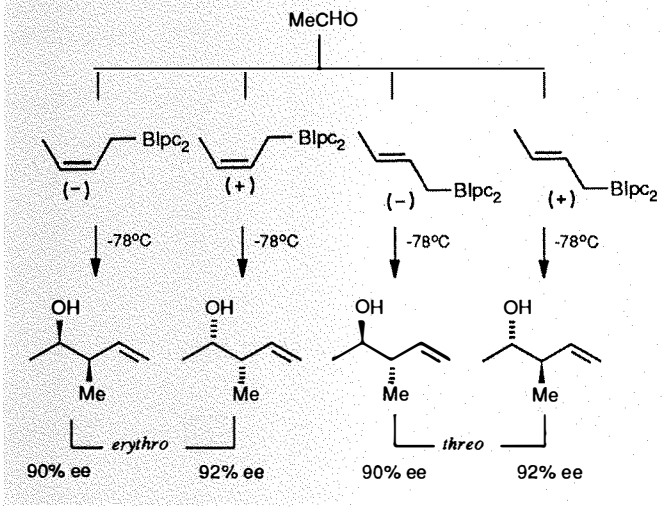
Scheme 43



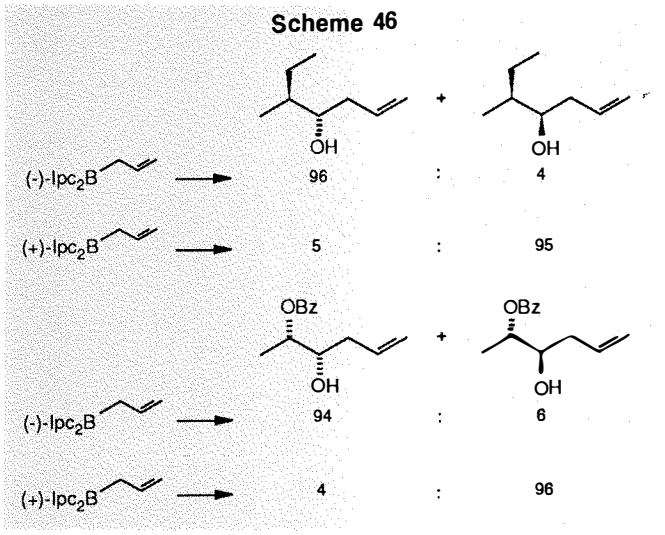
Scheme 44



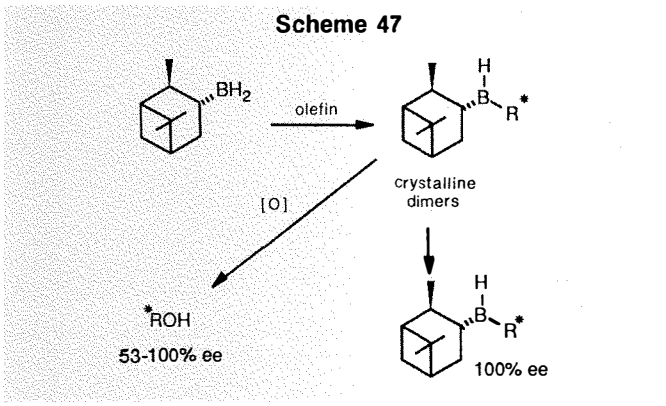
Scheme 45



Scheme 46



Scheme 47



Therefore, it is now possible to obtain the initial hydroboration products, IpcR*BH and the derived boronic esters [R*B(OR)$_2$], in essentially 100% ee[58,59] (Table 19). Heterocyclic boronic esters can be obtained similarly in high optical purity[14] (Table 20).

An alternative approach for obtaining optically pure boronic esters consists of treating the boronic esters prepared *via* asymmetric hydroboration with a chelating agent to furnish crystalline material. This is then recrystallized to yield the boronic ester derivatives in essentially optically pure form.[60] Thus, the chelate derived from diethyl 3-tetrahydropyranylborate of 83% ee and *N,N,N',N'*-tetrakis(2-hydroxyethyl)ethylenediamine upon recrystallization yields a product with optical purities approaching 100% ee. The optically pure boronic acid is then liberated with dilute HCl (Scheme 48).

Table 19
Representative Boronic Esters of Essentially 100% ee

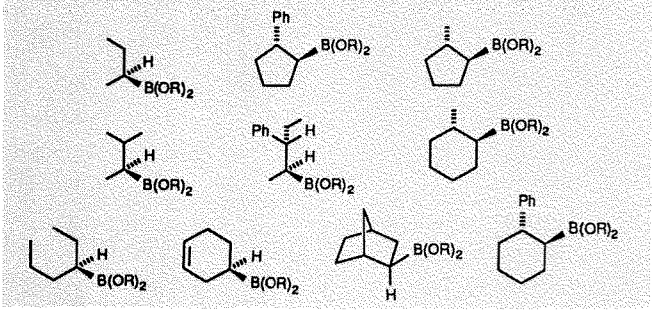
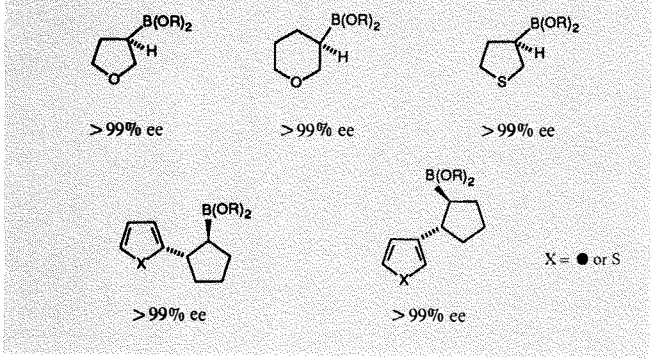
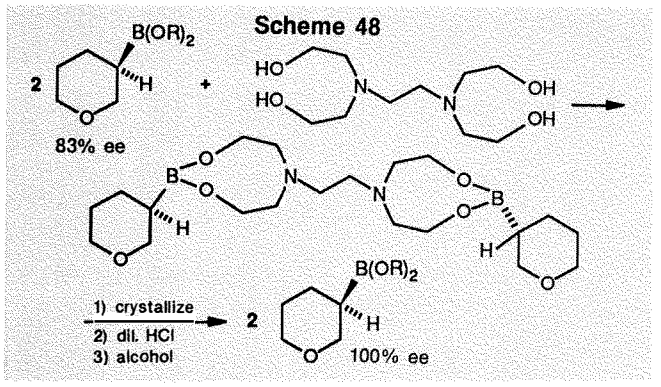


Table 20
Representative Heterocyclic Chiral Boronic Esters of High Optical Purity



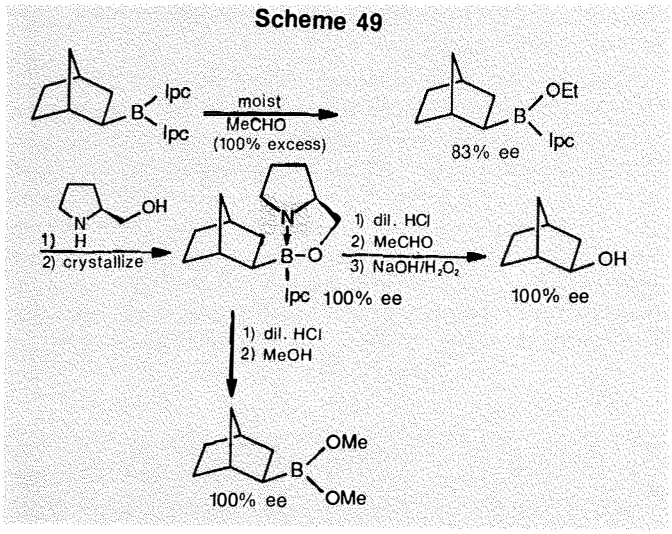
Scheme 48



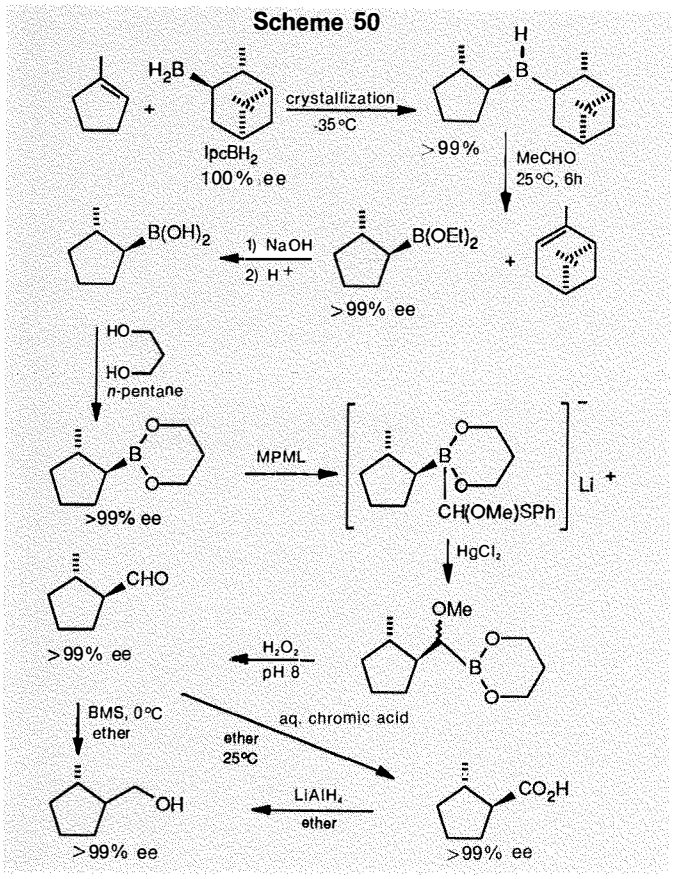
This method of optical upgrading can also be applied to borinic esters. Thus, norbornene, upon hydroboration with Ipc$_2$BH, produced a product of 83% ee. This trialkylborane, *exo*-norbornyldiisopinocampheylborane, eliminates one α-pinene moiety upon treatment with moist acetaldehyde. Treatment of the boronate [derived from (-)-α-pinene] with *S*-(+)-2-pyrrolidinemethanol forms a chelate which upon recrystallization from pentane-methanol yields the chelated borinic ester in essentially 100% ee (Scheme 49). The optically pure boronic ester can then be obtained by standard methods.

There is an ever-increasing number of reactions which can be applied to boronic esters. For instance, treatment of 2-alkyl-1,3,2-dioxaborinanes with methoxy(phenylthio)methyllithium (MPML) followed by $HgCl_2$ furnished the homologated α-methoxyalkyl derivatives which, upon oxidation with hydrogen peroxide in a pH 8 phosphate buffer, were smoothly converted into the corresponding aldehydes[61] (Scheme 50).

Scheme 49



Scheme 50



Using the above methodology, representative α-chiral aldehydes were prepared in essentially 100% ee (Table 21).

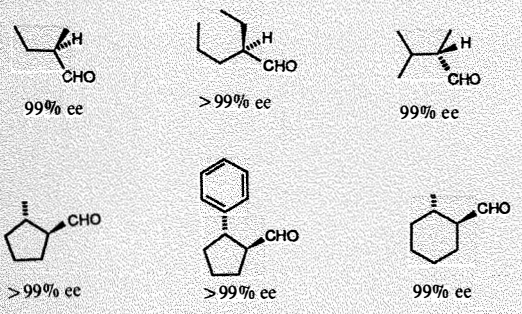
These aldehydes could then be reduced with BMS to the corresponding β-chiral alcohols or oxidized to the optically pure carboxylic acids with aqueous chromic acid (Scheme 51).

Terminal disubstituted alkenes cannot be hydroborated in high ee with either Ipc_2BH or $IpcBH_2$. However, the products of indirect hydroboration of terminal alkenes can now be obtained *via* homologation of chirally pure boronic esters using Matteson's homologation procedure.[57] Treatment of 2-alkyl-1,3,2-dioxaborinanes with dichloromethyllithium followed by reduction with potassium triisopropoxyborohydride (KIPBH) cleanly yields the homologated boronic esters. Utilizing this procedure, Brown and co-workers prepared a series of β-chiral boronic esters in very high optical purities[62] (Scheme 52).

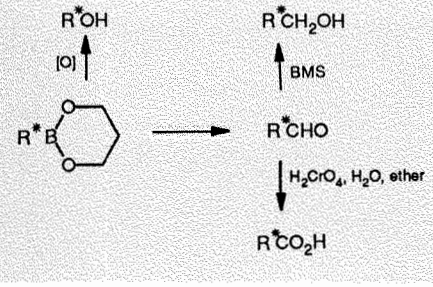
Upon oxidation, these chiral homologated boronic esters provide the corresponding chiral alcohols previously unobtainable by direct asymmetric hydroboration, in high optical purities. The homologation procedure can be repeated to produce $R^*CH_2CH_2B(OR)_2$. Utilizing known transformations, the latter can be converted into a multitude of useful products in essentially 100% ee (Scheme 53).

Optically pure boronic esters have been converted into amines with complete retention of optical activity.[63] A general method for obtaining these amines involves treatment of the optically pure boronic esters with methyllithium followed by quenching with acetyl chloride to give the borinates. The latter, upon treatment with two equivalents of hydroxylamine-*O*-sulfonic acid followed by alkaline hydrolysis, were converted to amines in high chemical yields and in essentially optically pure form (Scheme 54). In this procedure the methyl group was found to have low migratory aptitude.

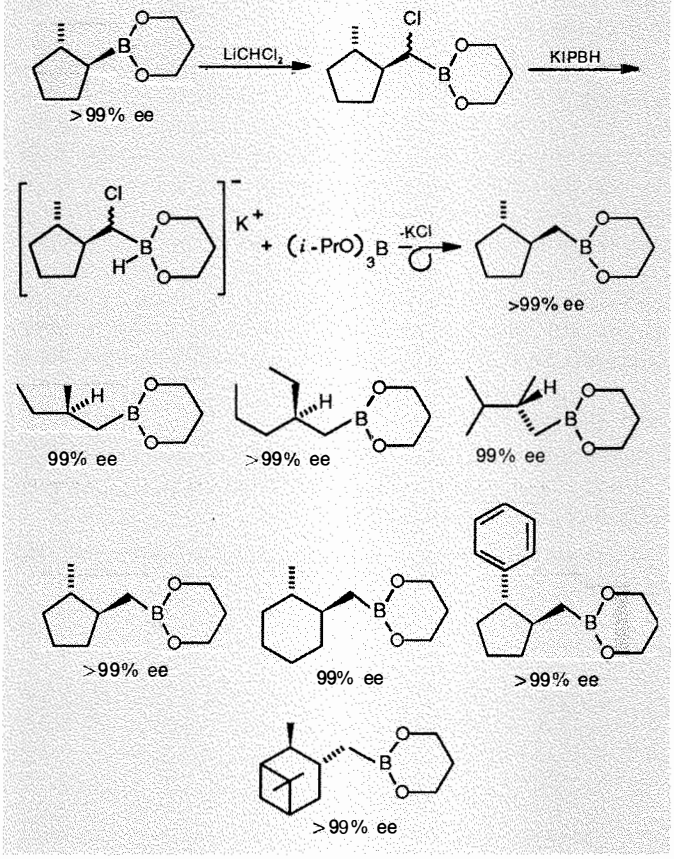
Table 21
Representative α-Chiral Aldehydes of Essentially 100% ee



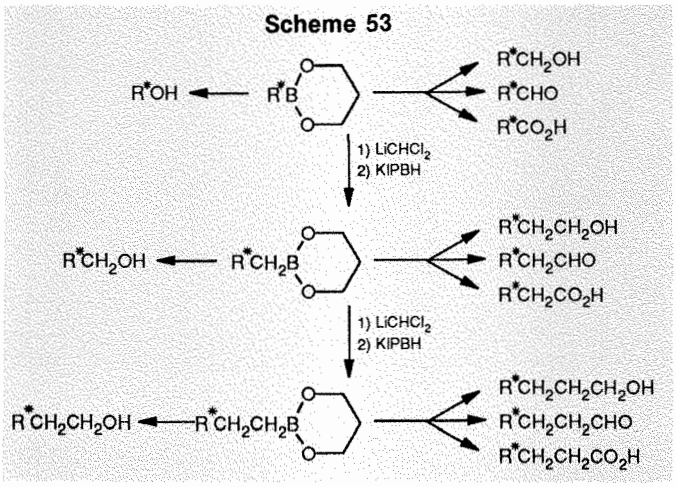
Scheme 51



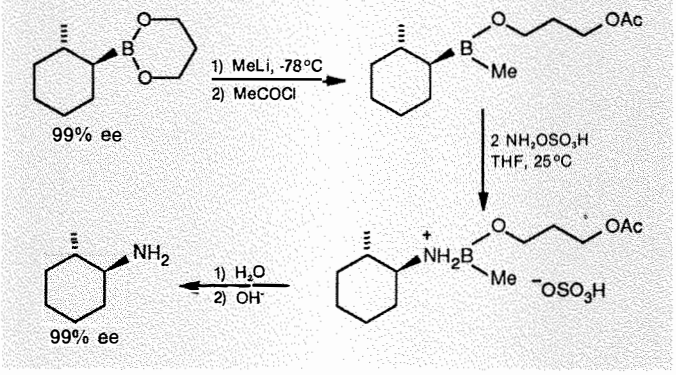
Scheme 52



Scheme 53



Scheme 54



Using this general methodology, a number of chiral primary amines of very high optical purities were prepared as their hydrochlorides (Table 22).

Chiral ketones are important in their own right and as intermediates in the elaboration of more complex structures. Using chiral boron chemistry, these ketones can now be readily prepared in high optical purity. Brown and co-workers have developed a general synthesis of α-chiral acyclic ketones based on optically pure boronic esters. Thus, treatment of the boronic ester with an organometallic reagent furnishes the corresponding borinate. The latter, when reacted with α,α-dichloromethyl methyl ether (DCME)[64] in the presence of base followed by oxidation with hydrogen peroxide in phosphate buffer, or with anhydrous trimethylamine-*N*-oxide, is smoothly converted into the corresponding ketone with complete retention of optical activity (Scheme 55).[65]

Representative ketones prepared by this method are listed in Table 23. The procedure is applicable for the preparation of both unhindered and hindered ketones.

This method of preparing α-chiral acyclic ketones is applicable to the preparation of certain pheromones.[66]

Table 22
Optically Pure Primary Amine Hydrochlorides

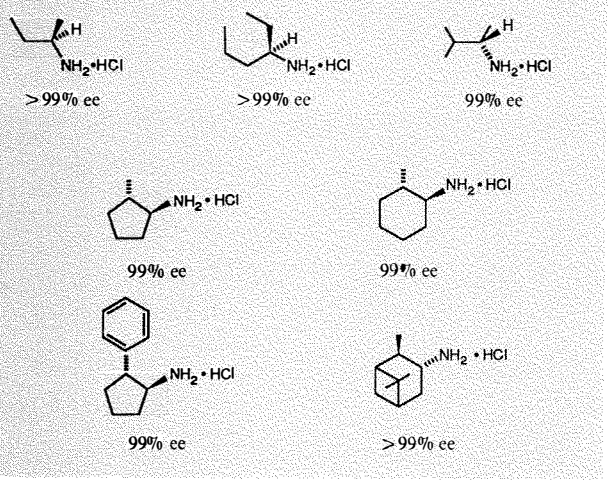
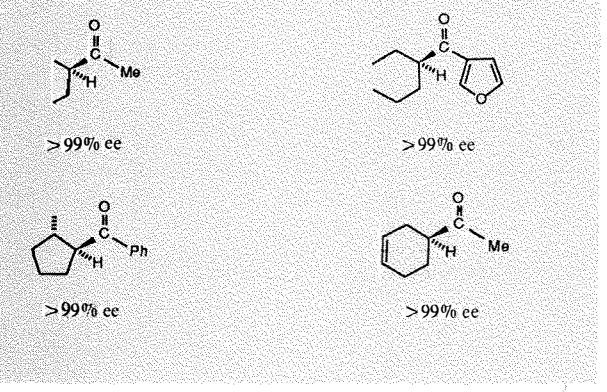


Table 23
Optically Pure α-Chiral Ketones



By utilizing similar methodology, the preceding reaction sequence was extended to the preparation of α-chiral-α′-alkynyl ketones in essentially 100% ee[67] (Table 24).

Clearly, optically pure boronic esters are useful intermediates in the elaboration of optically active compounds. The utility of these boronic esters has been further extended by conversion to the optically active borohydrides, LiR^*BH_3.[68] By an appropriate choice of the ester group, the aluminum by-product, $HAl(OR)_2$, is readily precipitated from solution (Scheme 56). We are now in a position to make all of the boron reagents previously found valuable in synthesis *via* organoboranes without loss of any alkyl groups.

VI. CONCLUSIONS AND SPECULATIONS

Hydroboration, discovered three decades ago, has in Professor Brown's words, "... grown into a tall oak from a little acorn...".[69] Now, we are in a position to obtain by relatively simple procedures a wide variety of organic groups attached to boron ($R^*B<$) in essentially 100% ee. We have simple procedures to convert these into common reagents: $R^*B(OR)_2$, R^*RBOR, LiR^*BH_3, LiR^*RBH_2, R^*BH_2, R^*BHX, R^*BX_2, R^*RBH, R^*RBX, R^*B◯ and R*RBThx.

All the above chiral boron reagents transfer chirality to other elements including carbon with essentially complete retention of configuration. Consequently, it should now be possible to duplicate Scheme 2, substituting R* for R (Scheme 57).

It is not unreasonable to assume that in the near future we will be able to synthesize any optically pure enantiomer *via* chiral organoboranes.

Scheme 55

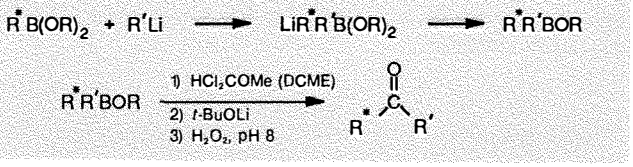
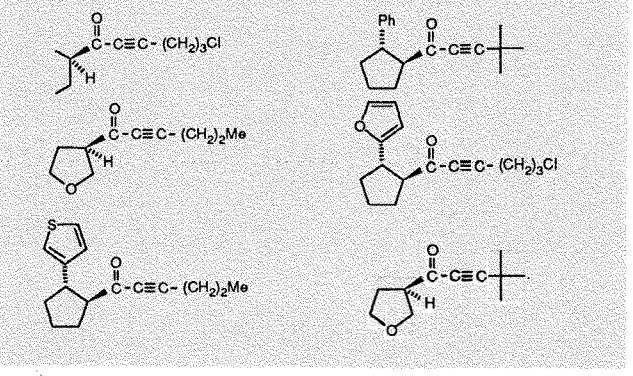
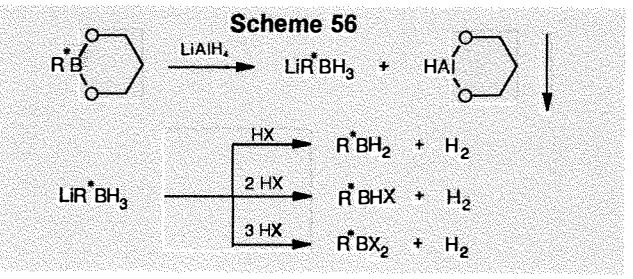


Table 24
α-Chiral α′-Alkynyl Ketones of Essentially 100% ee



Scheme 56



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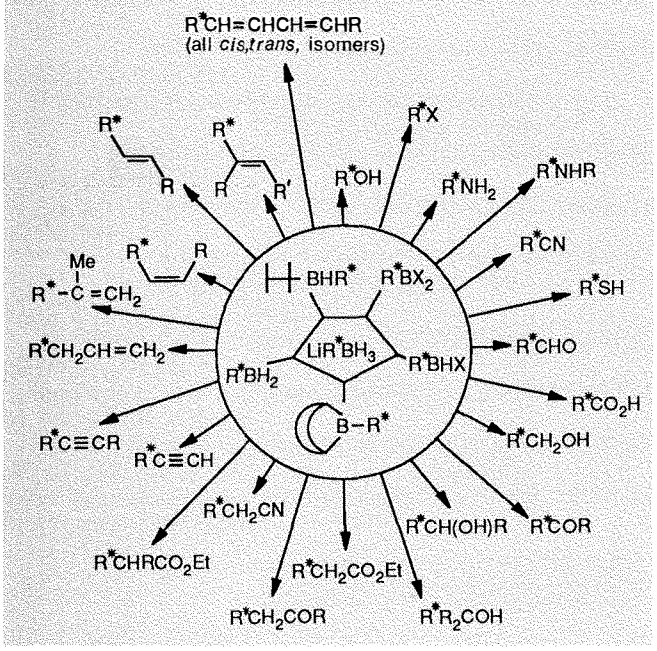
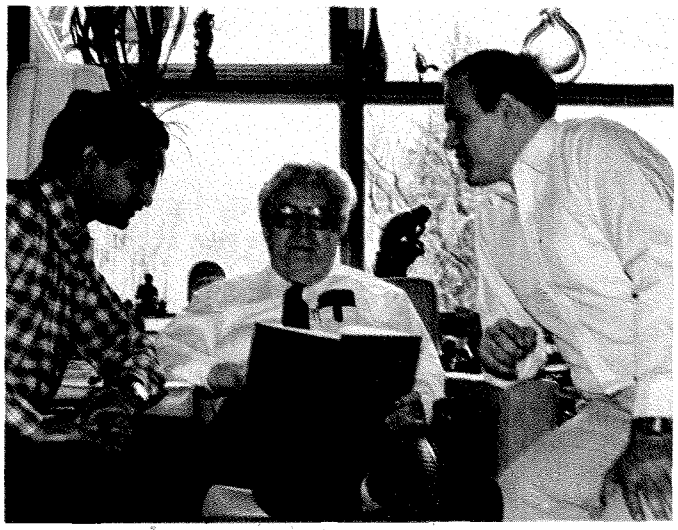
Scheme 57



About the Authors



P.V. Ramachandran (left) and M. Srebnik (right) discussing a book they are coauthoring with H.C. Brown.

Morris Srebnik obtained the Ph.D. (Prof. Raphael Mechoulam) at Hebrew University in Jerusalem. In 1984-1985 he was the recipient of a Lady Davis Fellowship. He spent 1984-1986 in the Laboratories of Prof. H. C. Brown, working on the applications of boron chemistry in organic synthesis. He joined Aldrich in September 1986.

Veerarghavan Ramachandran received the doctorate in 1983 from Indian Institute of Technology, Kanpur, under Professor Subramania Ranganathan. He has been a postdoctoral associate with Prof. H. C. Brown's group from 1984, and is currently developing new chiral borane reducing agents.

References and Notes:

1) In this review, we have placed emphasis on the contributions from Professor Brown's laboratories. Many researchers have contributed significantly to asymmetric synthesis utilizing organoboranes. Where appropriate, we have cited these contributions. However, we have omitted the area of chiral aldol condensations *via* boron enolates. Interested readers may consult the following articles: (a) Evans, D.A.; Nelson, J.V.; Taber, T.R. *Top. Stereochem.* **1982,** *13,* 1. (b) Hsiao, C.-N.; Ashburn, S.P.; Miller, M.J. *Tetrahedron Lett.* **1985,** *26,* 4855. (c) Reetz, M.T.; Kunisch, F.; Heitmann, P. *ibid.* **1986,** *27,* 4721. (d) Paterson, I.; Lister, M.A.; McClure, C.K. *ibid.* **1986,** *27,* 4787 and references cited therein.
2) Thalidomide is a tragic example of one optical isomer being a safe drug, whereas the other is a potent mutagen. Teratogenic activity is ascribed exclusively to the S-isomer. Blaschke, G. *et al. Arzneim.-Forsch.* **1979,** *29,* 1640.
3) (a) *Asymmetric Synthesis;* Morrison, J.D., Ed.; Academic Press: New York, 1983; Vol 1-5. (b) For a recent comprehensive review in asymmetric synthesis, see ApSimon, J.W.; Collier, T.L. *Tetrahedron* **1986,** *42,* 5157. (c) Matteson, D.S. *Synthesis* **1986,** 973.
4) Brown, H.C.; Subba Rao, B.C. *J. Am. Chem. Soc.* **1956,** *78,* 2582.
5) (a) Brown, H.C. *Hydroboration,* Benjamin: New York, **1963;** second printing (with Nobel Lecture), Benjamin/Cummings: Reading, MA, **1980.** (b) Brown, H.C.; Kramer, G.W.; Levy, A.B.; Midland, M.M. *Organic Synthesis via Boranes;* Wiley-Interscience: New York, **1975.**
6) Brown, H.C.; DeLue, N.R.; Kabalka, G.W.; Hedgecock, Jr., H.C. *J. Am. Chem. Soc.* **1976,** *98,* 1290.
7) Brown, H.C.; Zweifel, G. *ibid.* **1961,** *83,* 486.
8) Brown, H.C.; Ayyangar, N.R.; Zweifel, G. *ibid.* **1964,** *86,* 397.
9) Partridge, J.J.; Chadha, N.K.; Uskokovic, M.R. *ibid.* **1973,** *95,* 532.
10) Brown, H.C.; Moerikofer, A.W. *ibid.* **1962,** *84,* 1478.
11) Brown, H.C.; Yoon, N.M. *Isr. J. Chem.* **1977,** 1512.
12) Brown, H.C.; Desai, M.C.; Jadhav, P.K. *J. Org. Chem.* **1982,** *47,* 5065.
13) Brown, H.C.; Singaram, B. *ibid.* **1984,** *49,* 945.
14) (a) Brown, H.C.; Vara Prasad, J.V.N. *J. Am. Chem. Soc.* **1986,** *108,* 2049. (b) Brown, H.C.; Vara Prasad, J.V.N.; Gupta, A.K. *J. Org. Chem.* **1986,** *51,* 4296. (c) For a review on the preparation of chiral and achiral heterocyclic boronic esters, see Brown, H.C.; Vara Prasad, J.V.N. *Heterocycles* **1987,** *25,* 641.
15) Partridge, J.J.; Chadha, N.K.; Uskokovic, M.R. *J. Am. Chem. Soc.* **1973,** *95,* 535.
16) Partridge, J.J.; Chadha,N.K.; Uskokovic, M.R. *ibid.* **1973,** *95,* 7171.
17) Corey E.J.; Noyori, R. *Tetrahedron Lett.* **1970,** 311.
18) Ruttimann, A.; Mayer, H. *Helv. Chim. Acta* **1980,** *63,* 1456.
19) Brown, C.A.; Desai, M.C.; Jadhav, P.K. *J. Org. Chem.* **1986,** *51,* 162.
20) Brown, C.A.; Desai, M.C., unpublished results.
21) Verbit, L.; Heffron, P.J. *J. Org. Chem.* **1967,** *32,* 3199.
22) Brown, H.C.; Jadhav, P.K.; Desai, M.C. *ibid.* **1982,** *47,* 4583.
23) (a) Brown, H.C.; Mandal, A.K. *Synthesis,* **1978,** 146. (b) Pelter, A. *et al. Tetrahedron Lett.* **1979,** 4777. (c) Brown, H.C. *et al. J. Org. Chem.* **1982,** *47,* 5069.
24) Brown, H.C.; Schwier, J.R.; Singaram, B. *J. Org. Chem.* **1978,** *43,* 4395.
25) (a) Brown, H.C.; Jadhav, P.K. *J. Org. Chem.* **1981,** *46,* 5047. (b) Brown, H.C.; Yoon, N.M. *J. Am. Chem. Soc.* **1977,** *99,* 5514.
26) Brown, H.C.; Jadhav, P.K.; Mandal, A.K. *J. Org. Chem.* **1982,** *47,* 5074.
27) Mandal, A.K.; Jadhav, P.K.; Brown, H.C. *ibid.* **1980,** *45,* 3543.
28) Jadhav, P.K.; Brown, H.C. *ibid.* **1981,** *46,* 2988.
29) Jadhav, P.K.; Vara Prasad, J.V.N.; Brown, H.C. *ibid.* **1985,** *50,* 3203. (b) For a new chiral hydroborating agent based on chiral borolane, see Masamune, S. *et al. J. Am. Chem. Soc.* **1985,** *107,* 4549.
30) Jadhav, P.K.; Kulkarni, S.U. *Heterocycles* **1982,** *18,* 233.
31) Brown, H.C.; Mandal, A.K. *J. Org. Chem.* **1977,** *42,* 2996.
32) (a) Brown, H.C.; Mandal, A.K. *ibid.* **1984,** *49,* 2558. (b) However, Masamune and co-workers have recently reported a new chiral reducing agent for aliphatic ketones. Imai, T. *et al. J. Am. Chem. Soc.* **1986,** *108,* 7402.
33) Krishnamurthy, S.; Vogel, F.; Brown, H.C. *J. Org. Chem.* **1977,** *42,* 2534.
34) (a) Midland, M.M.; Greer, S.; Tramontano, A.; Zderic, S.A. *J. Am. Chem. Soc.* **1979,** *101,* 2352. (b) Midland, M.M.; McDowell, D.C.; Hatch, R.L.; Tramontano, A. *ibid.* **1980,** *102,* 867.
35) Midland, M.M.; Tramontano, A.; Zderic, S.A. *J. Organomet. Chem.* **1978,** *156,* 203.
36) Brown, H.C.; Pai, G.G. *J. Org. Chem.* **1985,** *50,* 1384.
37) (a) Midland, M.M.; Tramontano, A. *Tetrahedron Lett.* **1980,** 3549. (b) Midland, M.M.; Nguyen, N.H. *J. Org. Chem.* **1981,** *46,* 4107.
38) Johnson, W.S.; Frei, B.; Gopalan, A.S. *J. Org. Chem.* **1981,** *46,* 1513.
39) Brown, H.C.; Park, W.S.; Cho, B.T. *ibid.* **1986,** *51,* 1934.
40) Brown, H.C.; Cho, B.T.; Park, W.S. *ibid.* **1986,** *51,* 3396.
41) Chandrasekharan, J.; Ramachandran, P.V.; Brown, H.C. *ibid.* **1985,** *50,* 5446.

42) Brown, H.C.; Chandrasekharan, J.; Ramachandran, P.V. *ibid.* **1986,** *51,* 3394.
43) (a) Srebnik, M.; Ramachandran, P.V.; Brown, H.C., unpublished results. (b) Lednicer, D.; Mitscher, L.A. *The Organic Chemistry of Drug Synthesis;* Wiley-Interscience: New York, 1980; Vol. 2, Chapter 5.
44) Various new reagents have been prepared which give excellent optical induction for various classes of aliphatic ketones: Ramachandran, P.V.; Srebnik, M.; Brown, H.C., work in progress.
45) Mikhailov, B.M.; Pozdnev, V.F. *Izv. Acad. Nauk SSSR, Ser. Khim.* **1967,** 1477.
46) For a review of addition of crotylboronates to aldehydes, see Hoffmann, R.W. *Angew. Chem., Int. Ed. Engl.* **1982,** *21,* 555.
47) Roush, W.R.; Halterman, R.L. *J. Am. Chem. Soc.* **1986,** *108,* 294 and references cited therein.
48) Midland, M.M.; Preston, S.B. *ibid.* **1982,** *104,* 2330.
49) Brown, H.C.; Jadhav, P.K. *ibid.* **1983,** *105,* 2092.
50) *Idem J. Org. Chem.* **1984,** *49,* 4089.
51) Brown, H.C.; Jadhav, P.K.; Perumal, P.T. *Tetrahedron Lett.* **1984,** *25,* 5111.
52) Brown, H.C.; Jadhav, P.K. *ibid.* **1984,** *25,* 1215.
53) Brown, H.C.; Jadhav, P.K.; Bhat, K.S. *J. Am. Chem. Soc.* **1985,** *107,* 2564.
54) Brown, H.C.; Jadhav, P.K. Presented at the American Chemical Society meeting, St. Louis, 1984.
55) Brown, H.C.; Bhat, K.S. *J. Am. Chem. Soc.* **1986,** *108,* 293.
56) Brown, H.C.; Bhat, K.S.; Randad, R.S. *J. Org. Chem.* **1987,** *52,* 319.
57) Matteson, D.S. *et al. Pure Appl. Chem.* **1985,** *57,* 1741.
58) Brown, H.C.; Singaram, B. *J. Am. Chem. Soc.* **1984,** *106,* 1797.
59) Brown, H.C.; Vara Prasad, J.V.N.; Gupta, A.K.; Bakshi, R.K. *J. Org. Chem.,* **1987,** *52,* 310.
60) Brown, H.C.; Vara Prasad, J.V.N. *ibid.* **1986,** *51,* 4526.
61) Brown, H.C.; Imai, T.; Desai, M.C.; Singaram, B. *J. Am. Chem. Soc.* **1985,** *107,* 4980.
62) Brown, H.C. *et al. J. Org. Chem.* **1985,** *50,* 5586.
63) Brown, H.C.; Kim, K.W.; Cole, T.E.; Singaram, B. *J. Am. Chem. Soc.* **1986,** *108,* 6761.
64) Carlson, B.A.; Brown, H.C. *ibid.* **1973,** *95,* 6876.
65) Brown, H.C.; Srebnik, M.; Bakshi, R.K.; Cole, T.E. Presented in part at the 190th Meeting of the American Chemical Society, Chicago, IL, September, 1985; *J. Am. Chem. Soc.,* submitted for publication.
66) Brown, H.C.; Jadhav, P.K.; Desai, M.C. *Tetrahedron* **1984,** *40,* 1325.
67) Brown, H.C.; Vara Prasad, J.V.N.; Gupta, A.K.; Srebnik, M., unpublished results.
68) Brown, H.C.; Singaram, B.; Cole, T.E. *J. Am. Chem. Soc.* **1985,** *107,* 460.
69) Brown, H.C. *Les Prix Nobel 1979,* **1980,** 127.

On Opinion in Good Men: An Oblique Tribute to H.C. Brown

Derek A. Davenport
Department of Chemistry
Purdue University
West Lafayette, IN 47907

Herb Brown's achievement is largely split between the solid rock of synthetic organic fact and the sometimes shifting sands of physical organic theory. For the former he has been accorded both fame and honor; for the latter notoriety and at times even obloquy. At least on the surface, Herb appears to have relished the censure almost as much as the praise. Not much given to self-doubt he may even have found solace in Samuel Johnson's rationale:

> "All censure of a man's self is oblique praise. It is in order to show how much he can spare."

But at times the praise has been very oblique indeed.

Shortly after I came to Purdue in 1953, I was accosted in the corridor by a rather agitated Herb Brown. "Have you seen what your former bosses are doing to me?" he asked, thrusting at me the latest issue of *JCS*. The Journal was open at an article titled: "The Comparative Unimportance of Steric Strain in Unimolecular Olefin Elimination".[1] As a former student of Hughes and Ingold, the mandarin title alone was sufficient to suggest to me that Herb had become the latest victim of Ingoldian invective.[2] After making some sympathetic noises I took off for the library to check the gory details. In a short paper, earlier work by Brown and Fletcher[3] had been put to the verbal sword:

> "We shall explain (a) that Brown and Fletcher apply the polar theory incorrectly (b) that their experiments are imperfectly designed... (c) that in a few of their most complicated alkyl structures, special effects of hyperconjugation or synartesis might be expected (d) that ... exceptionally ramified features would be required in order to bring steric factors into prominence."
>
> "This is, of course, erroneous."
>
> "... this Brown and Fletcher did not do"
>
> "... we should expect the values to behave in the way which Brown and Fletcher could not comprehend"
>
> "In our view, this striking thesis needs better support than has yet been offered"
>
> "Naturally, we do not claim to have established this [our] interpretation; but it does seem to fit the few facts we know, as the theory of steric strain does not."

In view of the often strident criticism and the occasional verbal abuse to which he was later to be subjected, Herb may well look back on these almost gentlemanly rebukes with a certain nostalgia.

The studies of steric strain were Brown's first independent work to gain international attention. He took an almost childlike pleasure in elaborating and naming the FBI effects: F for front strain, B for back strain and I for internal strain. (He was later to find similar pleasure in noting the coincidence of his initials and ***H***ydro ***C***arbon ***B***oration.) Not everyone was equally pleased. One referee wrote:

> "The existence of such effects is entirely reasonable, and I am sure that Nature can be as complex as the mind of any chemist; so that I would not limit Brown's right to invoke one new kind of strain per year. I do wish, however, that he would reconsider his name for it — almost anything but eyestrain. Why not R for ring, or O for orbital or E for electronic? Please Brown!"

Somewhat put out, Brown wrote to Marshall Gates, then editor of *JACS:*

> "One month ago I presented the concept of I-strain at a symposium sponsored by the Canadian Institute of Chemists. There was considerable discussion and use of the term. There was no undue mirth."

But then Canadians, like Queen Victoria, are not easily moved to mirth. Brown might have found consolation in words written by G.N. Lewis to Irving Langmuir:

> "Sometimes parents show singular infelicity in naming their children, but on the whole they seem to enjoy having the privilege."

Then as now Herb Brown did not yield easily to criticism. Only the year before he had written to the editor of *JACS* concerning his 68th publication:

> "Incidentally, this has been the first time in my experience that the Referees of one of my papers have come up with a really constructive suggestion."

Nor did he like to lose. It must have been about this time that he was returning from lunch with Nathan Kornblum. Mercifully, Herb was driving but he was having trouble finding a suitable parking place. Finally a very tight spot was located. Nathan bet Herb he couldn't park. Herb lined up the car, put it into neutral, got out, and pushed the car into place. Legend does not say whether Nathan was trapped inside. Not all arguments were settled so easily.

In 1955 Brown was invited to England as Centenary Lecturer.[4] One of his first lectures was scheduled for University College, London, where his host was to be C.K. Ingold. He chose to speak not on steric strain but on selectivity effects in the reactions of aromatic compounds, in particular on his extension of Hammett's $\sigma\rho$ equation using modified σ^+ constants. The lecture was illustrated by a long series of log/log plots in which numerous experimental data lined up with the precision of soldiers on parade. Towards the end, Herb came to one slide in which several points fell lamentably far from linearity. "Since this slide was made," Herb explained, "my students have re-examined the errant points and I am happy to report that now they all fall close to the line." The lecture moved to its triumphant conclusion. Questions were solicited and a hand was raised. "Professor Brown, I am delighted that the points which fell off the line proved, on reinvestigation, to be in compliance. I wonder, however, if you have had your students reinvestigate all those points which previously fell on the line to find out how many no longer do so?" For once Herb was nonplussed. The lecture had been held in the Anatomy Theatre of the University of London. Hanging outside was a human skeleton

used in lectures to the medical students. "One of your previous seminar speakers I presume," Herb murmured to his host as they passed by.[5]

It was at about this time that the opening skirmishes took place in what was to become the nonclassical carbonium ion controversy. This was to occupy much of Herb Brown's attention for close to thirty years. The occasion was a paper by Brown and (Rachel) Kornblum[6] on the role of steric strain in carbonium ion reactions. Referee II comes out with critical guns blazing:

> "As usual, the author in his thorough, unobjective fashion has marshalled up all the good, indifferent and bad arguments... I offer the following detailed comments ... though I realize that many of them will arouse him to a vigorous, if not violent rebuttal. In order to preserve the pH of Dr. Brown's digestive system I would not require a rebuttal as a condition of publication..."

There follow three pages of cogent and acerbic suggestions for the improvement of the manuscript. There was no coyness in Referee II since the review concludes:

> "With heartiest greetings of the season to you and yours!
>
> Jack Roberts
>
> P.S. The above comments should [help] to reduce your winter heating bill!"

John Roberts was (and is) a superb critic. George Hammond has described him well:

> "To debate science with Roberts is a unique experience. He combines the style of a dyspeptic porcupine and the wily cunning of a Las Vegas dealer with fundamental integrity to produce a style that is both frightening and stimulating."[7]

The paper was resubmitted but the two referees were not yet satisfied. Roberts begins:

> "Despite the pious remarks of the author regarding the deep-seated changes he has made in his manuscript because of the remarks of the referees, I do not find the present version of the paper very much different from the original draft. Very few of my comments were really taken into account, although the arguments in the paper have been somewhat shuffled around."

and concludes:

> "I hope this manuscript is not going to be typical of the author's excursions into nonclassical carbonium ion theory. If he keeps on in this way, with his sweeping over-simplifications and bland confidence ... he is going to trample some wonderful and complex little flowers with his muddy boots."

This (1954) was probably the first use of the image of Herb Brown's muddy boots trampling on other people's complex little flowers but it was not to achieve public currency until the St. Louis shoot-out several years later.

While the fate of the paper trembled in the balance, Herb wrote to John Roberts who had fairly recently been translated from MIT to Cal Tech:

> "I was told that in Spain red peppers are quite sweet and do not exhibit the hot flavor which we in this country associate with them. A number of attempts have been made to transplant the sweet variety to the Southwest. However after a few years the originally sweet species is converted into the hot variety..."
>
> "Every time I say or write something which differs in the slightest with the views that you or Saul [Winstein] hold, I get a violent reaction which suggests the Southwest must have a similar effect upon the fauna of the region."

Roberts was not mollified:

> "So far as I have been able to determine, there seems to be no geographical discrimination with respect to those people who get annoyed with the irresponsible character of the remarks of the man who made [the] FBI world-famous."

Finally, the editor appointed Paul Bartlett as a kind of ombudsman:

> "The paper by Hughes, Ingold and Shiner (1953) represents quite an exercise in debating, but in its anxiety to pooh-pooh steric effects it makes no clear proposal about bridged-ions."
>
> "If I am to serve as Supreme Court Judge, I will sentence you to discussing your results with [brevity]. You can then omit the building up of a straw-man, credit your readers with putting one and one together, and condense the entire discussion section into two or three pages."

A seemingly contrite Herb Brown replied:

> "Having been judged guilty by a jury of my peers, I shall accept my sentence ... I certainly have no desire to engage in a polemic. I shall probably have my hands full soon with Ingold."

The paper finally appeared with its arguments essentially unchanged.[6] The anticipated battles with Ingold were not to materialize. The vision of a compliant H.C. Brown carefully avoiding polemics and humbly doing penance was to prove equally chimerical.

The nonclassical carbonium ion controversy was to go on for many years, though seldom at this exalted level. Herb's side of that controversy is exhaustively documented in the more than one thousand manuscript boxes which line the Herbert C. Brown Archives. Each box contains not only the usual reprints but also referees' reports, related correspondence and successive versions of the manuscript. They should prove treasure trove for some future historian of science. However, like that of the giant rat of Sumatra, the case of the nonclassical carbonium ion is a story for which the world is not yet prepared. Or at least, I am not.

There are no referee reports in Box #158 of the Herbert C. Brown Archives, a box which contains the seminal paper by Brown and Subba Rao on "A New Technique for the Conversion of Olefins into Organoboranes and Related Alcohols".[8] When, a couple of years ago, I went to see Herb concerning the missing reports, he merely said, "Sit down, I'll dictate part of it to you":

> "Dallas T. Hurd has previously demonstrated the addition of B_2H_6 to olefins at elevated temperatures. Consequently there is nothing new about the reaction. The fact that the addition of B_2H_6 to alkenes takes place in ether solution in a few seconds at zero degrees is a mere convenience. Moreover the reactions produce organoboranes for which there are no known applications. Consequently rejection is recommended."

Even given Herb's elephantine memory one cannot vouch for every word but the spirit of the referee's report was memorably conveyed. After all those years the words clearly still rankled. Particularly that next to last sentence.

The Presentation Introduction given at the 1979 Nobel Prize ceremony in Stockholm read in part:

> "Herbert C. Brown has systematically studied various boron compounds and their chemical reactions. He has shown how various specific reductions can be carried out using borohydrides. One of the simplest of these, sodium borohydride, has become one of the most used chemical reagents. The organoboranes, which he discovered, have become the most versatile reagents in organic synthesis. The exploitation of their chemistry has led to new methods for rearrangements, for addition to double bonds and for joining carbon atoms to one another."

There is no mention, and properly so, of the nonclassical carbonium ion to which Herb had devoted so large a fraction of his professional life. Among the many congratulatory letters was one in the fine italic hand of his long-time adversary John D. Roberts.

October 16, 1979

Dear Herb:

Congratulations! However much or little we agree on the nonclassical carbocation controversy, there is no question but that you deserve a Nobel Prize for your marvelous contributions to synthetic methods by way of organoboranes.

Best wishes to you and Sarah for your trip to Stockholm.

Sincerely,

Jack

The letter does honor to both men. It should even earn an approving nod from the ghost of John Milton:

"Where there is much desire to learn, there of necessity will be much arguing, much writing, many opinions; for opinion in good men is but knowledge in the making."

References:

With the exception of those from reference 1, all direct quotations are taken from unpublished material in the Herbert C. Brown Archives.

1) Hughes, E.D.; Ingold, C.K.; Shiner, V.J. *J. Chem. Soc.* **1953,** 3827.
2) Parts of this paper are taken from a lecture, "On the Comparative Unimportance of the Invective Effect in Physical Organic Chemistry," first given at the University of California, Santa Cruz, in August 1980. A fuller version of that lecture is scheduled for publication in *Chem. Tech.*
3) Brown, H.C.; Fletcher, R.S. *J. Am. Chem. Soc.* **1950,** *72,* 1223.
4) Brown, H.C. *J. Chem. Soc.* **1956,** 1248.
5) Herb Brown recalls the question as having been asked by R.P. Bell at Oxford. Tom Dunn, now of the University of Michigan, assures me that the incident took place at University College, London. Besides, what author could resist the skeletal ending? *Se non è vero, è molto ben trovato.*
6) Brown, H.C.; Kornblum, R.B. *J. Am. Chem. Soc.* **1954,** *76,* 4510.
7) George S. Hammond in his *foreword* to a volume reprinting papers by John D. Roberts, W.A. Benjamin (1969).
8) Brown, H.C.; Subba Rao, B.C. *J. Am. Chem. Soc.* **1956,** *78,* 5694.

About the Author

Both Herbert C. Brown and Derek A. Davenport were hired by Purdue University as inorganic chemists. Neither quite worked out. Brown was transmogrified into an historic organic chemist while Davenport modulated first to a pedagogical chemist and then to an historical chemist. The latter writes sparingly and lectures unsparingly on chemical education, history of chemistry, and various idiosyncratic mixtures of the two. He has served as Chairman of both the Division of Chemical Education and of the Division of History of Chemistry. He is the recipient of all four national awards in chemical education. So far Clio remains unimpressed.

SUPERCONDUCTIVITY!

Recent applications of metal oxide ceramics to studies of superconductive materials have radically altered the expectations of researchers in a field previously encumbered by severe technological obstacles.

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Chemical Week, March 18, 1987, p 25.
The Wall Street Journal, March 20, 1987.

AGE — CREATIVITY AND PRODUCTIVITY

Remarks at the September 9, 1986 Hearing of the Subcommittee on Health and Long-Term Care, ***Ability is Ageless,*** *Room 345, Cannon Office Building, Washington, DC*

Research over the short term is a relatively slow, often agonizing process. Day by day, week by week, it is often difficult to note any real progress. However, I have had the rare good fortune to have followed a research program consistently for many years. Actually, this year, 1986, is the fiftieth year. My experiences have led me to a number of conclusions, some of which may be pertinent to the deliberations of this Subcommittee. I am indebted to the Honorable Claude Pepper and the other members of the Subcommittee on Health and Long-Term Care for the opportunity to present some of these insights here.

My name is Herbert C. Brown; I am 74 years old. I hold the position of Wetherill Research Professor Emeritus at Purdue University. My research over fifty years has received many recognitions. In 1969 I received the National Medal of Science. In 1979 I was awarded the Nobel Prize. More recently I have achieved the "Triple Crown" of American chemistry: The Priestley Medal of the American Chemical Society (1981); the Perkin Medal of the American Section of the Society of Chemical Industry (1982) and the Gold Medal of the American Institute of Chemists (1985).

I reached retirement age (66) in 1978. The University held a grand retirement party. Many of my former co-workers, both graduate students and postdoctorates, numbering about 300 at that time, came to participate in the festivities.

I might easily have retired to a life of ease and vegetation. But my wife of nearly 50 years, a former classmate of mine in my undergraduate days, urged me to continue. Her observations had led her to the conclusion that men last longer, in better health, if they continue active.

Fortunately, the University came to me with an exceptional opportunity. I was invited to remain at the University and to continue my research activities with the same research space as in the past. There would be just two changes. First, I would no longer accept graduate students for training for the Ph.D. I would restrict myself only to postdoctorates. Secondly, I would no longer receive a salary.

Now some people might wonder why I would continue my research activities without salary. But there is nothing I find more enjoyable than my continued exploration of nature and the series of discoveries that our research uncovers. I accepted the invitation with thanks.

That was eight years ago — in 1978. With one exception, the various granting agencies have continued their support of my work at the same level. I have continued to work with a group of approximately 16 postdoctorate co-workers. These have come to me from all over the world: Japan, Korea, Taiwan, India, Israel, Italy, Germany, France, Great Britain, Poland, and the United States.

I have observed no diminution in my publications since my so-called retirement. I previously published approximately 30 scientific papers per year. Since my "retirement," I have published somewhat more, as many as 40 in a single year.

Prior to my "retirement," I delivered some 25 invited addresses per year on my work. The year after my "retirement" I received the Nobel. That brought an increased number of invitations to speak, often extended in such a manner that one could not decline. As a result, my lectures have increased in number. Now I give approximately 50 lectures per year.

Previously, I made approximately three trips abroad each year to attend conferences and give lectures. Now I make as many as 6 trips abroad each year. (My wife always accompanies me on these trips. That is one of my secrets for maintaining a happy marriage for fifty years.)

I should point out that some of my most prestigious awards, the Nobel and the three medals constituting the "Triple Crown," came in the years following my "retirement".

I should emphasize that I am not unusual. I know many other chemists who have continued to do productive research long past the usual retirement age.

If my productivity has not decreased, what about my creativity? That is a more difficult question to answer. One can count one's publications and invitations, but how does one judge his own creativity? However, I can say that two years ago I announced a development in my laboratories that I believe is the most important of my career. Let me attempt to give you a feeling for the significance of this development.

Many organic compounds exist in nature as a pair of optical isomers. These are related to each other in the way a right hand is related to a left. They cannot be superimposed. But the mirror image can be superimposed.

Unfortunately, when organic chemists synthesized such compounds in the laboratory, they invariably obtained a 50:50 mixture of the two optical isomers. These could usually be separated only by a long, tedious process, often very expensive. Such expenses added greatly to the cost of pharmaceuticals.

Two years ago, we discovered a simple way to prepare optically active groups attached to boron. We can now transfer these groups from boron to carbon, retaining all of the optical activity. For the first time organic chemists have available a general synthesis of either isomer of a pair of optically active compounds.

In the '30's at the time I was starting my career, conventional wisdom was that one did his most creative work by age 35. After that, it was all downhill.

I married my classmate, Sarah Baylen, in 1937 when I was 24. This was before the days of Women's Liberation. Husband and wife were considered to be a single unit with common goals. Accordingly, I discussed this problem with Sarah and she agreed to give me every possible opportunity to do such creative work as I could achieve by relieving me of all routine duties. She would handle the bills, do the banking, take care of the house and yard work, handle the income tax (a small matter in those days!), etc., etc.

I have now come to the conclusion that this 35 age limit is sheer nonsense, at least for chemists. I was 44 when my students and I discovered a new reaction, hydroboration, which made organoboranes readily available for the first time. I was 54 when we initiated our systematic study of organoboranes and discovered their rich potential — the work that led to the Nobel. I was 64 when we discovered we could achieve 100% optical purity in many hydroborations. Finally, I was 72 when I realized we had in our hands a truly general procedure to synthesize optically pure compounds.

When this happened, I went to Sarah and apologized. Evidently I had been mistaken when I had accepted conventional wisdom, but she brushed off my apologies. She had enjoyed our joint efforts and she had no regrets. Indeed, her responsibilities had their compensations. When we went to Stockholm to receive the Medal and the Award, she let me carry the Medal back, but she took charge of the $100,000 Award.

I hope that my experiences will prove helpful to the Subcommittee in its deliberations.

Herbert C. Brown
Department of Chemistry
Purdue University
West Lafayette, IN 47907

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Aldrichimica Acta

Volume 20, Number 2, 1987

O-Acyl Thiohydroxamates: New and Versatile Sources of Alkyl Radicals for Use in Organic Synthesis

Allylic Tin Compounds in Organic Synthesis

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About Our Cover:

When our chemist-collector first saw this splendidly direct portrait of a man (oil on panel, 18 x 15 inches) at a London auction, it was ill-framed and dirty, although in fact, in fine condition. This hitherto unrecorded portrait is signed and dated 1656 by one of Rembrandt's ablest students, Nicholas Maes, who was 22 years old at the time. The man's dress is so informal and his gaze so searching that one wonders whether this is a self-portrait. Maes depicted himself in one or two genre paintings, on one occasion in a mirror, but it is difficult to make comparison with such a small-scale sketch. Another self-portrait by Maes (Fig. 1), painted some 30 years later, is now in his birthplace, Dordrecht; but the wig and considerable difference in age again make comparison difficult.

Fig. 1

Rembrandt and the Bible - in Japan

We are offering a limited number of a 174-page catalog of an exhibition in Japan, the first of its kind there, on Rembrandt and the Bible. The scholarly essays in Dutch, English, German and Japanese deal with works by Rembrandt and his students — 38 paintings, 7 drawings and 44 etchings, all beautifully illustrated. Thirteen of the paintings, all in full color, have appeared on covers of the *Acta*. The works are fully described in English and Japanese. An unusual and wonderful buy for lovers of art and the Bible!

Pictures from the Age of Rembrandt

Twenty-five paintings that have been reproduced on our *Acta* covers, and six that have been on our catalog covers are among thirty-six paintings in an exhibition of Dutch paintings at Queen's University in Kingston, Ontario. The fully illustrated catalog written by Professor David McTavish contains a wealth of art-historical information — enough for several evenings of relaxed enjoyment — probably the best value in art-history anywhere.

Reprints of Aldrich Catalog Covers

Eight beautiful 14 x 11 inches, full-color reproductions of paintings on our catalog covers are available, ready for framing, to add beauty to your laboratory.

Selections from the Aldrichimica Acta, 1968-1982

Because of the ever-increasing demand for earlier issues of the *Acta*, we now offer a collection of articles from volumes 1-15. We chose those articles which we believe are still of interest to our readers — 354 pages of great review articles, in one beautiful hardbound volume.

Lab Notes

There is often a need for pure potassium *tert*-butoxide which is one of the most commonly used bases in organic synthesis. The impurities which are usually present (*i.e.*, potassium hydroxide and potassium carbonate) may be removed by subliming the *t*-BuOK. However, the sublimation in the laboratory is limited to relatively small quantities. I have found that due to the very good solubility of *t*-BuOK in tetrahydrofuran, it may be easily purified by dissolving in dry THF, filtering off the insoluble material quickly, followed by removal of the solvent by evaporation. The solution to be filtered should not be more than 10g of *t*-BuOK/100ml of THF to prevent clogging of the filter funnel by the *t*-BuOK crystals which might form when the THF cools and evaporates during the vacuum filtration. Samples of up to 20g of potassium *tert*-butoxide have been successfully purified in this way.

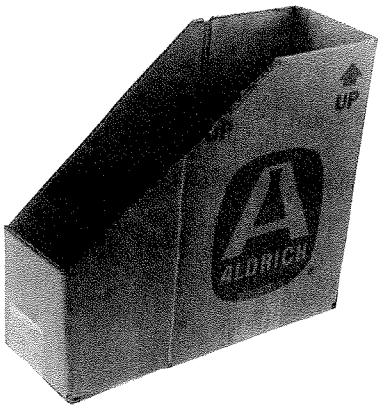
Tomasz Glinka
Institute of Organic Chemistry
Polish Academy of Sciences
Warsaw, Poland

Editor's note: It has been suggested that pressure-filtering under nitrogen might eliminate crystallization caused by cooling and evaporation of the solvent.

We carry the reagents used above.

We order many chemicals from Aldrich and have accumulated the 7½ x 7½ x 9½-inch boxes in which the chemicals are shipped. With some tape, a pair of scissors or a carton opener, these can be converted to shelf files, using the following simple instructions.

1) ***Cut off top flaps.***
2) ***Slit tape on bottom and extend bottom flaps.***
3) ***Cut flaps that are connected to the blank sides in half, vertically.***
4) ***Fold blank sides in half.***
5) ***Fold box into a rectangle with the Aldrich symbol facing you and in the right ⅔ of the side.***



6) ***Fold end flaps in.***
7) ***Fold side flaps in.***
8) ***Tape bottom securely.***
9) ***Draw a diagonal line on Aldrich side of the box.***
10) ***Draw a parallel line on opposite side.***
11) ***Draw a connecting line across the front.***
12) ***Cut along lines.***

Hugh Emerson
Supervisor of Science Stores
University of Missouri
123 Chemistry Building
Columbia, MO 65211

Unless sophisticated cooling systems are available, Dewar flasks are required for low-temperature reactions. This invariably precludes magnetic stirring if the flask is not shallow. While a totally submersible magnetic stirrer may be used (such as the model manufactured by Troemner), its placement is still a problem.

I have devised an adjustable holder for the Troemner model that can be used in a relatively large (> 12cm i.d.) Dewar flask and can also be easily made in a machine shop. It consists of two concentric aluminum rings welded to a flat plate. The ring i.d.'s are 51mm and 80mm, respectively, and the height *ca.* 2cm. A wall section *ca.* 12mm is cut out of the inner ring to accommodate the stirrer shape. The outer ring has three round rubber feet mounted equidistantly and perpendicularly to the metal surface. Each foot is attached *via* a threaded screw that allows the foot to be extended by 15-20mm. The thickness of the outer-ring wall should be at least 2mm to permit threading of the holes. The feet allow the holder to be positioned firmly at any height within the flask, thus permitting stirring while the holder is partially or totally submerged. The arrangement still permits the addition of dry ice to the coolant or the inclusion of a cryogenic probe.

Dr. Stephen J. Carter
Dartco Manufacturing
P.O. Box 5867
Augusta, GA 30906

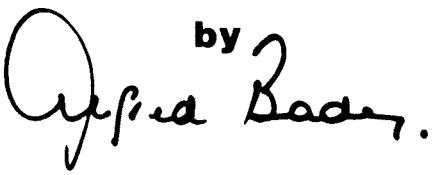
This technique was devised while at GTE Laboratories.

Editor's note: We are pleased to offer both the Troemner stirrer and a stirrer adapter as described by Dr. Carter.

Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt**. *We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by



Me_3SiOK

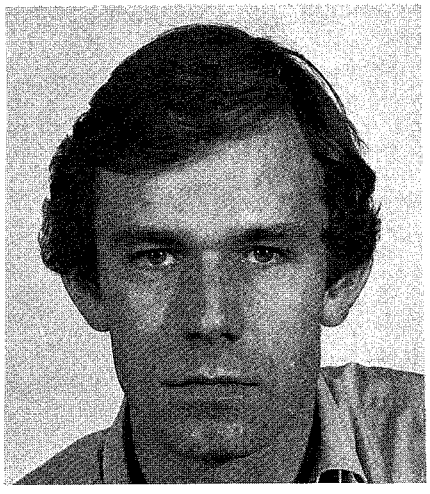
Professor Ralph A. Raphael at Cambridge University suggested that we offer potassium trimethylsilanolate, an organic-solvent-soluble, completely anhydrous KOH equivalent. This useful reagent is appreciably soluble in a variety of organic solvents (ether, THF, toluene, methylene chloride, etc.) and has been used to convert carboxylic acid derivatives directly into their corresponding anhydrous potassium salts under mild and nonaqueous conditions.

Naturally, we made the compound.

Laganis, E.D.; Chenard, B.L. *Tetrahedron Lett.* **1984**, *25*, 5831.

It was no bother at all, just a pleasure to be able to help.

O-Acyl Thiohydroxamates: New and Versatile Sources of Alkyl Radicals for Use in Organic Synthesis



David Crich
Department of Chemistry
University College London
20 Gordon Street
London, WC1H 0AJ
England

O-Acyl thiohydroxamates (mixed anhydrides of carboxylic acids with thiohydroxamic acids) provide a mild and convenient source of carbon radicals which are ideally suited for the synthesis or modification of sensitive molecules. Their use is limited only by the availability of the carboxylic acid precursors.

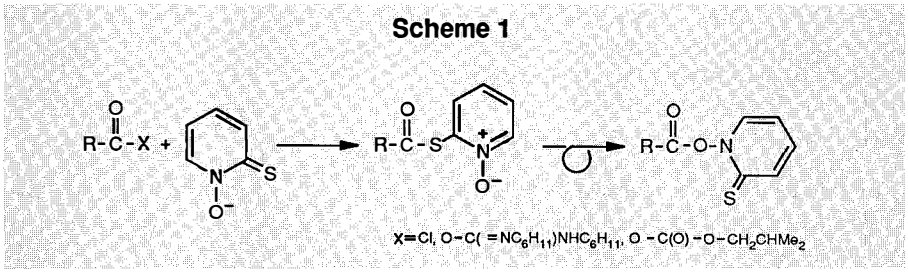
1. Preparation and Structure of O-Acyl Thiohydroxamates

The reaction of suitably activated carboxylic acids with a salt of the cyclic thiohydroxamic acid *N*-hydroxypyridine-2-thione (2-mercaptopyridine-*N*-oxide) results in the formation of bright yellow O-acyl thiohydroxamate esters,[1,2] most probably *via* the isomeric 2-acylthiopyridine-N-oxides[3] (Scheme 1). These esters can be isolated as crystalline solids [4,5] and stored at room temperature provided that they are shielded from light. Support for the hypothesis of the intermediacy of the S-acyl-N-oxides in the formation of O-acyl thiohydroxamates is provided by the fact that 2-mercaptopyridine-*N*-oxide reacts with methyl iodide to give isolable, stable 2-methylmercaptopyridine-*N*-oxide[3,4] whose unobserved[6] intramolecular rearrangement to *N*-methoxypyridine-2-thione would be a highly disfavored process[7] (Scheme 2), and also by the fact that acylation of the vinylogous thiohydroxamic acid 4-mercaptopyridine-*N*-oxide[8] leads mainly to the 4-acylthiopyridine-N-oxide[3] which is incapable of intramolecular rearrangement to the O-acyl compound (Scheme 3).

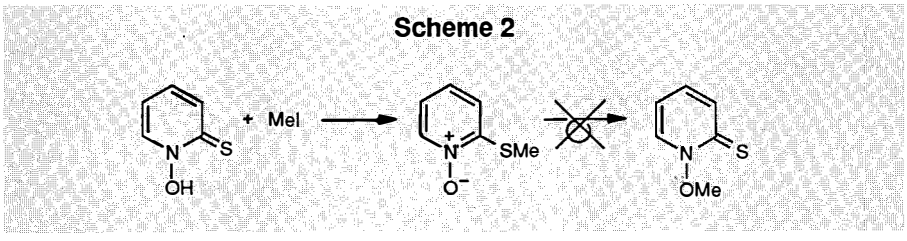
That O-acyl thiohydroxamates exist as such and not as the isomeric 2-acylthiopyridine-N-oxides is clear from their infrared spectra which exhibit a strong carbonyl absorption in the region 1790-1810cm^{-1}. The analogous O-acyl-2-pyridones have two carbonyl absorptions, 1780 and 1670cm^{-1}, thus eliminating the isomeric 2-acyloxypyridine-N-oxide structure. The latter of these two frequencies is clearly attributable to the pyridone carbonyl leaving the former one for the O-acyl carbonyl whose value is in excellent agreement with the value found for the O-acyl thiohydroxamates. Furthermore, the 4-acylthiopyridine-N-oxides have a single typical thiol ester carbonyl absorption frequency at 1710cm^{-1}.

O-Acyl thiohydroxamate formation *via* carboxylic acid activation (Scheme 1) is best achieved, wherever possible, by means of the acid chloride, which is easily prepared using oxalyl chloride and a trace of dimethylformamide.[2] Direct condensation of carboxylic acids with 2-mercaptopyridine-*N*-oxide by means of dicyclohexylcarbodiimide/*p*-dimethylaminopyridine is an efficient method for primary acids[1,2] but results in formation of N-acylureas[1,2,9] with secondary and presumably tertiary acids. In the amino acid field, condensation of the thiohydroxamic acid with the mixed anhydride formed from the acid and isobutyl chloroformate in the presence of *N*-methylmorpholine is the method of choice.[10,11]

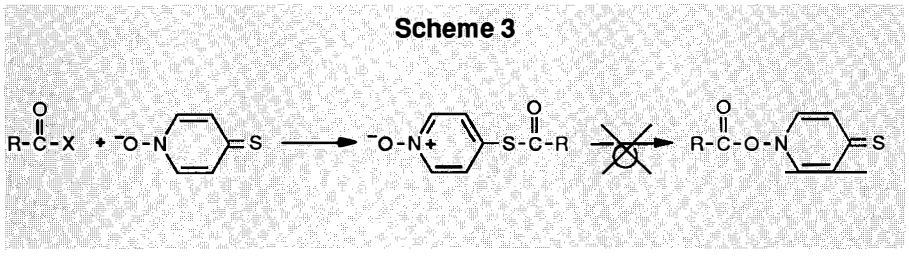
Scheme 1



Scheme 2



Scheme 3



A conceptually different approach to O-acyl thiohydroxamates involves the activation of the thiohydroxamic acid rather than the carboxylic acid. Treatment of 2-mercaptopyridine-*N*-oxide with phosgene in benzene gives the cyclic carbonate salt (Scheme **4**) as a white amorphous powder which, on reaction with a carboxylic acid in refluxing benzene gives the O-acyl thiohydroxamates (Scheme 5). (In this study the esters were not isolated but further reacted with tri-*n*-butyltin hydride.)

A third approach to O-acyl thiohydroxamates is the thiation of O-acyl hydroxamates with Lawesson's Reagent,[12] although this method gives only moderate yields (Scheme 6).

2. Non-Carbon-Carbon Bond-Forming Radical Chain Reactions of O-Acyl Thiohydroxamates

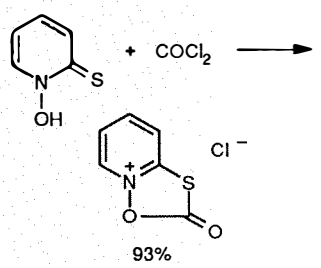
The simplest and most characteristic reaction of the O-esters of 2-mercaptopyridine-*N*-oxide is their decarboxylative rearrangement to alkyl 2-pyridyl sulfides[1,2,13] (Schemes 7 and 8). This facile rearrangement is achieved simply by heating the esters to reflux in an appropriate solvent or by photolyzing with a white-light source. No radical initiator is required.

The ease of this rearrangement and, indeed, of all the radical chain reactions described in this article, can be rationalized[1,2] in terms of several thermodynamic driving forces. During the course of the reaction, a strong carbonyl bond (CO_2) is formed at the expense of a weak thiocarbonyl bond. The well known Barton/McCombie reductive deoxygenation procedure[14,15] and its variants[16-18] rely on this same driving force. Aromatization of the pyridine nucleus provides a second essential driving force. The ability of aromatization to aid the β-elimination of carboxyl radicals had been observed previously[19] for a different radical decarboxylation sequence. Finally, the reaction is favored from an entropy point of view, two product molecules being formed from one molecule of substrate.

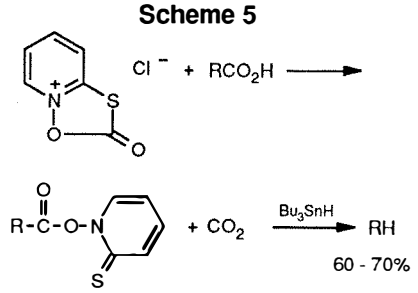
O-Acyl thiohydroxamates of other thiohydroxamic acids, as well as of 2-mercaptopyridine-*N*-oxide, undergo similar decarboxylative rearrangement reactions, although under a variety of different conditions. Thus the O-esters of 4-methyl[3,20] and 4-phenyl[3] *N*-hydroxythiazoline-2-thione undergo smooth thermal decarboxylative rearrangement in refluxing toluene but require UV photolysis (medium Hg pressure) for the photochemical reaction. O-Esters of thiohydroxamic acids, not including the driving force of aromatization in their radical reactions, rearrange rapidly on UV photolysis[21] but undergo thermal rearrangement reluctantly,[3,20] if at all, demonstrating the necessity of aromatization as a driving force for the thermal reactions (Scheme 9). The thiohydroxamic acids 4-methyl-*N*-hydroxythiazoline-2-thione and *N*-hydroxy-*N*-methyl-*S*-phenyldithiocarbamate are easily synthesized (Schemes 10 and 11) and, by virtue of the differing reactivities of their O-esters, provide useful alternatives to 2-mercaptopyridine-*N*-oxide.

Two radical mechanisms can be written for the decarboxylative rearrangement of O-acyl thiohydroxamates. (Two electron intramolecular processes can be eliminated[22] on stereoelectronic grounds.) The first mechanism (Scheme 12) involves a simple radical chain process and requires no further comment. The alternative is a cage mechanism brought about by homolytic cleavage of the N-O bond (Scheme 13). Radical cage mechanisms involving such N-O homolytic bond cleavages and the passage of thiocarbonyl to carbonyl have been extensively investigated[23] by the Hudson group (Scheme 14).

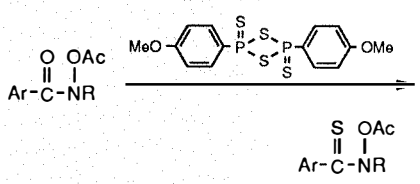
Scheme 4



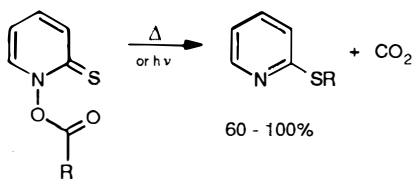
Scheme 5



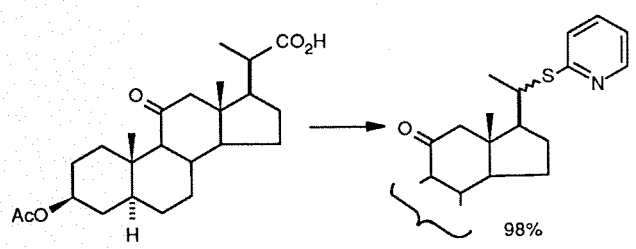
Scheme 6



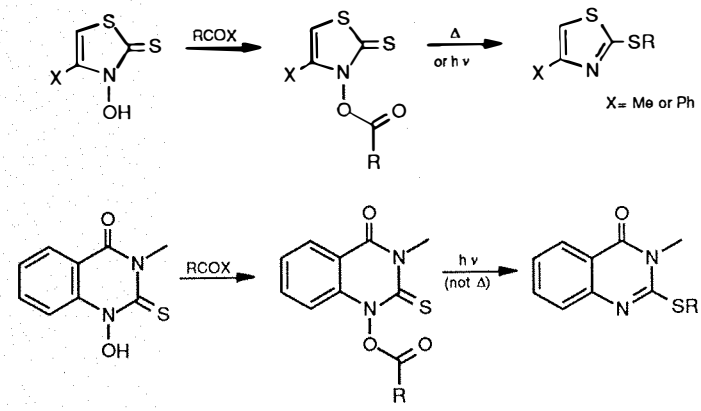
Scheme 7



Scheme 8



Scheme 9

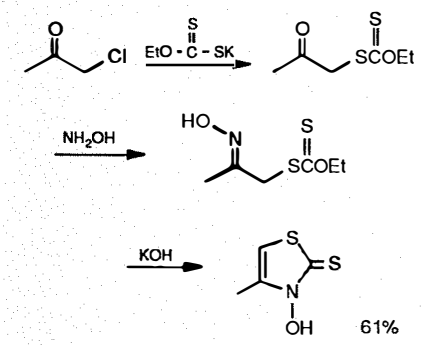


A somewhat different but nonetheless relevant reaction is the formation of β-lactams from tetrahydro-1,2-oxazine-3,6-diones,[24] which involves not only a homolytic N-O bond cleavage but also a subsequent decarboxylation step (Scheme 15). Crossover experiments (Scheme 16) enable the conclusion to be drawn[21] that the photochemically induced reactions proceed exclusively *via* a chain mechanism (Scheme 12). In the thermal reaction, the chain mechanism is also the dominant process but *ca.* 20% of the reaction appears to follow the cage pathway.

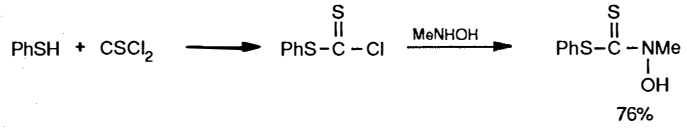
Mechanistic considerations aside, this decarboxylative rearrangement reaction provides a facile route to alkyl heteroaryl sulfides which have proven useful as reactive intermediates due to their facile formation of a chelated lithio anion[25] and have also been used in the synthesis of thiiranes[26] and olefins.[27] The reaction proceeds in neutral solution *via* radical intermediates and, as such, tolerates a wide variety of functional groups, a high degree of steric hindrance and does not normally provoke rearrangement of, or elimination from, the various intermediates.

On photolysis or thermolysis in the presence of a suitable hydrogen donor such as *tert*-butyl mercaptan or tri-*n*-butyltin hydride, O-acyl thiohydroxamates undergo reductive decarboxylation *via* a radical chain mechanism to give the noralkane in high yield[1-3,20] (Schemes 17 and 18). *tert*-Butyl mercaptan is preferred over tri-*n*-butyltin hydride as hydrogen donor as the work-up is considerably simplified. The reaction, which is best carried out by dropwise addition of the activated carboxylic acid to a mixture of thiol and a salt of the thiohydroxamic acid in refluxing benzene, can be performed on primary, secondary or tertiary aliphatic carboxylic acids and in the presence of many common organic functional groups.

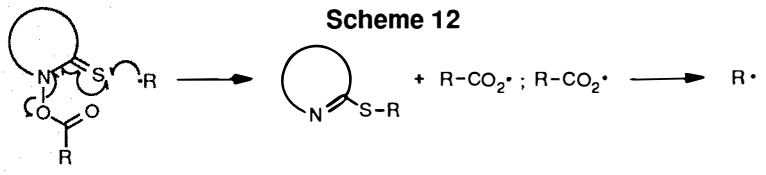
Scheme 10



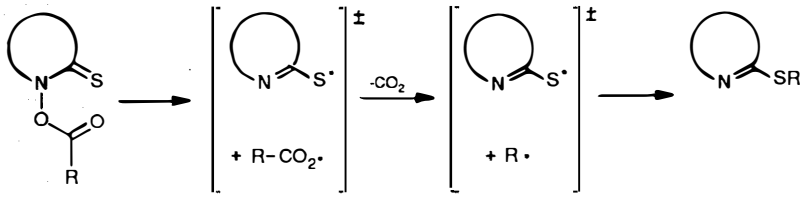
Scheme 11



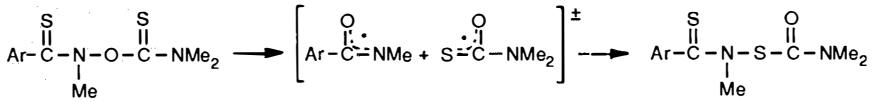
Scheme 12



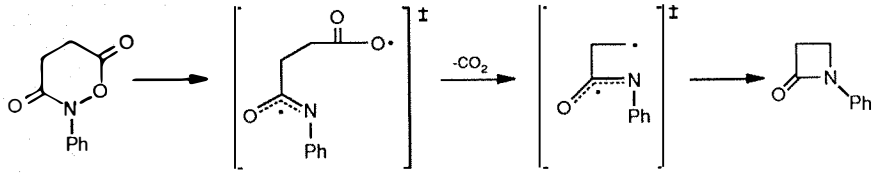
Scheme 13



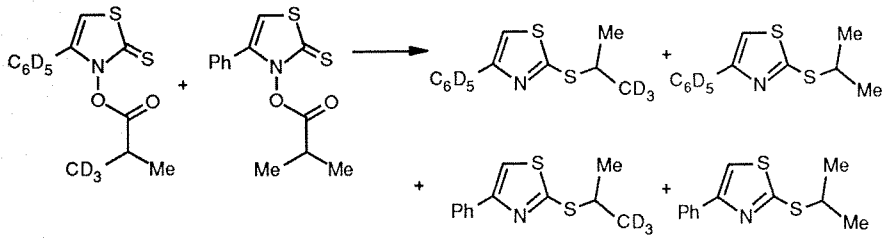
Scheme 14



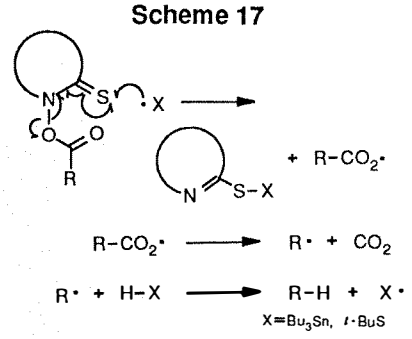
Scheme 15



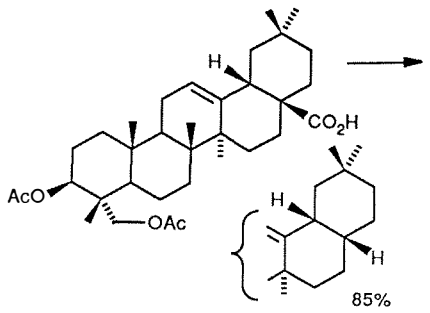
Scheme 16



Scheme 17



Scheme 18



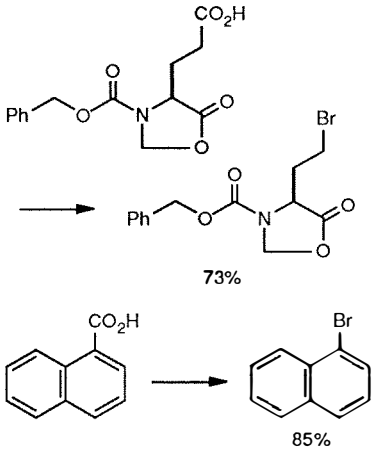
The equivalent of the Hunsdiecker reaction can be achieved in the absence of heavy-metal salts and/or strongly electrophilic reagents simply by photolyzing or by heating the esters in refluxing bromotrichloromethane for the bromides or tetrachloromethane for the chlorides (Scheme 19).[2,28] The use of iodoform in benzene/cyclohexene mixtures gives the iodides.[2] Once again a chain mechanism is implicated[29] (Scheme 20). Addition of azobisisobutyronitrile (AIBN) as a radical initiator to the Hunsdiecker mixture allows the decarboxylative halogenation of aryl acids (Scheme 19). This latter application is particularly useful since electron-rich aryl acids suffer extensive electrophilic aromatic bromination under normal Hunsdiecker conditions (silver salt and bromine).[30,31]

Alkyl hydroperoxides can be obtained from carboxylic acids *via* O-acyl thiohydroxamates.[2,32] Simple passage of triplet oxygen through a solution of the O-acyl thiohydroxamate in refluxing benzene or under photolysis at the appropriate wavelength results in a complicated reaction mixture presumably due to remote hydrogen abstraction by the intermediate hydroperoxyl radicals. Addition of *tert*-butyl mercaptan as a hydrogen donor to the reaction mixture completely eliminates this unwanted side reaction and leads to excellent yields of hydroperoxides. The mechanism is once again a simple radical chain sequence.[2] It was found to be more convenient not to isolate the hydroperoxides but to convert them *in situ* to the corresponding alcohols by treatment with dimethyl sulfide or trimethyl phosphite, or to the corresponding carbonyl compound by the action of *p*-toluenesulfonyl chloride in pyridine (Scheme 21).

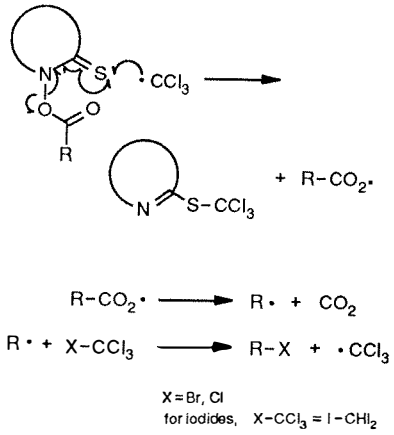
An alternative method for the formation of alcohols from carboxylic acids involves reaction of the O-acyl thiohydroxamates with tris(phenylthio)antimony and subsequent aerial oxidation of the so-formed alkyl antimony bonds.[33] One disadvantage of this method is the necessity for highly pure, thiophenol-free, tris(phenylthio)antimony. Once again the radical reaction takes place *via* a chain mechanism (Scheme 22, X = Sb). Thus, exposure of the organoantimony compounds to air and subsequent hydrolysis provides the alcohols in excellent yield (Scheme 23).

Reaction of O-acyl thiohydroxamates with tris(phenylthio)phosphorus also proceeds *via* a chain mechanism (Scheme 22, **X = P**) giving, in the first instance, alkyl di(phenylthio)phosphines.[34] Once again, these compounds are not isolated but

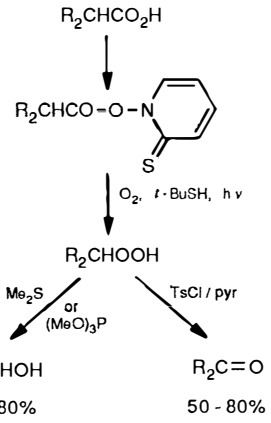
Scheme 19



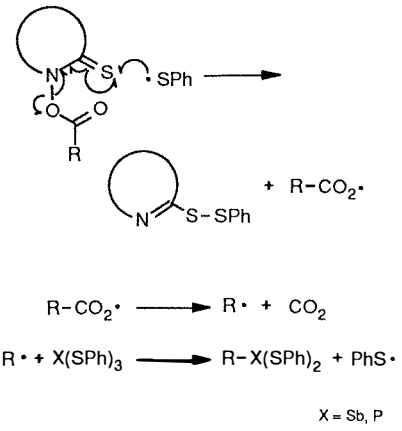
Scheme 20



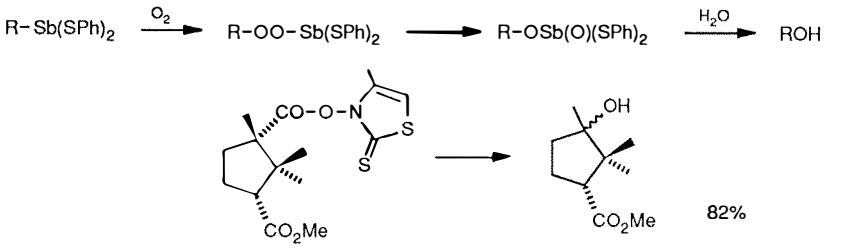
Scheme 21



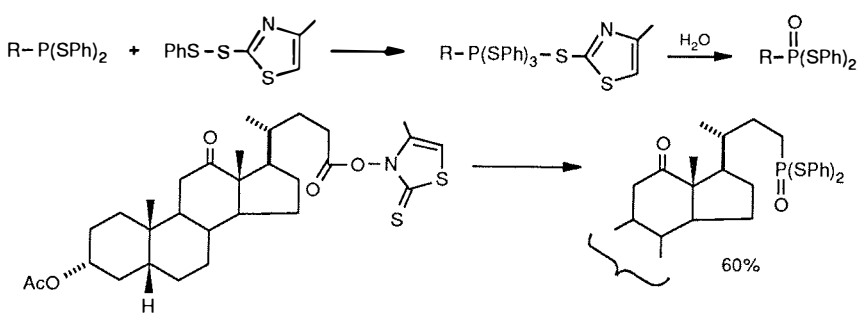
Scheme 22



Scheme 23



Scheme 24



undergo addition of the disulfide by-product giving a pentavalent phosphorus species which is hydrolyzed to the alkyl di(phenylthio)phosphonate (Scheme 24).

Alkyl aryl selenides and tellurides can be obtained by the reaction of O-acyl thiohydroxamates with diaryl diselenides or ditellurides.[35] The reaction involves attack of the alkyl radical on the diselenide or ditelluride with expulsion of an arylselenenyl or aryltelluryl radical as chain carrier (Scheme 25). In the case of diphenyl diselenide, the reaction is carried out in refluxing toluene while diaryl ditellurides give best results on initiation by white light at 35°C. Reasonable yields of alkyl aryl selenides and tellurides can be obtained in this way (Scheme 26) although, in the case of selenides, large excesses of the diselenide are required. Radicals generated from O-acyl thiohydroxamates can also be trapped with dimethyl and dibenzyl diselenides or with dicyanogen triselenide to give mixed alkyl selenides and alkyl selenocyanates.[36]

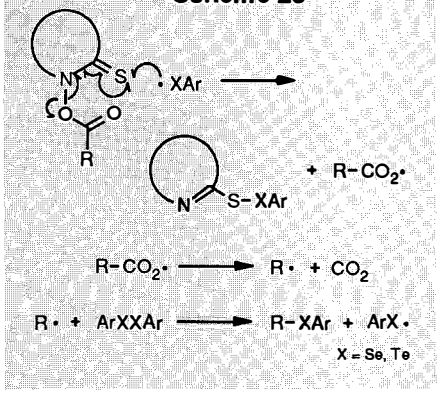
Alkyl 2-pyridyl selenides can be prepared readily by photolysis or thermolysis of the O-acyl esters of *N*-hydroxypyridine-2-selenone[11] (Scheme 27). This reaction presumably proceeds *via* a chain mechanism analogous to that of the O-acyl thiohydroxamate rearrangement (Scheme 7, S = Se). When applied to an appropriately protected L-glutamic acid derivative and with subsequent ozonolysis and selenoxide elimination, this reaction can be used to synthesize optically pure L-vinylglycine[11] in yields that compare well with other routes[37,38] to this sensitive amino acid (Scheme 28). The selenohydroxamic acid is readily available on a multigram scale[11] (Scheme 29).

3. Carbon-Carbon Bond-Forming Radical Chain Reactions of O-Acyl Thiohydroxamates

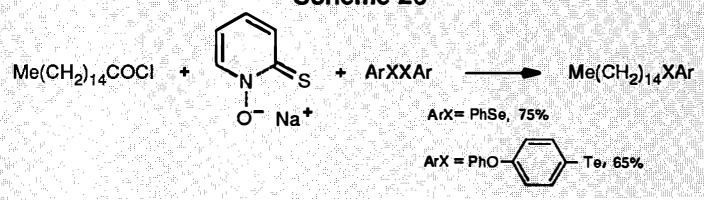
In recent years, a great deal of effort has been put into the development of radical methods for the controlled inter- and intramolecular formation of carbon-carbon bonds.[39-41] The majority of these methods focus on the addition of a carbon radical to an olefin giving an adduct radical which abstracts hydrogen from a suitable donor (Scheme 30). The overall effect is the addition of R• and H• across a double bond. Relatively few efficient methods exist in which chain transfer is achieved not by hydrogen abstraction but by abstraction of a different group [42,43] or by addition to a further multiple bond.[44]

The reaction of O-acyl thiohydroxamates with electron-poor alkenes is one such method in which the elements of R• and ArS• add, regioselectively, across a double bond.[3,4,45] The general reaction mechanism is given in Scheme 31. With simple activat-

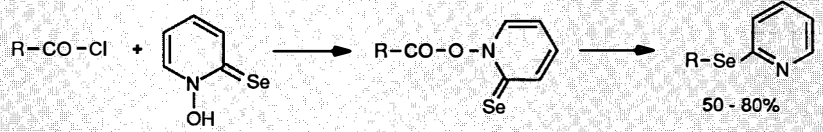
Scheme 25



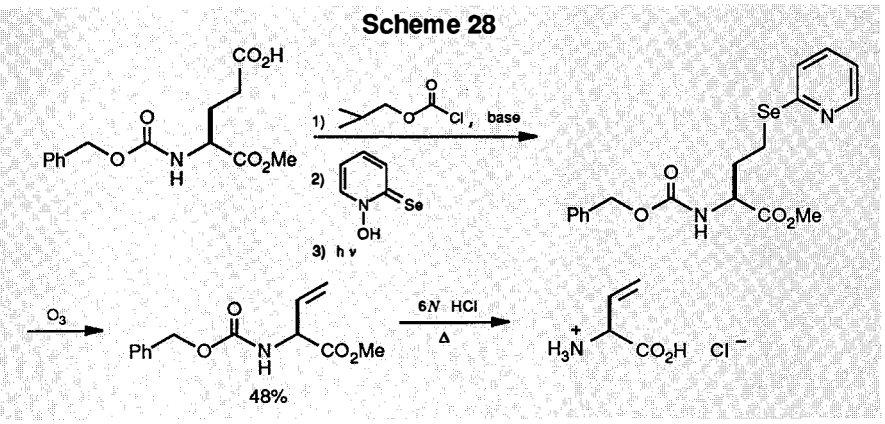
Scheme 26



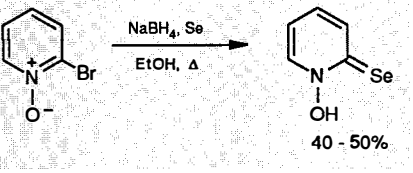
Scheme 27



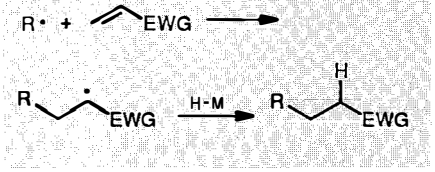
Scheme 28



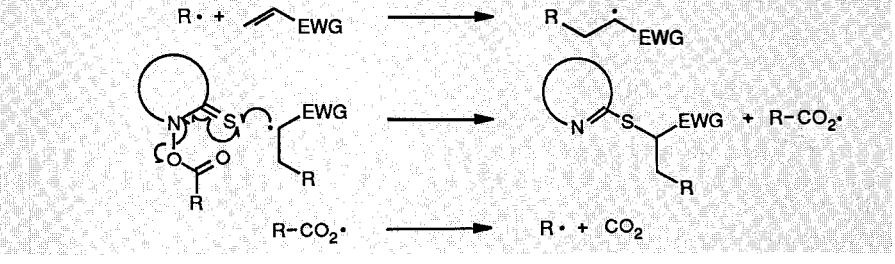
Scheme 29



Scheme 30



Scheme 31



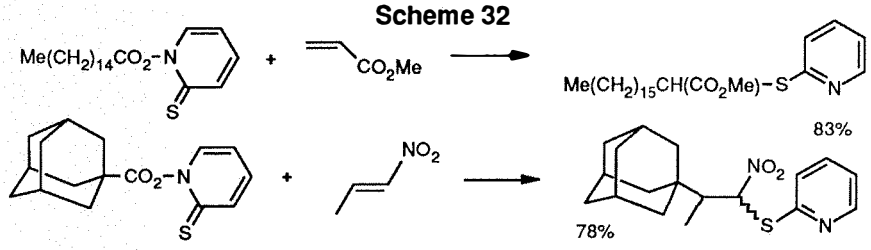
ed terminal alkenes, yields vary from moderate to good, depending on the nature of the activating group (Scheme 32). The rich synthetic potential of these adducts is far too varied to detail here. The use of the strongly electron-withdrawing nitro group as the activating group allows radical addition to internal alkenes[4] (Scheme 32). The use of nitroalkenes as radical traps in this sequence is especially beneficial as the product α-nitro sulfides can be easily converted into carboxylic acids by treatment with either iodoxybenzene/*tert*-butyltetramethylguanidine[3] or alkaline hydrogen peroxide[4] (Scheme 33). With aqueous titanium trichloride, α-nitro sulfides yield aldehydes[4] (Scheme 33). Use of maleic anhydride as the radical trap leads to 2-alkyl-3-arylthiosuccinic anhydrides which, under the reaction conditions, spontaneously eliminate the thiol providing an excellent entry into substituted maleic anhydrides (Scheme 34). The method is not limited to the use of classical Michael acceptors. Vinyl phosphonium salts prove to be excellent radicalophiles, and base hydrolysis of the resultant adducts leads to simple alkyl pyridyl sulfides[46] (Scheme 35). Radical addition to electron-deficient acetylenes has also been achieved in reasonable yield by this method[3,45] (Scheme 36).

Radical cyclization reactions have been achieved using an intramolecular variant of these new carbon-carbon bond-forming reactions[3] (Scheme 37). Indeed, the cyclization of a 5-hexenyl radical derived from *O*-(6-heptenoyl)thiohydroxamate has been used recently as a radical clock reaction in the measurement of rates of hydrogen transfer from various hydrogen donors.[5]

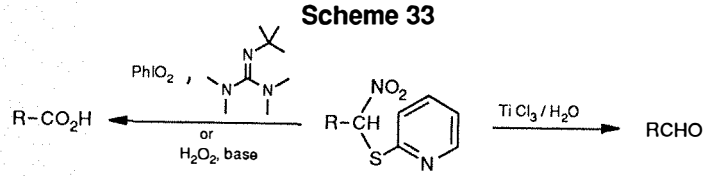
Electrophilic perfluoroalkyl radicals generated from the corresponding O-acyl thiohydroxamates can be added to electron-rich olefins in moderate yield[13] (Scheme 38).

A somewhat different approach to the formation of carbon-carbon bonds by radical methods involves radical addition/-elimination reactions.[39-41] Radicals generated from O-acyl thiohydroxamates add to 2-(carboethoxy)allyl *tert*-butyl sulfide with concomitant expulsion of the *tert*-butylthiyl radical from the allylic position.[47,48] The *tert*-butylthiyl radical then acts as chain carrier, adding onto the thiocarbonyl sulfur of another molecule of starting thiohydroxamate (Schemes 39 and 40). The presence of an olefin activating group is necessary for the efficient formation of carbon-carbon bonds by this method.[48] Similarly the presence of a suitable activating group significantly increases the rate of radical ad-

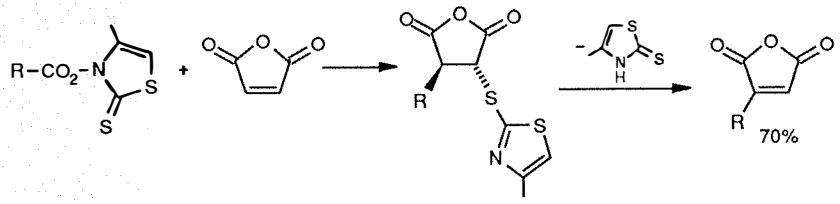
Scheme 32



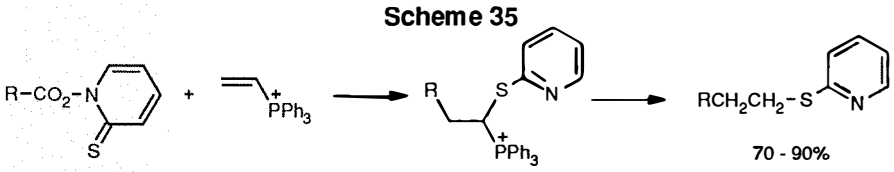
Scheme 33



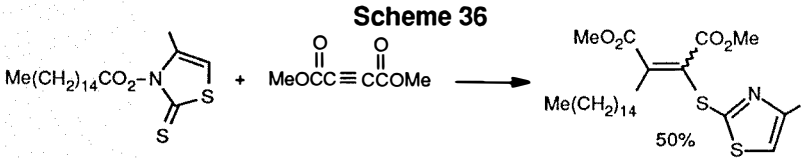
Scheme 34



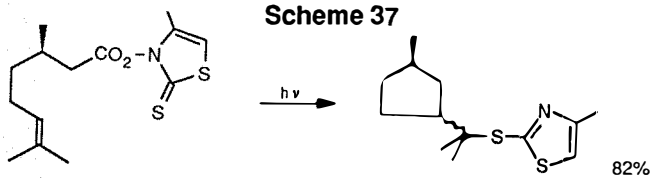
Scheme 35



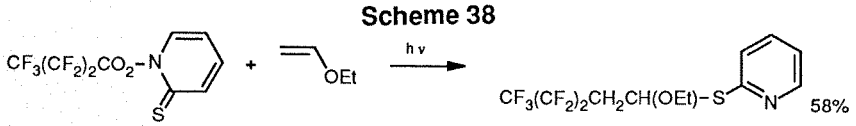
Scheme 36



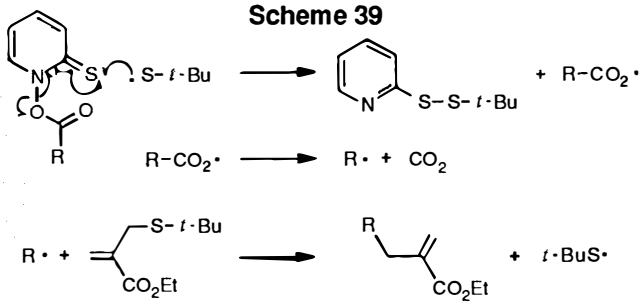
Scheme 37



Scheme 38



Scheme 39



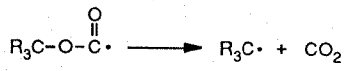
dition to the allylstannanes.[49] 2-Nitroallyl phenyl sulfide is also a good substrate for this type of S_H2', or distal, addition/elimination radical carbon-carbon bond-forming process[4] (Scheme 41). Attempts to set up a proximal type addition/elimination sequence[50,51] using O-acyl thiohydroxamates and diethyl methylthiomethylenemalonate were unsuccessful.[48]

A final method for radical carbon-carbon bond formation with O-acyl thiohydroxamates involves the addition of radicals to protonated heteroaromatic bases[52,53] (Scheme 42). Addition to pyridinium salts leads, whenever possible, to mixtures of 2- and 4-substituted pyridines in which the 2-isomer predominates.

4. Related Processes

The facile loss of carbon dioxide from *tert*-alkoxycarbonyl radicals (Scheme 43)

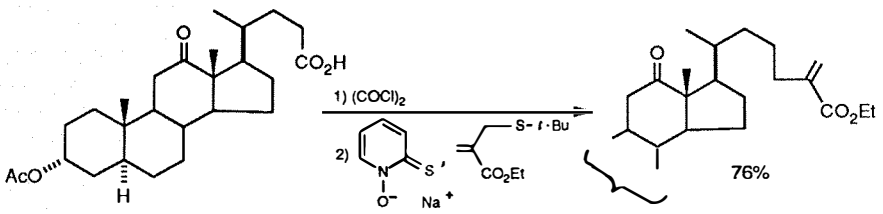
Scheme 43



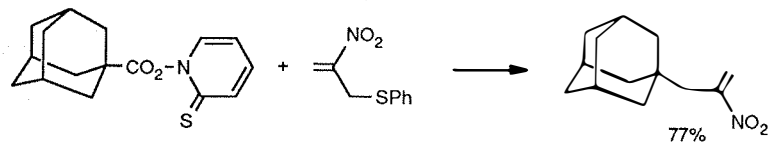
allows the formation of tertiary radicals from tertiary alcohols by means of their mixed oxalate esters with 2-mercaptopyridine-*N*-oxide. *In situ* formation and decomposition of these mixed oxalates in the presence of the highly hindered hydrogen donor triethylmethyl mercaptan gives good yields of hydrocarbons[54,55] (Scheme 44). This radical deoxygenation procedure for tertiary alcohols parallels those of Graf[56] and Jackson[57] insomuch as it involves the same basic fragmentation (Scheme 43) but proceeds under much milder conditions and does not require the use of tin hydride as in the Graf procedure. The hydrogen donor triethylmethyl mercaptan is easily prepared from triethylmethanol by treatment with hydrogen sulfide and acid.[55] In refluxing carbon tetrachloride the same mixed oxalate esters lead, *via* a radical chain reaction, to *tert*-alkyl chlorides in good yield[58] (Scheme 45). A related non-chain radical reaction involves pyrolysis of alkoxy-*tert*-butylperoxy oxalates in carbon tetrachloride.[59]

Quaternary carbon centers can be formed in moderate yields from tertiary alcohols by decomposition of the 2-mercaptopyridine-*N*-oxide mixed oxalate in the presence of simple Michael acceptors (Scheme 46) or in the presence of 2-(carboethoxy)allyl *tert*-butyl sulfide[54,55] (Scheme 47). Once again intramolecular radical capture is possible. Treatment of allyldiethylmethanol, first with oxalyl chloride and then with 2-mercaptopyridine-

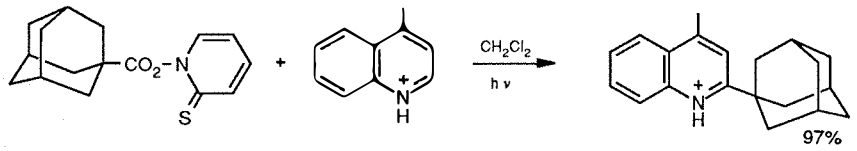
Scheme 40



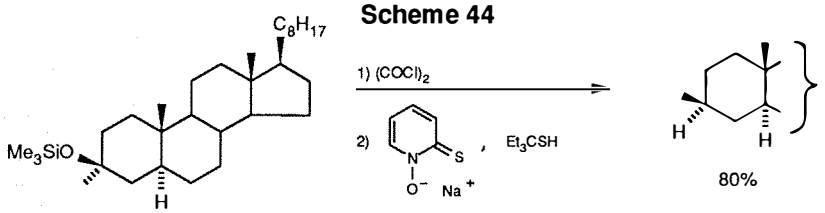
Scheme 41



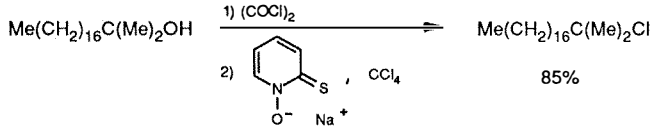
Scheme 42



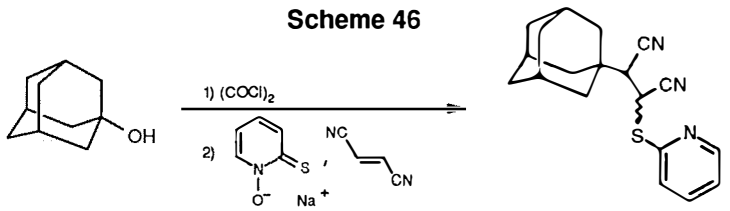
Scheme 44



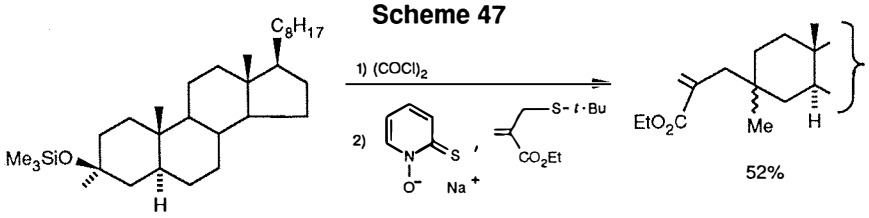
Scheme 45



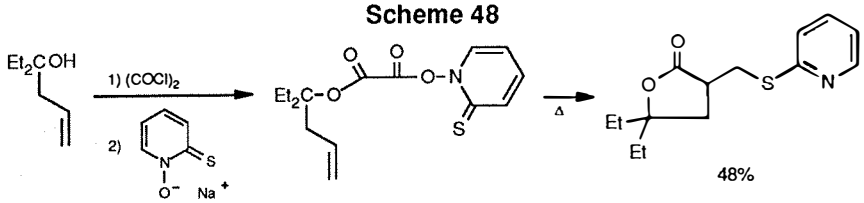
Scheme 46



Scheme 47



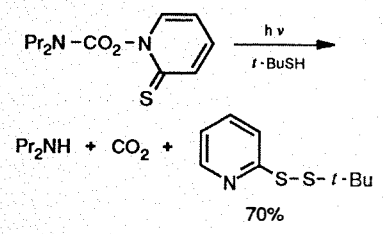
Scheme 48



N-oxide, sodium salt in refluxing benzene, leads to a highly substituted γ-lactone formed by intramolecular capture of the intermediate alkoxycarbonyl radical[55] (Scheme 48). This reaction is obviously of potential use in the α-methylene-γ-lactone field.

Finally, esters (mixed anhydrides) of carbamic acids with 2-mercaptopyridine-*N*-oxide provide a useful source of aminyl radicals on tungsten lamp photolysis[60] (Scheme 49).

Scheme 49



In summary, the readily available carboxylic esters of potentially aromatic thiohydroxamic acids, particularly 2-mercaptopyridine-*N*-oxide and 4-methyl-*N*-hydroxythiazoline-2-thione, are a clean, useful source of carbon radicals and should find wide use in organic synthesis. These O-acyl thiohydroxamates can be formed in the presence of many functional groups frequently encountered in organic synthesis and have the advantage over the more commonly used reagents in that they do not generate troublesome organotin halides or elemental mercury as by-products.

The author wishes to express his gratitude to Professors Sir Derek Barton, FRS, and also to Dr. W.B. Motherwell, for the privilege, honor and, above all, the pleasure of being able to work with them at the Institut de Chimie des Substances Naturelles in Gif sur Yvette, France.

About the Author

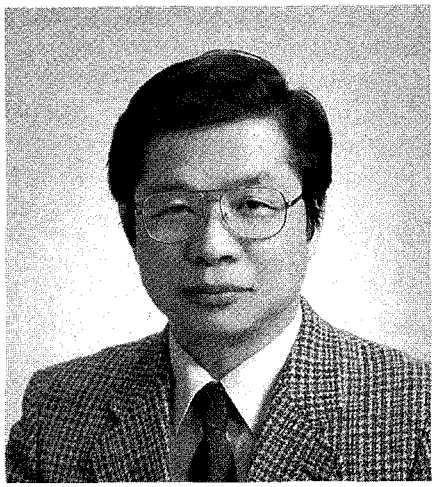
Dr. David Crich received the B.Sc. degree in chemistry with French from the University of Surrey in 1981 and the degree of Docteur ès Sciences from the Université de Paris XI in 1984. After a period of postdoctoral research with Professors Barton and Potier in Gif, he was appointed to his current position as lecturer at University College London in October 1985.

References:

1) **Barton**, D.H.R.; Crich, D.; Motherwell, W.B. *Chem. Commun.* **1983,** 939.
2) *Idem Tetrahedron* **1985,** *41,* 3901.
3) **Barton, D.H.R.**; Crich, D.; Kretzschmar, G. *J. Chem. Soc., Perkin Trans. 1* **1986,** 39.
4) Barton, D.H.R.; Togo, H.; Zard, S.Z. *Tetrahedron* **1985,** *41,* 5507.
5) Newcomb, M.; Seung, U.P. *J. Am. Chem. Soc.* **1986,** *108,* 4132.
6) Kohrman, R.E.; West, D.X.; Little, M.A. *J. Heterocycl. Chem.* **1974,** *11,* 101.
7) Baldwin, J.E. *Chem. Commun.* **1976,** 734.
8) Katritzky, A.R.; Jones, R.A. *J. Chem. Soc.* **1960,** 2937.
9) Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron* **1981,** *37,* 233.
10) Barton, D.H.R.; Hervé, Y.; Potier, P. ; Thierry, J. *Chem. Commun.* **1984,** 1298.
11) Barton, D.H.R.; Crich, D.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1985,** *41,* 4347.
12) Prabhakar, S.; Lobo, A.M.; Santos, M.A.; Rzepa, H.S. *Synthesis* **1984,** 829.
13) Barton, D.H.R.; Lacher, B.; Zard, S.Z. *Tetrahedron* **1986,** *42,* 2325.
14) Barton, D.H.R.; McCombie, S.W. *J. Chem. Soc., Perkin Trans. 1* **1975,** 1574.
15) Barton, D.H.R.; Crich, D.; Lobberding, A.; Zard, S.Z. *Tetrahedron* **1986,** *42,* 2329.
16) Hartwig, W. *ibid.* **1983,** *39,* 2609.
17) Robins, M.J.; Wilson, J.S.; Hansske, F. *J. Am. Chem. Soc.* **1983,** *105,* 4059.
18) Cristol, S.J.; Seapy, D.G. *J. Org. Chem.* **1982,** *47,* 132.
19) Barton, D.H.R.; Dowlatshahi, H.A.; Motherwell, W.B.; Villemin, D. *Chem. Commun.* **1980,** 732.
20) Barton, D.H.R.; Kretzschmar, G. *Tetrahedron Lett.* **1983,** *24,* 5889.
21) Barton, D.H.R.; Crich, D.; Potier, P. *ibid.* **1985,** *26,* 5943.
22) Tenud, L.; Farooq, S.; Seibl, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970,** *53,* 2059.
23) Ankers, W.B.; Brown, C.; Hudson, R.F.; Lawson, A.J. *Chem. Commun.* **1972,** 935.
24) Nally, J.; Ordsmith, N.H.R.; Proctor, G. *Tetrahedron Lett.* **1985,** *26,* 4107.
25) Mukaiyama, T.; Ikeda, S.; Kobayashi, S. *Chem. Lett.* **1975,** 1159; Mukaiyama, T.; Narasaka, K.; Hayashi, M. *ibid.* **1972,** 259.
26) Johnson, C.R.; Nakanishi, A.; Nakanishi, N.; Tanaka, K. *Tetrahedron Lett.* **1975,** 2865.
27) Mukaiyama, T.; Narasaka, K.; Furusato, M. *Bull. Chem. Soc. Jpn.* **1972,** 652.
28) Barton, D.H.R.; Lacher, B.; Zard, S.Z. *Tetrahedron Lett.* **1985,** *26,* 5939.
29) Barton, D.H.R.; Crich, D.; Motherwell, W.B. *ibid.* **1983,** *24,* 4979.
30) Johnson, R.G.; Ingham, R.K. *Chem. Rev.* **1956,** *56,* 219.
31) Wilson, C.V. *Org. React.* **1957,** *9,* 332.
32) Barton, D.H.R.; Crich, D.; Motherwell, W.B. *Chem. Commun.* **1984,** 242.
33) Barton, D.H.R.; Bridon, D.; Zard, S.Z. *ibid.* **1985,** 1066.
34) *Idem Tetrahedron Lett.* **1986,** *27,* 4309.
35) *Idem ibid.* **1984,** *25,* 5777.
36) Barton, D.H.R. *et al. Tetrahedron* **1986,** *42,* 4983.
37) Afzali-Ardakani, A.; Rapoport, H. *J. Org. Chem.* **1980,** *45,* 4817.
38) Hanessian, S.; Sahoo, S.P. *Tetrahedron Lett.* **1984,** *25,* 1425.
39) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon Carbon Bonds;* Pergamon Press: Oxford, 1986.
40) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985,** *24,* 553.
41) Hart, D.J. *Science* **1984,** *223,* 883.
42) Kraus, G.A.; Landgrebe, K. *Tetrahedron* **1985,** *41,* 4039; *idem Tetrahedron Lett.* **1984,** *25,* 3939.
43) Curran, D.P.; Chen, M.H.; Kim, D. *J. Am. Chem. Soc.* **1986,** *108,* 2489.
44) Stork, G.; Sher, P.M. *ibid.* **1983,** *105,* 6765.
45) Barton, D.H.R.; Crich, D.; Kretzschmar, G. *Tetrahedron Lett.* **1984,** *25,* 1055.
46) Barton, D.H.R.; Togo, H.; Zard, S.Z. *ibid.* **1985,** *26,* 6349.
47) Barton, D.H.R.; Crich, D. *ibid.* **1984,** *25,* 2787.
48) *Idem J. Chem. Soc., Perkin Trans. 1* **1986,** 1613.
49) Baldwin, J.E. *et al. Chem. Commun.* **1986,** 1339.
50) Baldwin, J.E.; Kelly, D.R. *ibid.* **1985,** 682.
51) Russell, G.A.; Tashtoush, H.; Ngoviwatchai, P. *J. Am. Chem. Soc.* **1984,** *106,* 4622.
52) Barton, D.H.R.; Garcia, B.; Togo, H.; Zard, S.Z. *Tetrahedron Lett.* **1986,** *27,* 1327.
53) See page 221 of ref. 39 for a discussion of other reactions of this type.
54) Barton, D.H.R.; Crich, D. *Chem. Commun.* **1984,** 774.
55) *Idem J. Chem. Soc., Perkin Trans. 1* **1986,** 1603.
56) Pfenninger, J.; Heuberger, C.; Graf, W. *Helv. Chim. Acta* **1980,** *63,* 2328.
57) Billingham, N.C.; Jackson, R.A.; Malek, F. *Chem. Commun.* **1977,** 344.
58) Crich, D.; Fortt, S.M. *Synthesis* **1987,** 35.
59) Jensen, F.R.; Moder, T.I. *J. Am. Chem. Soc.* **1975,** *97,* 2281.
60) Newcomb, M.; Park, S.-U.; Kaplan, J.; Marquardt, D.J. *Tetrahedron Lett.* **1985,** *26,* 5651.

Allylic Tin Compounds in Organic Synthesis*

Yoshinori Yamamoto
Department of Chemistry
Faculty of Science
Tohoku University
Sendai 980
Japan



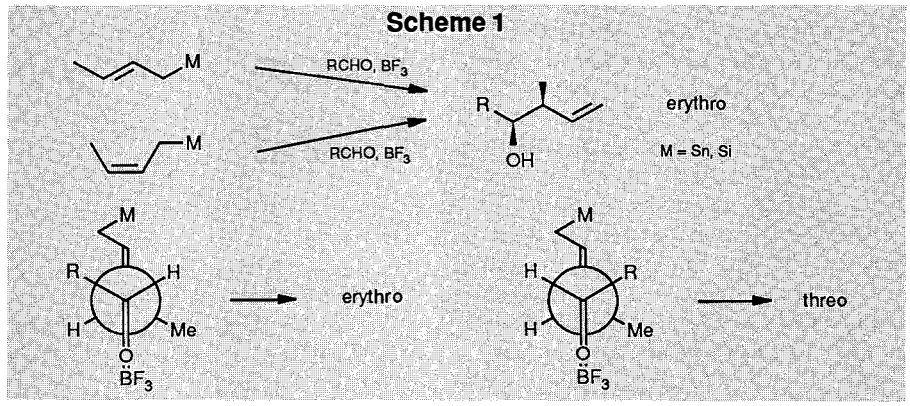
Neumann reported in 1967 that allylation of aldehydes with allyltrialkyltins took place at high temperature.[1] In 1972, Pereyre found that the allylation proceeded at relatively low temperatures when activated aldehydes were used.[2] More recently, Tagliavini demonstrated that the allylation could be carried out under very mild conditions by utilizing allyltin chlorides.[3] In 1979, Naruta, Ushida and Maruyama[4] developed a facile allylation procedure *via* allyltrialkyltins in the presence of BF_3•OEt_2, which was in the same category as the allyltrialkylsilane-Lewis acid procedure.[5] Although the initial scope of the allylation *via* allylic tins did not make a strong impact upon the field of organic synthesis, the diastereoselective aspect of crotyltin-BF_3•OEt_2 reactions later developed by Yamamoto[6] significantly increased the synthetic utility of allyltin derivatives.

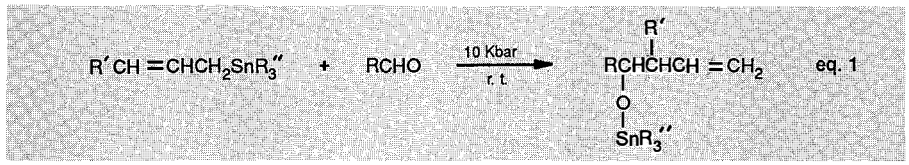
Erythroselective Allylation of Aldehydes of Crotyltin-BF_3 Systems

Generally speaking, the thermal reactions of crotyl organometallic compounds (M = Li, Mg, B, Al, Sn, Ti, Zr, Cr, etc.) with aldehydes proceed through a six-membered cyclic transition state.[7] It is thus widely accepted that the trans crotylmetal produces the threo homoallyl alcohol, while the cis derivative gives the erythro isomer. However, in 1980, we discovered that the Lewis acid-mediated reaction of crotyltins and silanes with aldehydes produces the erythro homoallyl alcohol regardless of the geometry of the crotyl unit.[6a] Boron trifluoride coordinates to the carbonyl oxygen, preventing the coordination of the metal to the oxygen atom. Consequently, the acyclic transition state may be involved in the Lewis acid-mediated reactions. It is easily determined that among several possible transition-state geometries, the conformation leading to the erythro isomer must be favored for steric reasons (Scheme 1).

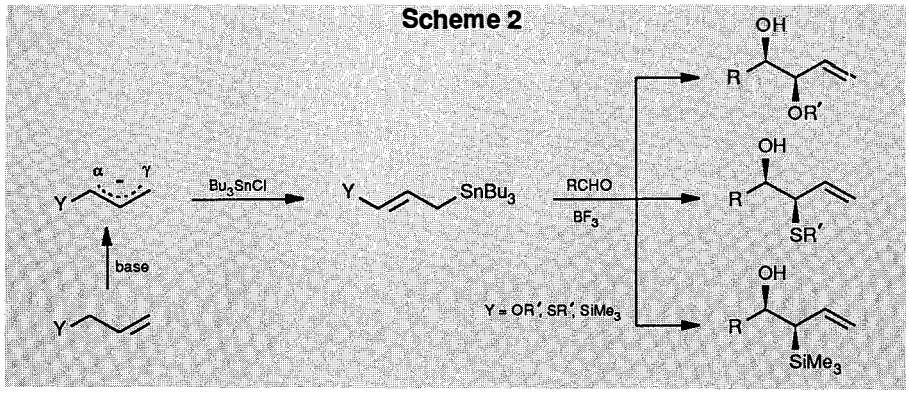
A similar selective inversion from threo to erythro by BF_3 coordination to aldehydes, as observed in the tin reaction, was also seen with other crotyl organometallic compounds that possess relatively high electronegativity (M = Zr, Ti, Cu, Hg, Tl, etc.). On the other hand, the metals which exhibited low electronegativity or possessed a vacant orbital did not show this selective inversion even under the influence of BF_3.[8] The allylation with allylic tin compounds took place at room temperature under high pressure[9] (eq. 1). The reaction proceeded almost quantitatively and the stereoselectivity was in agreement with the selectivity *via* a six-membered cyclic transition state. In addition to simple crotyltins, the functional-group-substituted allylic tins also exhibited erythro diastereoselectivity in the Lewis acid-mediated reaction with aldehydes.[10] The heteroatom-substituted allylic carbanions (Y = OR′, SR′ or $SiMe_3$) were trapped with Bu_3SnCl to produce the corresponding allylic tins in high yield, which were then converted to the erythro homoallyl alcohols (Scheme 2).

Scheme 1

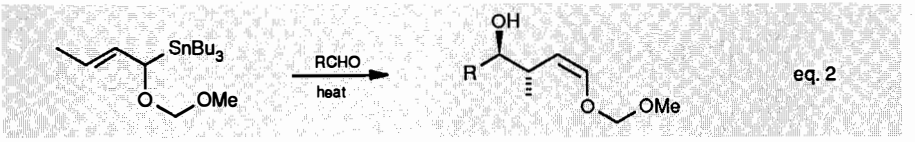




Scheme 2

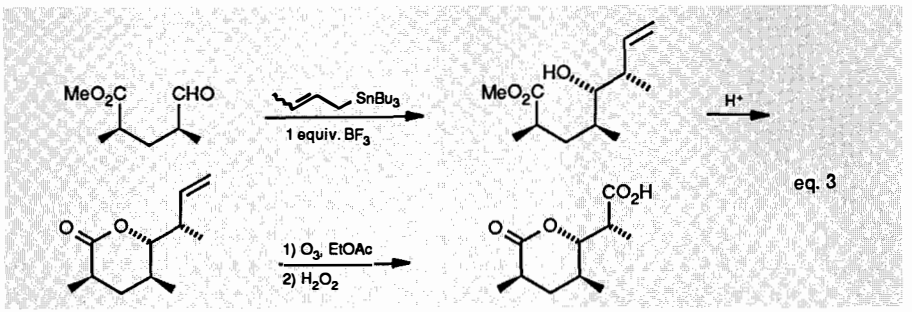


Although most of the Lewis acid-mediated reactions of allyltins produced the erythro alcohol, the addition of (*E*)-2-cinnamyltins to aldehydes in the presence of BF_3 afforded the threo isomer.[11] The stereoselectivity was also dependent upon the choice of Lewis acid and mode of addition.[12] The $TiCl_4$-mediated additions gave high erythro or threo selectivity depending simply on the order in which reactants were mixed. The normal sequence of addition [1) RCHO, 2) $TiCl_4$, 3) crotyltin] produced erythro selectivity as expected, while the reversed addition [1) crotyltin, 2) $TiCl_4$, 3) RCHO] afforded threo selectivity. (*E*)-1-Alkoxy-substituted crotyltin gave threo (*Z*)-homoallyl alcohol on heating with aldehydes[13] (eq. 2).

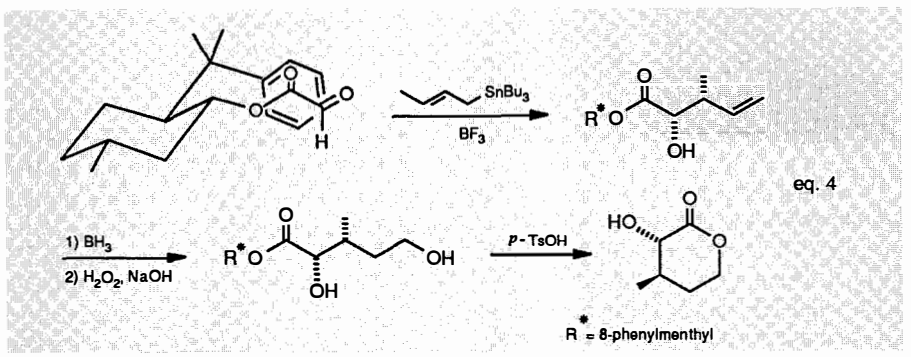


eq. 2

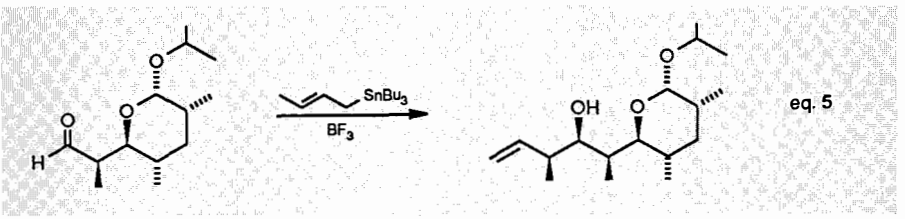
Reaction of *meso*-4-carbomethoxy-2-methylpentanal with crotyltin in the presence of one equivalent of BF_3•OEt_2 followed by lactonization produced the anti-Cram erythro adduct with greater than 94% selectivity in 90% isolated yield.[14] This was then converted into the (±)-Prelog-Djerassi lactonic acid in 85% yield (eq. 3). On the other hand, the reaction of the corresponding (±)-isomer with crotyltin-BF_3 produced the Cram erythro adduct predominantly.[15] The BF_3-mediated reaction of crotyltin with 8-phenylmenthyl glyoxylate produced the erythro isomer with high stereoselectivity. The erythro isomer was then converted to optically active verrucarinolactone[16] (eq. 4). Quite high erythro Cram selectivity (>30:1) was realized in the course of macrolide total synthesis[17] (eq. 5). The crotyltin-BF_3 reaction was also applied to the synthesis of cembranolide precursors,[18] (-)-sesbanimide A[19] and several other complex molecules.[20]



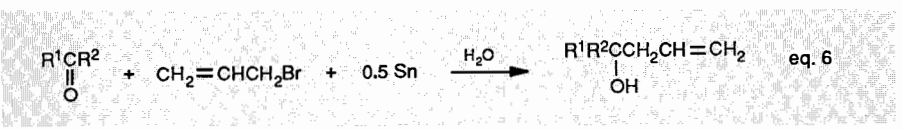
eq. 3



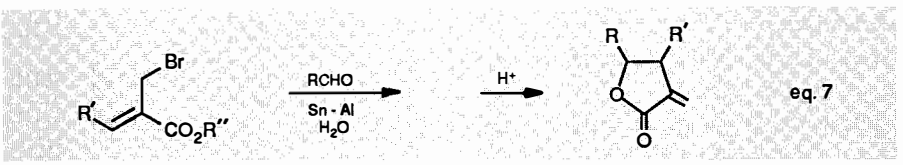
eq. 4



eq. 5



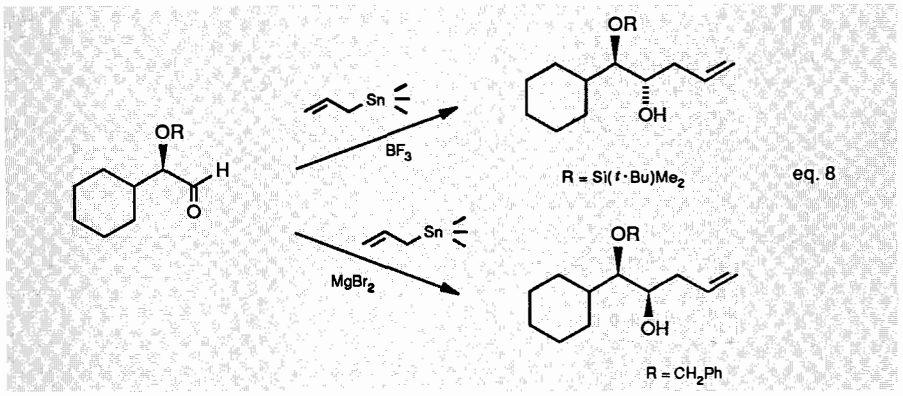
eq. 6



eq. 7

Metallic Tin- or Tin Halide-Mediated Allylation

The allylation can be carried out with allylic tins generated *in situ*. The reactions of aldehydes and ketones with allylic iodides or bromides in the presence of Sn or $SnCl_2$ produced the corresponding homoallyl alcohols.[21] Quite interestingly, the allylation was carried out successfully by allyl bromide and Sn in the presence of water (eq. 6), and also proceeded smoothly in the presence of water by using Sn and Al.[22] Although the allylation *via* the *in situ* generation method produced low diastereoselectivity,[21,22] the reaction of (*E*)-cinnamyl chloride with aldehydes in the presence of Sn-Al-H_2O/THF/HBr[23a] or $SnCl_2$-Al-H_2O/THF[23b] gave high threo selectivity. 2-Methylene-4-butyrolactones were synthesized in good yield by using this procedure[24] (eq. 7). The electrochemical



eq. 8

allylation of aldehydes and ketones was achieved by electroreductive regeneration of diallyltin in the presence of a catalytic amount of Sn.[25] Tin-graphite was used to prepare diallyltin dibromide complexes which in turn reacted with aldehydes to give homoallyl alcohols.[26] Treatment of allylic phosphates with the reagent prepared from Bu_3SnLi and Et_2AlCl or from SnF_2 and Et_2AlCl afforded allyltins which reacted with aldehydes to produce homoallyl alcohols;[27] but unfortunately the diastereoselectivity was low in comparison with the Lewis acid-mediated allylation.

High Asymmetric Induction with Allyltin-Lewis Acid

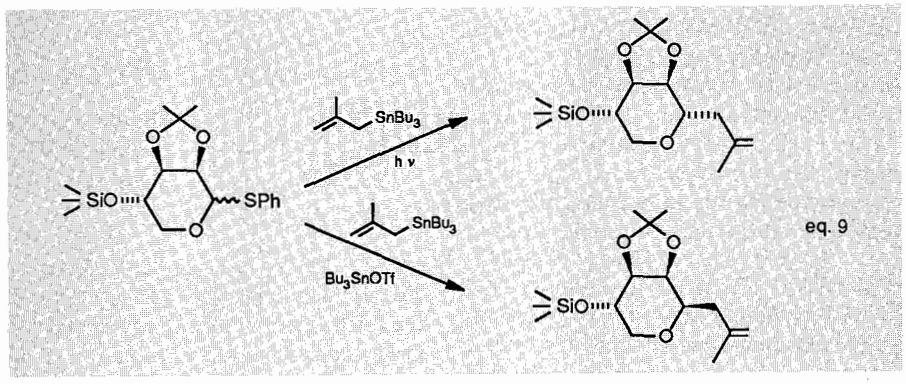
Generally, the reaction of allylmetals with ordinary chiral aldehydes having no ability to be chelated results in low Cram selectivity; the highest Cram selectivity attained in the reaction of 2-phenylpropanal with allyltin was 5:1.[28] On the other hand, very high 1,2-asymmetric allylation was realized in the reaction of α-hydroxyaldehyde derivatives.[29] By proper choice of Lewis acid and protecting group, both diastereomers were prepared with excellent stereoselectivity (eq. 8). Quite similarly, proper choice of Lewis acid was crucial for controlling diastereofacial selectivity in the reaction of crotyltin with α-alkoxyaldehydes[30a] and β-hydroxyaldehyde derivatives.[30b] The importance of Lewis acids for controlling the selectivity was also demonstrated in the reaction of α-methylthioaldehydes with allyltriphenyltin.[31] Thiophenyl glycosides were converted to C-glycosides *via* the reaction of allylic tins either in the presence of Lewis acid or under the influence of light, giving different stereoselectivities in some cases[32] (eq. 9). Optically active diallylbis(2-phenylbutyl)tin was prepared and reacted with aldehydes in the presence of $BF_3{\cdot}OEt_2$.[33] Unfortunately, the enantiomeric excess of the resulting homoallyl alcohols was only in a range of 20-79%. Allyltin complexes containing (+)-diethyl tartrate as the chiral auxiliary ligand reacted with aldehydes to produce optically active homoallyl alcohols with moderate ee.[34] A high enantiodivergent synthesis of steroidal side chains was accomplished *via* the Lewis acid-mediated reaction of steroidal acetals with allyl- and alkynyltributyltins.[35]

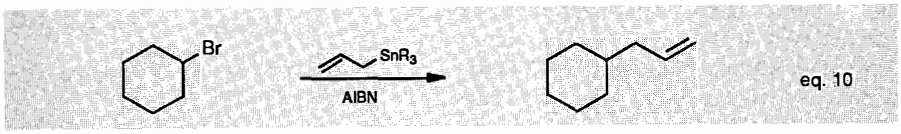
Allylation *via* the Radical Process

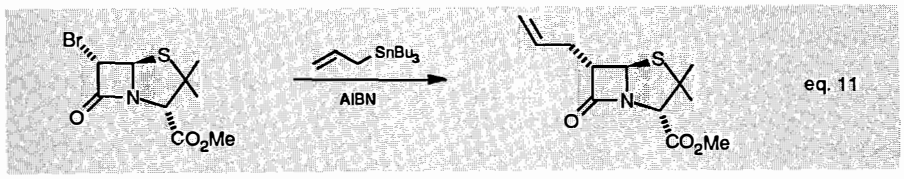
The allyl transfer from allyltrialkyltins to organic halides was discovered by Migita,[36] Kosugi[36] and Pereyre,[37] and subsequently exploited by Keck[38] (eq. 10). The radical allylation procedure was applied to the synthesis of pseudomonic acid C[39] and 6-α-allyl penicillanates[40] (eq. 11; see also eq. 9). The simple pyrrolizidine alkaloid (±)-isoretronecanol was efficiently constructed by the radical cyclization of an allyltin derivative[41] (eq. 12). Radical C-C bond formation *via* Bu_3SnH[42] or allyltin[43] is becoming an important synthetic procedure. Certain allylic phenyl sulfides reacted with alkyl halides or selenides upon irradiation in the presence of $Bu_3SnSnBu_3$ to give formal S_N2' substitution products.[44] Quite similarly, free-radical substitution reactions of allyltin[45a] have been observed with disulfides,[45b] sulfonyl chlorides[45b] and aliphatic nitro compounds.[45c] The allene transfer from propargyltriphenyltin to organic halides has also been reported.[46]

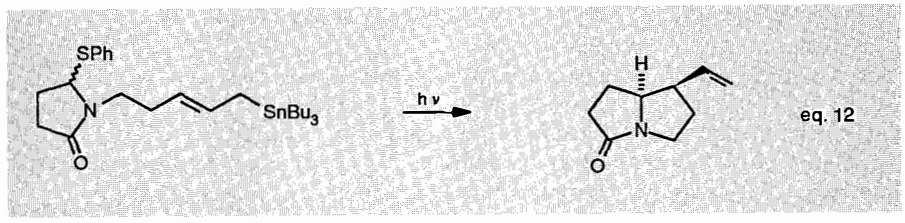
The Palladium-Catalyzed Cross-Coupling Reactions

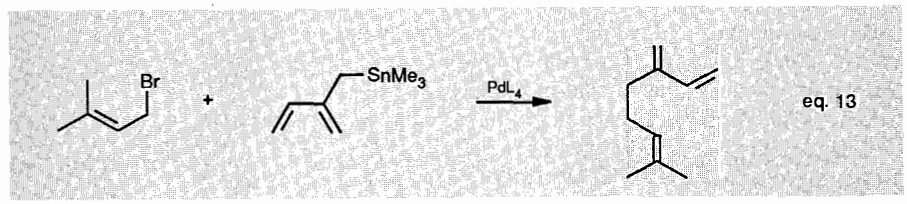
In 1977, Migita and Kosugi found that the reaction of allyltributyltin with aryl bromides in the presence of PdL_4 gave coupling products in good yield.[47a] These researchers further demonstrated that $RhCl(PPh_3)_3$ catalyzed the coupling between allyltins and acyl halides.[47b] Since then, the palladium-catalyzed reactions have been extensively investigated, primarily by Stille[48] and Trost.[49] This area has been reviewed quite recently,[48,50] so only one example of the allylic-allylic coupling reaction is shown in eq. 13.











Regiochemistry and High-Pressure Reactions

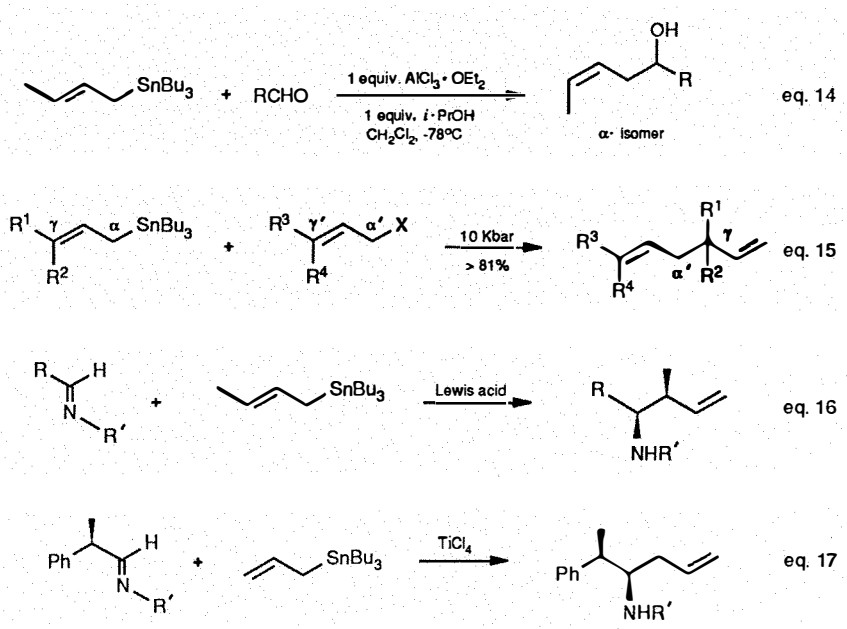
In general, the reaction of unhindered carbonyl compounds with substituted allylic organometallic reagents (M = Li, Mg, B, Si, Sn, Cd, Zn, Cu, Cr, Mn, Zr, etc.) results in the γ-adduct in which the allylic group is attached at the more highly substituted position. The regioreversed addition to unhindered carbonyl compounds to produce the linear adduct is very rare, despite its great potential importance. The reaction of crotyltin with certain aldehydes in the presence of $AlCl_3$-*i*-PrOH produced the α-adduct either predominantly or exclusively[51] (eq. 14), while use of $AlCl_3$ or BF_3 gave the γ-adduct as mentioned above. Allyltrialkyltin regioselectively reacted with allylic halides at room temperature under high pressure (10 Kbar) to give head-to-tail coupling products in high yields[52] (eq. 15). Benzoyl chloride reacted with prenyltin at room temperature under 10 Kbar pressure to give the condensation product at the γ-position. In conclusion, the high-pressure-induced reactions may provide a new type of C-C bond-forming process.

Reactions with Imines, Quinones and Related Compounds

The reaction of aldimines with crotyltin in the presence of Lewis acids produced erythro homoallylamines[53] (eq. 16). Very high Cram selectivity was achieved in the $TiCl_4$-mediated reaction of chiral imines with allyltin[54] (eq. 17). 4-Acetoxy-2-azetidinone derivatives were converted into 4-(*R*)-allylazetidinones with allyltins in the presence of Lewis acids.[55] N-(Alkoxycarbonyl)pyridinium salts were regioselectively allylated in the α-position by using allyltins to give α-allyl-1,2-dihydropyridines.[56] Allylation of quinones with allyltin reagents was extensively investigated by Maruyama and Naruta.[57] Vitamin K_2, coenzyme Qn and related compounds were prepared by this procedure.

Concluding Remarks

Allylsilane chemistry occupies an important position in modern organic synthesis. Allylic tin chemistry is becoming equally important, despite its short history. The organotin compounds are fairly stable and can be handled easily. In some cases, the reaction can be carried out in the presence of water. Nevertheless, the tin compounds are more reactive than the corresponding silicon compounds and exhibit wide reactivity: radical reactions, transition-metal-catalyzed reactions, Lewis acid-mediated reactions, photochemical reactions, and so on. Undoubtedly, broader awareness of organotin chemistry and the tremendous potential of the tin methodology will result in greater application to organic synthesis.



References:

*Taken mainly from the plenary lecture in the Fifth International Conference on the Organometallic and Coordination Chemistry of Germanium, Tin and Lead, at Padua, Italy, September 8, 1986.

1) Konig, K.; Neumann, W.P. *Tetrahedron Lett.* **1967,** 495.
2) Servens, C.; Pereyre, M. *J. Organomet. Chem.* **1972,** *35,* C20. Abel, E.W.; Rowley, R.J. *ibid.* **1975,** *84,* 199.
3) Tagliavini, G.; Peruzzo, V.; Plazzogna, G.; Marton, D. *Inorg. Chim. Acta* **1977,** *24,* L47.
4) Naruta, Y.; Ushida, S.; Maruyama, K. *Chem. Lett.* **1979,** 919.
5) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976,** 1295.
6) a) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980,** *102,* 7107. b) Yamamoto, Y. *et al. Tetrahedron Symp.* **1984,** *40,* 2239. c) Yamamoto, Y. *Silicon, Germanium, Tin and Lead Compounds* **1986,** *9,* 279. d) Yamamoto, Y. *Acc. Chem. Res.* **1987,** in press.
7) a) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982,** *18,* 357. b) Hoffmann, R.W. *Angew. Chem., Int. Ed. Engl.* **1982,** *21,* 555.
8) a) Reetz, M.T.; Sauerwald, M. *J. Org. Chem.* **1984,** *49,* 2292. b) Yamamoto, Y.; Maruyama, K. *J. Organomet. Chem.* **1985,** *284,* C45. Although we proposed the antiperiplanar transition state (Scheme 1), the synclinal geometry was suggested in certain intramolecular reactions; Denmark, S.E.; Weber, E.J. *J. Am. Chem. Soc.* **1984,** *106,* 7970.
9) Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *Chem. Commun.* **1983,** 489.
10) a) Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Organomet. Chem.* **1985,** *292,* 311. b) Quintard, J.; Elissondo, B.; Pereyre, M. *J. Org. Chem.* **1983,** *48,* 1559. c) Yamamoto, Y.; Hatsuya, S.; Yamada, J. *Chem. Commun.* **1987,** 561.
11) Koreeda, M.; Tanaka, Y. *Chem. Lett.* **1982,** *1297,* 1299.
12) Keck, G.E.; Abbott, D.E.; Boden, E.P.; Enholm, E.J. *Tetrahedron Lett.* **1984,** *25,* 3927.
13) Jephcote, V.J.; Pratt, A.J.; Thomas, E.J. *Chem. Commun.* **1984,** 800.
14) Maruyama, K.; Ishihara, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1981,** *22,* 4235.
15) Yamamoto, Y.; Taniguchi, K.; Maruyama, K. *Chem. Commun.* **1983,** 1429.
16) Yamamoto, Y.; Maeda, N.; Maruyama, K. *ibid.* **1983,** 774.
17) Nakajima, N. *et al. J. Am. Chem. Soc.* **1986,** *108,* 4645.
18) Marshall, J.A.; Dehoff, B.S. *J. Org. Chem.* **1986,** *51,* 863.
19) Schlessinger, R.H.; Wood, J.L. *ibid.* **1986,** *51,* 2621.
20) Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1985,** *26,* 6109. Suzuki, K. *et al. J. Am. Chem. Soc.* **1986,** *108,* 5221.
21) a) Mukaiyama, T.; Harada, T.; Shoda, S. *Chem. Lett.* **1980,** 1507. b) Mukaiyama, T.; Harada, T. *ibid.* **1981,** 1527. c) Augé, J.; David, S. *Tetrahedron Lett.* **1983,** *24,* 4009. d) Augé, J. *ibid.* **1985,** *26,* 753.
22) a) Nokami, J.; Otera, J.; Sudo, T.; Okawara, R. *Organometallics* **1983,** *2,* 191. b) Petrier, C.; Einhorn, J.; Luche, J.L. *Tetrahedron Lett.* **1985,** *26,* 1449. c) For allyltin chloride-H_2O, see Boaretto, A.; Marton, D.; Tagliavini, G. *J. Organomet. Chem.* **1985,** *286,* 9.
23) a) Coxon, J.M.; van Eyk, S.J.; Steel, P.J. *Tetrahedron Lett.* **1985,** *26,* 6121. b) Uneyama, K.; Nanbu, H.; Torii, S. *ibid.* **1986,** *27,* 2395.
24) Nokami, J.; Tamaoka, T.; Ogawa, H.; Wakabayashi, S. *Chem. Lett.* **1986,** 541. Tanaka, K. *et al. J. Org. Chem.* **1986,** *51,* 1856. Baldwin, J.E. *et al. Tetrahedron Lett.* **1986,** *27,* 5423.
25) Uneyama, K.; Matsuda, H.; Torii, S. *Tetrahedron Lett.* **1984,** *25,* 6017.
26) Boldrini, G.P. *et al. J. Organomet. Chem.* **1985,** *280,* 307.
27) Matsubara, S. *et al. Bull. Chem. Soc. Jpn.* **1985,** *58,* 1196.
28) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Organomet. Chem.* **1985,** *285,* 31.
29) Keck, G.E.; Boden, E.P. *Tetrahedron Lett.* **1984,** *25,* 265.
30) a) *Idem ibid.* **1984,** *25,* 1879. b) Keck, G.E.; Abbott, D.E. *ibid.* **1984,** *25,* 1883.
31) Shimagaki, M.; Takubo, H.; Oishi, T. *ibid.* **1985,** *26,* 6235.
32) Keck, G.E.; Enholm, E.J.; Kachensky, D.F. *ibid.* **1984,** *25,* 1867.
33) Otera, J.; Kawasaki, Y.; Mizuno, H.; Shimizu, Y. *Chem. Lett.* **1983,** 1529.
34) Boldrini, G.P.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *Chem. Commun.* **1986,** 685.
35) Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986,** *108,* 7116.
36) Kosugi, M.; Kurino, M.; Takayama, K.; Migita, T. *J. Organomet. Chem.* **1973,** *56,* C11.

37) Grignon, J.; Pereyre, M. *ibid.* **1973,** *61,* C33.
38) Keck, G.E.; Yates, J.B. *J. Am. Chem. Soc.* **1982,** *104,* 5829; *J. Org. Chem.* **1982,** *47,* 3591; *J. Organomet. Chem.* **1983,** *248,* C21.
39) Keck, G.E.; Kachensky, D.F.; Enholm, E.J. *J. Org. Chem.* **1985,** *50,* 4317.
40) Hanessian, S.; Alpegiani, M. *Tetrahedron Lett.* **1986,** *27,* 4857.
41) Keck, G.E.; Enholm, E.J. *ibid.* **1985,** *26,* 3311; see also, Ueno, Y.; Okawara, M. *J. Am. Chem. Soc.* **1979,** *101,* 1893.
42) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985,** *24,* 553.
43) Moriya, O. *et al. Chem. Commun.* **1985,** 1401.
44) Keck, G.E.; Byers, J.H. *J. Org. Chem.* **1985,** *50,* 5442.
45) a) Bristow, G.S. *Aldrichim. Acta* **1984,** *17*(3), 75. b) Russell, G.A.; Herold, L.L. *J. Org. Chem.* **1985,** *50,* 1037. c) Ono, N.; Zinsmeister, K.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1985,** *58,* 1069.
46) Baldwin, J.E.; Adlington, R.M.; Basak, A. *Chem. Commun.* **1984,** 1284.
47) a) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977,** 301. b) Kosugi, M.; Shimizu, Y.; Migita, T. *J. Organomet. Chem.* **1977,** *129,* C36.
48) Stille, J.K. *Angew. Chem., Int. Ed. Engl.* **1986,** *25,* 508; Negishi, E. *Acc. Chem. Res.* **1982,** *15,* 340.
49) Trost, B.M.; Keinan, E. *Tetrahedron Lett.* **1980,** *21,* 2591, 2595. Trost, B.M. *Angew. Chem., Int. Ed. Engl.* **1986,** *25,* 1.
50) Mitchell, T.N. *J. Organomet. Chem.* **1986,** *304,* 1. Beletskaya, I.P. *ibid.* **1983,** *250,* 551.
51) Yamamoto, Y.; Maeda, N.; Maruyama, K. *Chem. Commun.* **1983,** 742. See also Gambaro, A.; Boaretto, A.; Marton, D.; Tagliavini, G. *J. Organomet. Chem.* **1984,** *260,* 255.
52) Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *Chem. Commun.* **1984,** 548.
53) a) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Org. Chem.* **1985,** *50,* 3115. b) Keck, G.E.; Enholm, E. *ibid.* **1985,** *50,* 146. c) Hoffmann, R.W.; Endesfelder, A., submitted for publication.
54) Yamamoto, Y. *et al. J. Am. Chem. Soc.* **1986,** *108,* 7778.
55) Fliri, H.; Mak, C. *J. Org. Chem.* **1985,** *50,* 3438. Fujimoto, K.; Iwano, Y.; Hirai, K. *Bull. Chem. Soc. Jpn.* **1986,** *59,* 1363.
56) Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanishi, M. *J. Org. Chem.* **1985,** *50,* 287.
57) Naruta, Y. *J. Am. Chem. Soc.* **1980,** *102,* 3774. Takuwa, A.; Naruta, Y.; Soga, O.; Maruyama, K. *J. Org. Chem.* **1984,** *49,* 1857. Maruyama, K. *et al. Chem. Lett.* **1986,** 1719. Naruta, Y.; Nishiguchi, Y.; Maruyama, K. *ibid.* **1986,** 1703.

About the Author

Professor Yoshinori Yamamoto was born in Kobe, Japan, in 1942. He received the B.Sc. degree in 1965 and the Ph.D. degree in 1970 from Osaka University. He joined the faculty of Osaka University as Instructor in 1970. He spent 1970-1972 as a postdoctoral fellow at Purdue University with Herbert C. Brown. He was appointed Associate Professor at Kyoto University in 1977 and moved to Tohoku University as Professor of Chemistry in 1986.

Dr. Yamamoto is the author of about 150 scientific publications, including a book entitled "Organometallic Chemistry" written in Japanese (Maruzen, Tokyo, 1983). In 1976, he received the Award of the Chemical Society of Japan for young scientists. His present research interests include the development of new synthetic methodologies *via* organometallic compounds, stereocontrol of acyclic systems, and asymmetric synthesis. Some reactions and reagents developed by his group include organocopper-Lewis acid reagents, allylic tin/boron trifluoride-based stereocontrol, and zirconium and enolate chemistry.

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About Our Cover:

Our chemist-collector loves puzzles and has never encountered a greater puzzle than that on this cover. When he bought this *Dancing Fishermen* (oil on panel, 12½ x 16¾ inches) in a small gallery in Surrey some years ago, he was told it was 18th-century Italian. Since then, various Italian, French, Flemish and Dutch artists from the 17th to the 19th century have been suggested. The panel is old and the paint film could be 17th-century; so our chemist-collector is inclined to think it is by an out-of-the-way Dutch artist of the late 17th century, one greatly influenced by the Italianate artists of Utrecht, such as Abraham Bloemaert. Now a puzzle within a puzzle: are these just dancing fishermen, or is this possibly a New Testament subject, Peter the Fisher of Men, at an Atlantic fishing port? Our chemist-collector would greatly welcome help from our readers.

Lab Notes

Prompted by Alberto Haces' lab note concerning visualization of compounds on TLC plates with iodine, [*Aldrichim. Acta* **1986,** *19*(2), 30], I am describing an alternative, even quicker method.

Almost instant visualization can be achieved by sprinkling a mixture of silica gel and iodine (*ca.* 10:1) over the TLC plate placed on a piece of paper. Tipping the powder off the plate onto the paper after a few seconds leaves the plate clearly developed. The silica gel and iodine can then be poured from the paper into a storage jar for reuse.

D. Levin
ICI Organics Division
P.O. Box A38
Leeds Road
Huddersfield HD2 IFF
England

I have designed a glass water bath which has proved very convenient over the years. It fits on a magnetic stirrer and allows easy observation of the beaker or flask contents.

Felix Friedberg
Department of Biochemistry
Howard University
Washington, D.C. 20059

Editor's note: We have made and listed the water bath following Dr. Friedberg's recommendations.

We have perfected a small-scale filtration device which allows convenient filtration into any small vessel.

The bottom of a Buchner flask (100 or 250ml) is removed and the new edge ground flat in order to form a reasonably airtight seal with a thick glass plate (6mm).

A small flask or sample tube is placed inside the Buchner flask under the funnel, and the sample is filtered in the usual way. Exchange of flasks is easy, and we have used this system for both small-scale dry flash chromatography and hot filtration during recrystallization.

Maxwell H. Muir
Robert A. Johnson
Chemistry Department
Brunel University
Uxbridge, Middlesex UB8 3PH
England

Working with surfactants in the lab, we have found that all sorts of solutions can be freed of bubbles by placing the container in an ultrasonic bath filled with tap water. Some products like sulfosuccinates trap bubbles created by mechanical agitation so well that this is one of the few methods that allows for rapid color determinations. A few seconds of exposure to the ultrasound, and *voilà* — clear bubble-free solutions ready to be checked for turbidity and color.

Raymond E. Bilbo
Alkaril Chemicals, Inc.
P.O. Box 1010
Winder, Georgia 30680

The safe sampling of hazardous solutions for analysis can be a difficult problem, especially when air-, light- or heat-sensitive compounds may decompose in the process. Moreover, the use of a syringe generally can cause the liquid to be sprayed as the needle is withdrawn from the septum.

Recently, we devised an inexpensive aliquoting device for sampling under negative pressure.

The device was made from such readily accessible materials as a ½-cc disposable syringe, a "Microcap" tube, septa (Aldrich Z10,072-2) and a 4-in. needle. By sliding a small Tygon tubing collar down the plunger against the barrel of the syringe, the plunger is locked in place and both hands are free to operate the device.

To sample, simply insert the needle through the solvent chamber, dry the needle bore with nitrogen, then penetrate the flask septum. While holding the solvent chamber firmly against the flask septum, withdraw the aliquot into the syringe. Pull the needle into the solvent chamber containing reaction solvent or quench medium. After mixing the aliquot with solvent, push the needle back through the chamber septum for chromatographic analysis. The diluted aliquot in the solvent chamber can be saved for further analysis.

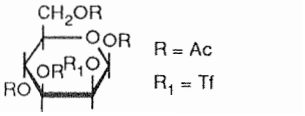
Minor modifications of this method allow air-, light- and heat-sensitive materials to be sampled; for example, the chamber can be filled with inert gas, wrapped with foil, or cooled.

Steve de Keczer
Institute of Organic Chemistry
Syntex Research
Palo Alto, CA 94304

Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt**. *We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by



Professor Henry C. Padgett at UCLA School of Medicine suggested that we offer 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-β-D-mannopyranose. As reported recently,[1] this sugar derivative, when treated with ^{18}F-fluoride ion under phase-transfer catalysis followed by acetate hydrolysis, affords high yields of 2-^{18}FDG (2-deoxy-2-fluoro-D-glucose). 2-^{18}FDG is the most widely used radiochemical in positron emission tomography diagnostic imaging.[2]

Naturally, we made the suggested triflate.

1) Hamacher, K.; Coenen, H.H.; Stöcklin, G. *J. Nucl. Med.* **1986,** *27,* 235.
2) Phelps, M.E.; Mazziotta, J.C. *Science* **1985,** *228,* 799.

It was no bother at all, just a pleasure to be able to help.

New Methods in the Formation of Macrocyclic Lactams and Lactones of Biological Interest

Harry H. Wasserman
Department of Chemistry
Yale University
New Haven, CT 06511

The following report summarizes our recent investigations at Yale on some new methods useful in organic synthesis. These methods involve the chemistry of reactive intermediates such as cyclopropanone, singlet oxygen and 1,2,3-vicinal tricarbonyls. Although β-lactams have not usually been considered to be reactive intermediates, the opening of this strained ring system by intramolecular attack of nucleophiles has provided a novel, general pathway for the synthesis of a series of spermine and spermidine alkaloids recently isolated from plant sources. The discussion will deal first with the development of new azetidinone syntheses and then, with their application to the above polyamine alkaloid syntheses.

Our continuing interest in the chemistry of singlet oxygen has led us to explore the oxazole-triamide rearrangement as a means of protection/activation of carboxylates. The use of this method for macrolide and peptide syntheses will be outlined in the second section. The third part of the report will deal with the incorporation of 1,2,3-tricarbonyl units as substituents in β-lactam systems in such a way as to permit synthesis of the fused-ring systems present in the carbapenems, carbacephems and penems.

Azetidinones as Building Blocks in Polyamine Alkaloid Synthesis

Recently, studies in our laboratories aimed at the development of new methods for forming β-lactams have focused on ring expansions of cyclopropanones,[1] cyclizations of β-halopropionamides,[2] and investigations on the oxidative decarboxylation of azetidinecarboxylates.[3] The oxidative procedures (Scheme 1) have included a) triplet-oxygen oxygenation of dianions,[4] b) singlet-oxygen addition to the enol silylates of the azetidinecarboxylic esters[6] and c) the addition of peracids to iminium salts formed by the decarbonylation of acid halides.[5]

The availability of these new methods prompted us to test their applicability to the synthesis of 3-aminonocardicinic acid (3-ANA, **1**), the nucleus of the nocardicins[7] (Table 1). The procedures utilized in this

Scheme 1

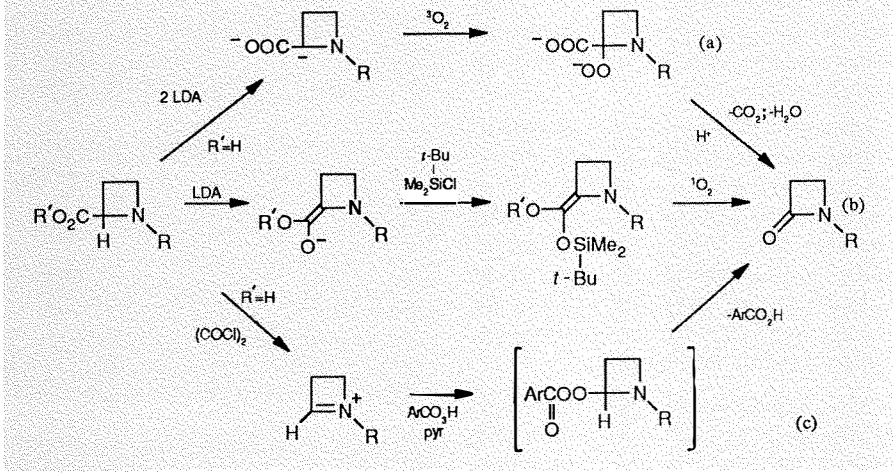
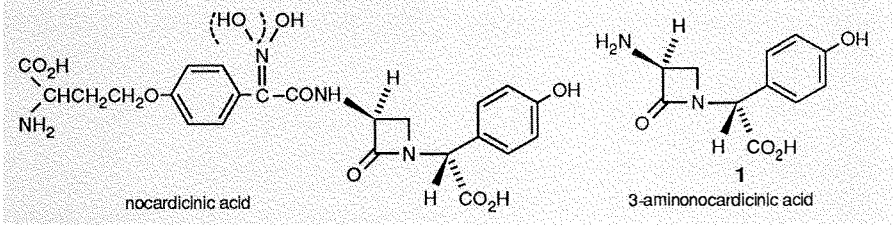


Table 1



Professor Harry H. Wasserman (left) receiving the A.C.S Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich, from Dr. Irwin Klundt, Vice-President, Aldrich Chemical Co., Inc.

work included a) ring expansion of a cyclopropanolamine, b) the oxidative decarbonylation of a substituted azetidinecarboxylate and c) the ring closure of a β-halopropionamide.

The details of the synthetic investigations on 3-ANA will not be covered here. However, a significant finding arising from that work commanded our attention and, indirectly, opened the door to further investigations on the chemistry of β-lactams. Thus, in the course of attempting to purify 3-ANA, we found, as did Kamiya in his early work,[8] that this substance readily isomerizes to the piperizonecarboxylic acid **2** (Scheme 2).

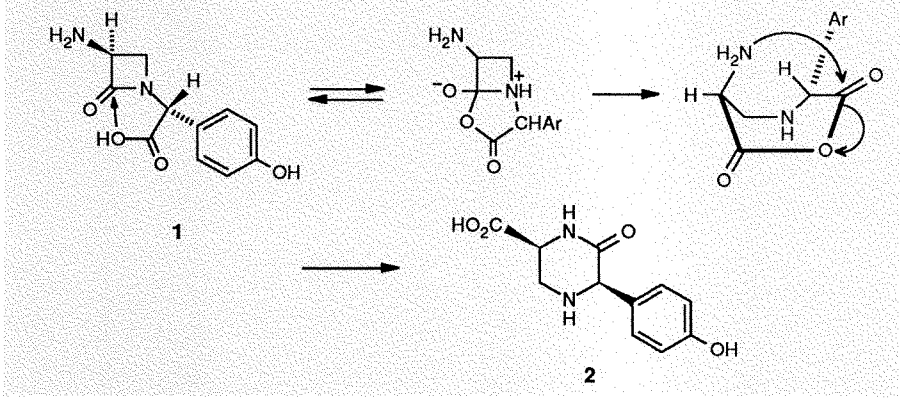
The mechanism of this rearrangement, which takes place during silica gel chromatography, may be visualized as shown in Scheme 2. The carboxylic acid of **1** interacts with the β-lactam carbonyl group, leading to ring opening and formation of an unsymmetrical anhydride in which the amino group is well disposed for intramolecular acylation leading to **2**.

We were interested in the intramolecular ring opening of the β-lactam ring as a means of introducing a β-aminopropionic acid residue in synthetic operations. Earlier, Manhas and Bose reviewed the possibility of using β-lactams as synthons[9] and had, in fact, carried out ring-opening reactions involving intramolecular attack of a phenolic hydroxyl, while Testa formed an azaazepinone by similar reaction of an anilino derivative[10] (Scheme 3). More recently, Ojima has utilized a different type of β-lactam ring opening as a route to peptides.[11]

About the same time that we were thinking about the possibility of using β-lactams as synthons, reports appeared on the isolation of a number of spermine and spermidine alkaloids from plant sources. These products included celacinnine (**3**),[12] homaline (**4**)[13] and dihydroperiphylline (**5**).[14] Celacinnine had been synthesized by Ganem[15] using the catecholborane-promoted cyclization of an ω-aminocarboxylic acid, and work aimed at homaline synthesis had been reported. We visualized the possibility of preparing these products by intramolecular opening of β-lactams as suggested by the accented lines in the structures in Table 2.

Our first target using this approach was the synthesis of homaline. Our synthetic procedure began with the addition of 1,4-diaminobutane in conjugate fashion to acrylonitrile followed by hydrolysis, esterification and reduction according to known procedures (Scheme 4).[16] The two secondary nitrogens were then protected as their *tert*-butoxycarbonyl (BOC) derivatives. The optically active phenylazetidinone was then converted to the anion with sodium hydride and allowed to react with the ditosylate of the diprotected diamine to form the corresponding bis β-lactam **6** (Scheme 5). Intramolecular opening of **6** through a 6-membered transition state was accomplished *via* deprotection in acid followed by heating in quinoline to yield the bis 8-membered amino lactam **7**. Alternatively, we found that direct pyrolysis of the di-BOC derivative in diphenyl ether charged with dry air led to better yields of **7**. The synthesis was completed by bis methylation using Eschweiler-Clarke procedures to avoid racemization.

Scheme 2



Scheme 3

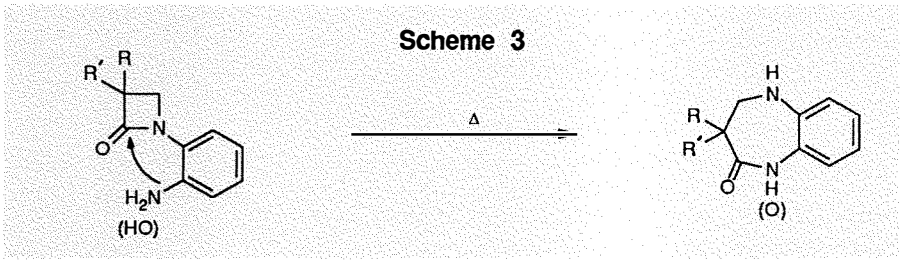
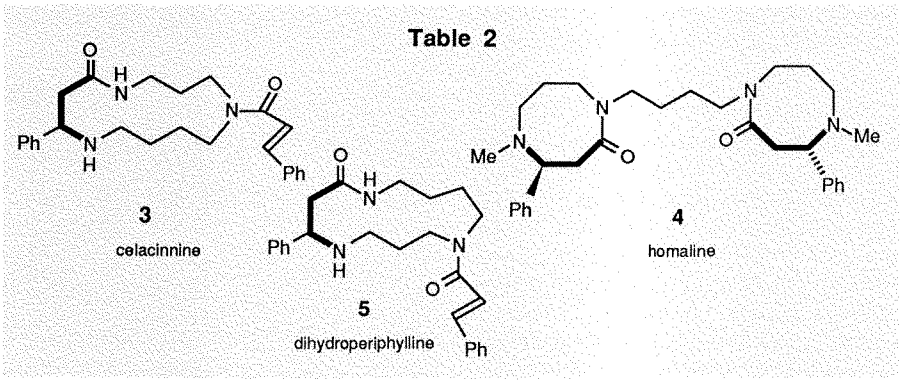
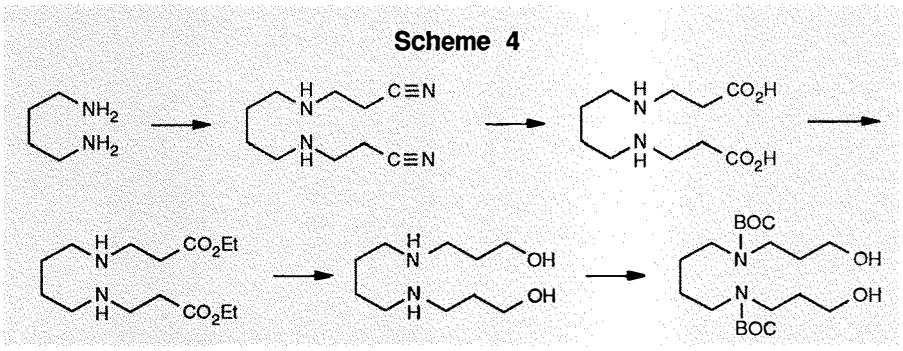


Table 2



Scheme 4

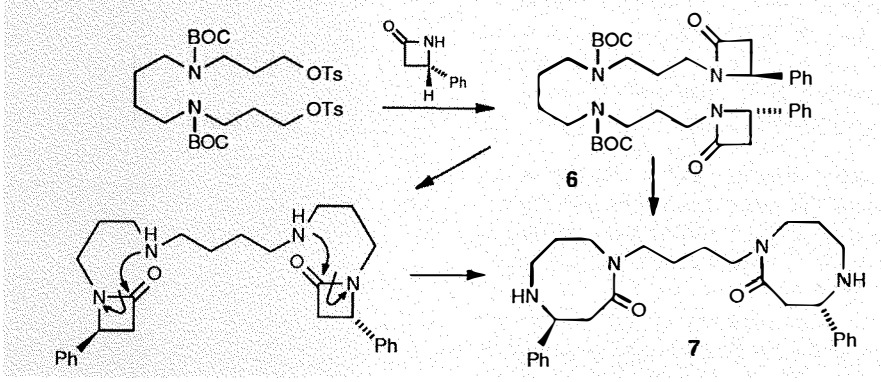


Our next objective was the synthesis of celacinnine and dihydroperiphylline. We visualized the possibility of coupling a 9-membered-ring amino lactam with a β-lactam to form the corresponding 13-membered ring in both of these alkaloids, and studied the feasibility of forming suitable 9-membered-ring precursors. Two methods appeared applicable for this purpose (Scheme 6): one was the coupling of a β-lactam with a 5-membered-ring imino ether discovered by Bormann,[17] yielding a fused-ring product on heating in chlorobenzene. We found that the diazabicyclononenone thus formed readily underwent reductive cleavage with sodium cyanoborohydride ($NaBH_3CN$) in acetic acid. An alternative procedure utilized the sodium/ammonia cleavage of a diazabicyclononanone according to the method developed by Kemp.[18]

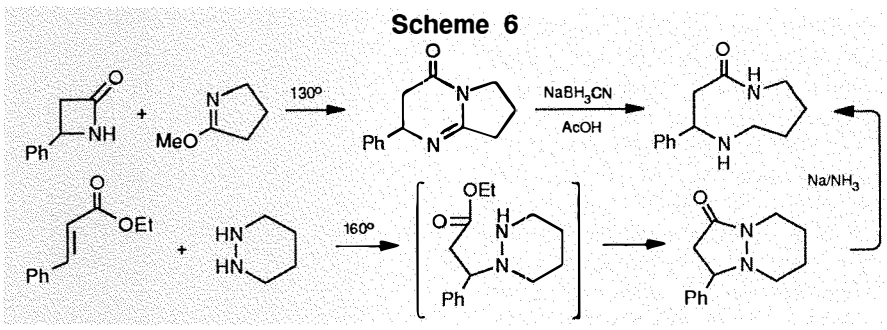
For the synthesis of dihydroperiphylline (Scheme 7), we coupled piperidazine with ethyl acrylate to form the fused-ring system which, on reductive cleavage (sodium/ammonia) yielded the 9-membered amino lactam **8**. This could then be treated with *trans*-cinnamoyl chloride and the protected material converted to the lactim ether **9** using Meerwein's Reagent. The last stages of the synthesis involved the coupling of the lactim ether with the β-lactam followed by reductive cleavage with $NaBH_3CN$ to form the 13-membered dihydroperiphylline. The synthesis of celacinnine[19] also used a 9-membered-ring precursor and incorporated the aminopropyl residue by a transamidation reaction.

About the same time that we completed the dihydroperiphylline synthesis, Hesse reported the isolation of verbascenine[20] and we applied our ring-expansion techniques to the synthesis of this 17-membered triamino lactam. The synthesis of this material (Scheme 8)[21] required differential protection of the three secondary amino groups, and again employed the β-lactam-lactim ether coupling to accomplish the conversion of a 13-membered ring to the 17-membered-ring product. Our precursor was lactam **10** containing the two amino groups protected as trichloroethoxycarbonyl (TROC) and BOC residues, respectively. Conversion of this material to the iminomethyl ether and coupling with a phenylazetidinone gave low yields (18%) of the coupled product along with substantial demethylation, regenerating the parent lactam. We therefore used the iminoethyl ether instead to provide an extra element of steric inhibition to the dealkylation reaction. Under these circumstances, the coupling took place in 60% yield to form

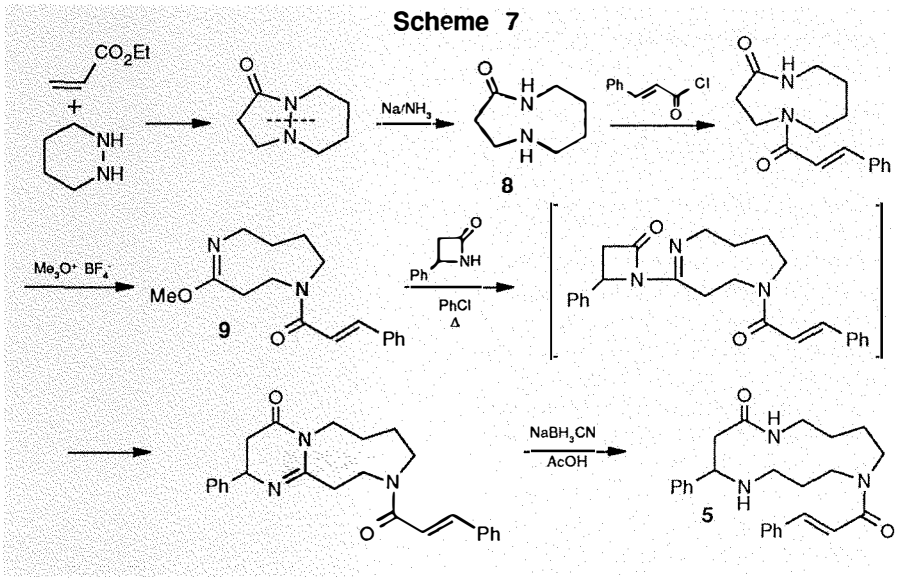
Scheme 5



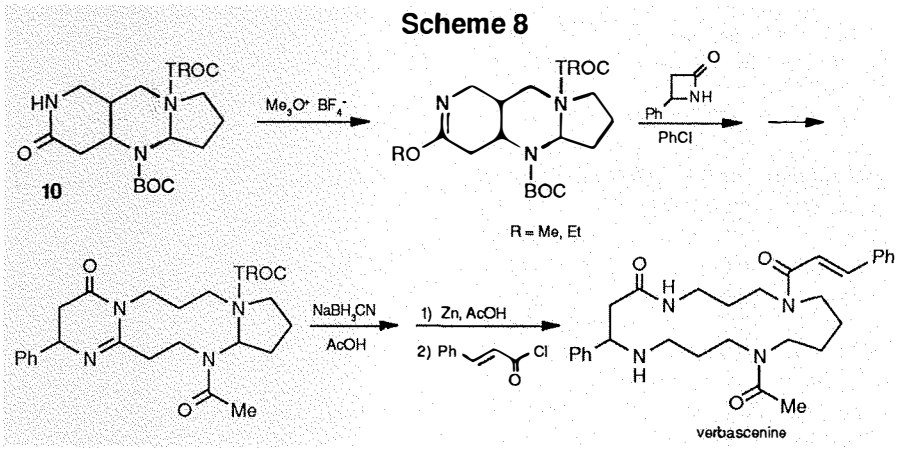
Scheme 6



Scheme 7



Scheme 8

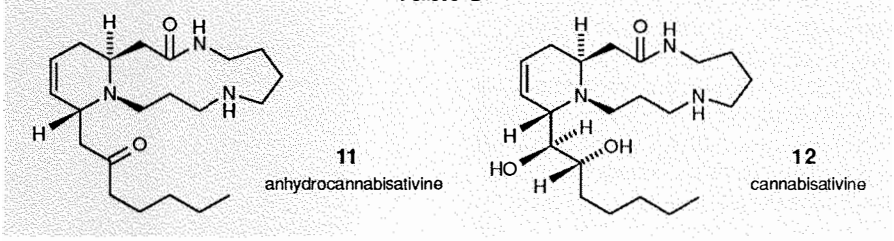


the product. After replacement of the BOC group by an acetyl residue, reductive cleavage of the bicyclic system, reductive removal of the TROC group at N-5 and introduction of a cinnamoyl residue took place smoothly.

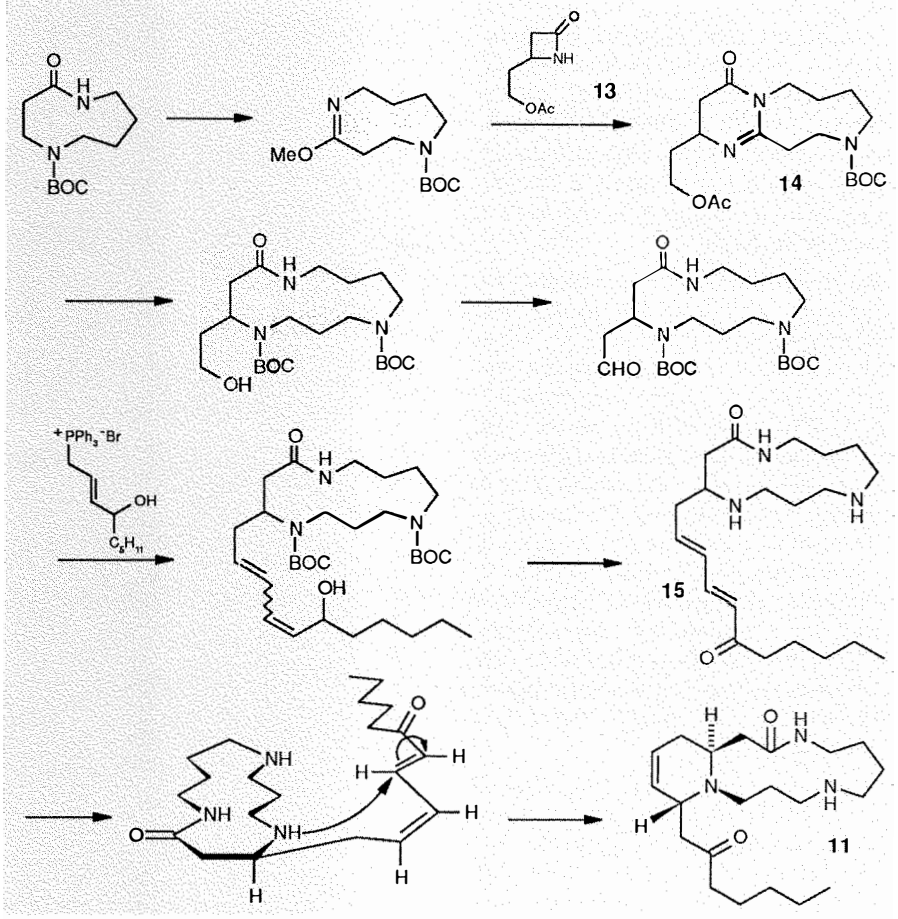
Two spermidine alkaloids found in the roots and leaves of the marijuana plant, anhydrocannabisativine (**11**) and cannabisativine (**12**)[22] (Table 3), were the polyamine lactams to which we next directed our attention. Our strategy for the synthesis of these materials involved the coupling of 9-membered-ring precursors with substituted amino lactams, thereby generating the precursors of the required 13-membered rings and providing substituents for appending the required fused 6-membered rings. We made use of the acetoxyethyl β-lactam **13**, readily available from the coupling of 1-acetoxy1,3-butadiene with *N*-chlorosulfonyl isocyanate followed by reduction as reported by the Merck group in their synthesis of thienamycin.[23] This β-lactam was readily converted to the fused-ring system **14**, which was useful for both the cannabisativine and anhydrocannabisativine syntheses as shown in Schemes 9 and 10.

In the anhydrocannabisativine synthesis (Scheme 9),[24] the acetoxyethyl derivative **14** was hydrolyzed to the corresponding alcohol and then oxidized to the aldehyde, which was then coupled *via* the Wittig reaction with the required triphenylphosphonium bromide. The resulting diene of undefined stereochemistry was oxidized with manganese dioxide to the ketone and then subjected to the action of trifluoroacetic acid for removal of the BOC groups. At this stage, the NMR spectrum showed that the product **15** contained *E,E* stereochemistry. Our synthetic plan required an intramolecular addition of the secondary amino group to a *Z,E* dienone to generate the required tetrahydropyridine ring. Thus, the conversion to the *E,E* configuration under the above conditions of acid-catalyzed deprotection represented an obstacle to the success of these last steps. As expected, our product **15** failed to undergo cyclization on thermolysis up to 260°C, with or without amine catalyst. This problem was solved very easily by irradiation of the dienone overnight at 254nm in ethanol. Under these circumstances, *trans* to *cis* isomerization took place, and the resulting *Z,E* form underwent cyclization to form anhydrocannabisativine (**11**) as the sole product, in nearly quantitative yield. An interesting aspect of this reaction which deserves further study involves the selective cyclization

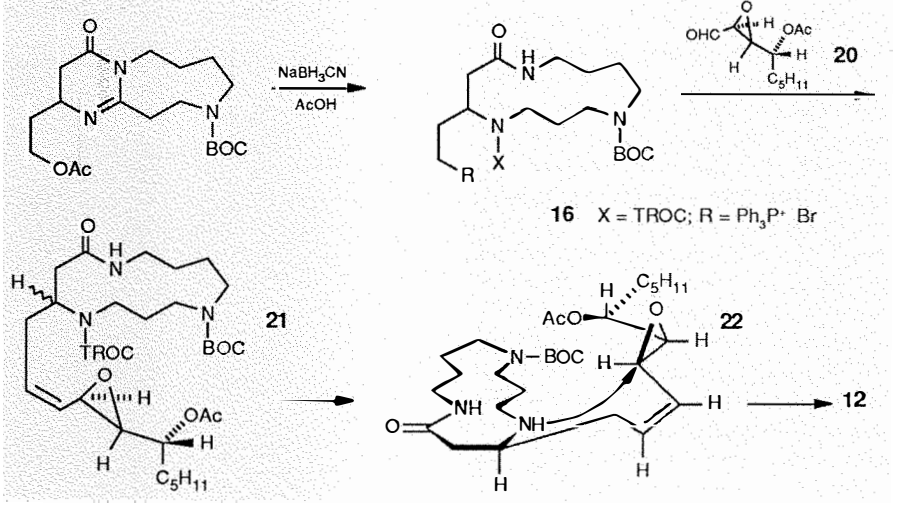
Table 3



Scheme 9



Scheme 10



of only one of the possible diastereomers, corresponding to the natural configuration.

For the synthesis of cannabisativine (**12**) (Scheme 10),[26] we were able to make use of the same acetoxyethylazetidinone (**13**) as we used in our anhydrocannabisativine synthesis. Coupling of **13** with the 9-membered imino ether followed by $NaBH_3CN$ reduction yielded the 13-membered lactam which could be converted to the differentially protected triphenylphosphonium salt **16**. This was then allowed to react with the acetoxy epoxy aldehyde **20** to form the *cis* unsaturated epoxide **21** (Scheme 10). By this Wittig coupling, we were able to introduce the double bond and the epoxide in the desired location for formation of the tetrahydropyridine ring. To form the aldehyde component **20** (Scheme 11), the dianion of propargyl alcohol was added to hexanal, yielding an acetylenic diol which was reduced to the *trans* allylic diol and then epoxidized using *tert*-butyl hydroperoxide/vanadyl acetylacetonate to form **17** and **18** as a 1:3 mixture of diastereomers. Since this Sharpless catalyst is known to produce the erythro epoxide preferentially,[25] the major isomer (60%) was assigned structure **18**. The primary alcohols were then selectively protected with *tert*-butyldimethylsilyl chloride (TBDMSCl), 4-dimethylaminopyridine (DMAP) and the secondary alcohols acetylated without isolation of the intermediate. At this stage, the two diastereomers were separated to provide **19** (50%) as the less polar isomer. Cleavage of the silyl ether and oxidation of the resulting primary alcohol under Swern conditions gave the required aldehyde **20** as a single diastereomer.

Wittig coupling then gave the completed assembly of the alkaloid **21** (Scheme 10) and only removal of the TROC protecting group was required to free the secondary amino groups for intramolecular epoxide opening. Deprotection-cyclization was carried out in one step (zinc/tetrahydrofuran/water) providing a mixture of the natural and unnatural diastereomers which were separated by flash chromatography. Cyclization leading to the natural configuration **22** is illustrated. Cleavage of the acetyl group with sodium methoxide, and the BOC group with hydrochloric acid gave pure (±)-cannabisativine.[26]

Syntheses of the macrocyclic polyamine alkaloids *O*-methylorantine (**23**) and chaenorhine (**24**)[27,28] (Table 4) represented somewhat more complex problems in that

Scheme 11

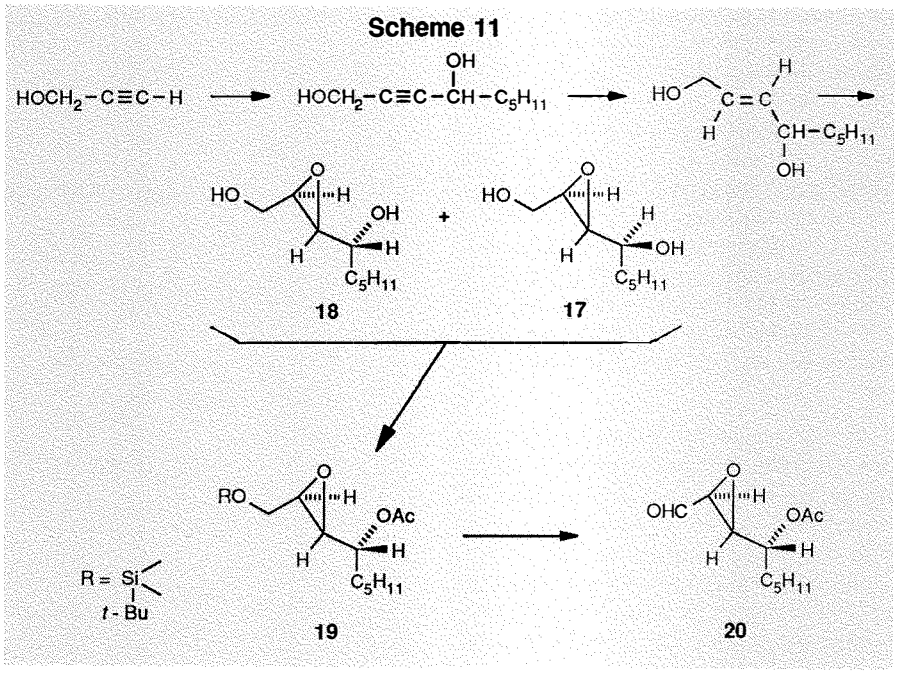
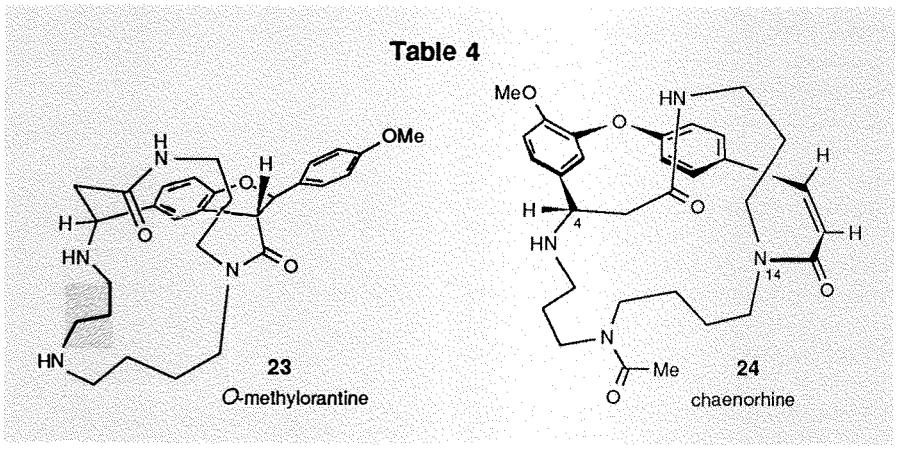
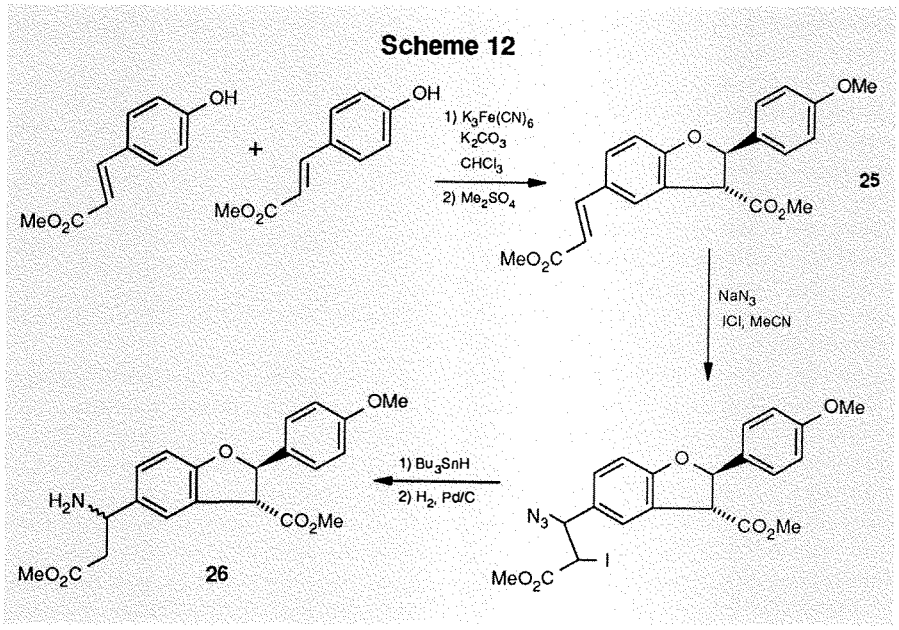


Table 4



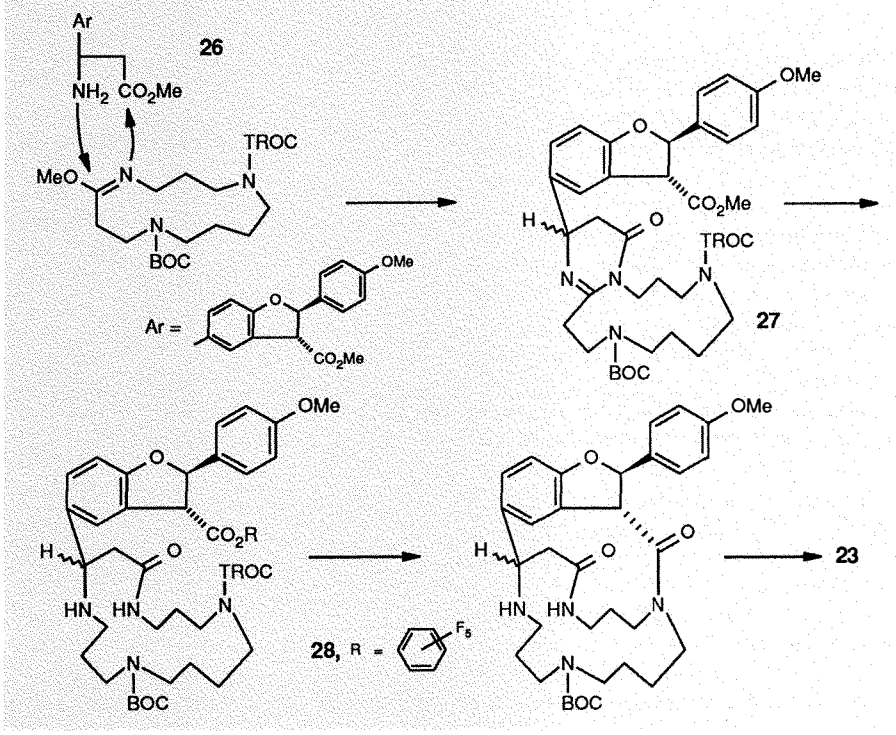
Scheme 12



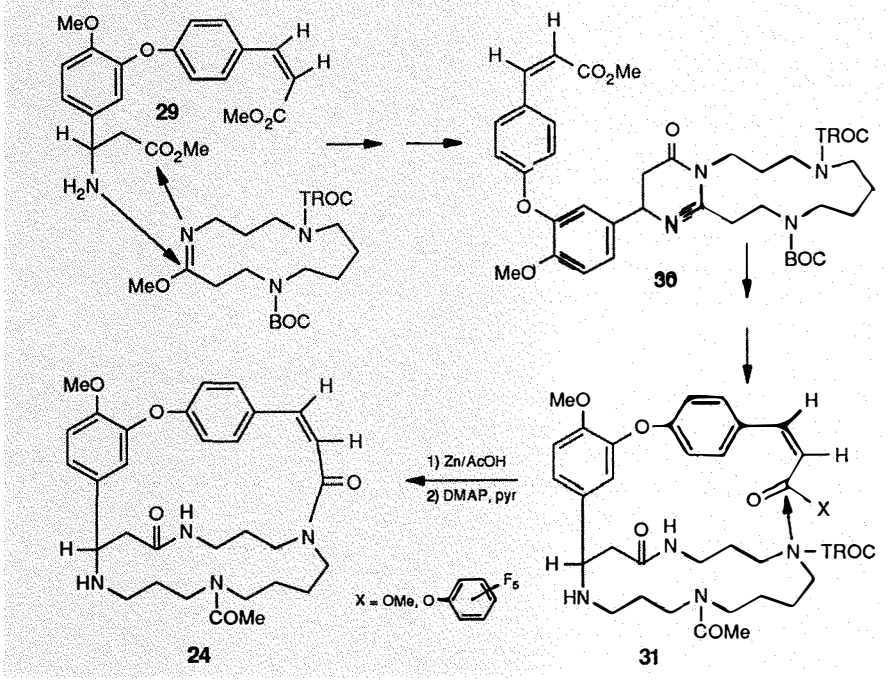
they required construction of a polyfunctional bridge between the carbon at position 4 and the nitrogen at position 14 of the 17-membered ring. We first considered the possibility of preparing β-lactams containing the required substitution at the 4-position of the azetidinone for coupling with a 13-membered lactim ether. However, the construction of these particular β-lactams appeared to be rather difficult, and we therefore took advantage of the fact that Bormann coupling could be accomplished with the corresponding β-amino esters.[17]

In the case of ephedradine *O*-methylorantine (**23**), the above approach called for the preparation of the β-amino ester **26** (Scheme 12). We did not concern ourselves with the stereochemistry of the amino group in **26** as long as the *trans* orientation of substituents on the dihydrobenzofuran residue was correct. This would then give us a mixture of diastereomers in the final product which we hoped we would be able to separate. Our synthesis of **26** was accomplished starting with methyl *p*-hydroxycinnamate. Employing a known oxidative coupling procedure using potassium ferricyanide, we formed the *trans* coupling product **25**. Precedent for the stereochemistry observed in this reaction could be found in a number of such oxidations carried out by Stoessl in the preparation of hordatine A.[29] Compound **25** was converted to **26** by addition of iodoazide to form a mixture of products from which the desired regioisomer could be isolated and reduced to **26** in 48% yield using an excess of tributyltin hydride. Coupling of **26** with the 13-membered imino ether was accomplished in the usual way in warm chlorobenzene to form **27** (Scheme 13). This was followed by a reductive ring opening to yield the 17-membered lactam. Completion of the conversion of this product to *O*-methylorantine required gentle treatment because of the sensitivity of the dihydrobenzofuran residue toward oxidation, acid and base. Accordingly, the methyl ester was hydrolyzed under mild conditions with barium hydroxide in tetrahydrofuran/methanol and the resulting acid was activated by 1,3-dicyclohexylcarbodiimide (DCC) and pentafluorophenol to give the ester **28**. Cleavage of the TROC group, cyclization in dilute solution in the presence of *N*,*N*-diisopropylethylamine and 1-hydroxybenzotriazole, and removal of the BOC group yielded a mixture of diastereomers from which the pure product **23**, corresponding to the natural alkaloid, could be isolated.[30]

Scheme 13



Scheme 14

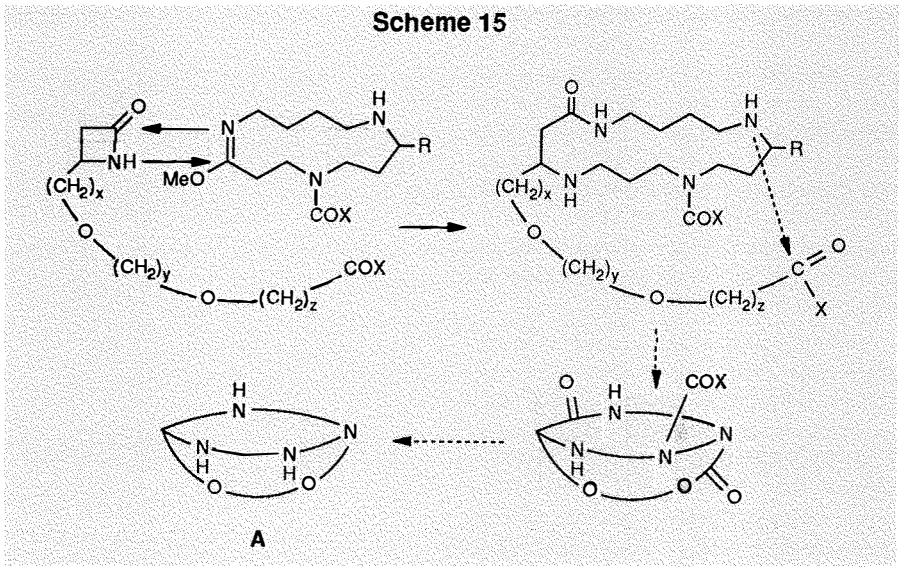


For the synthesis of chaenorhine (**24**), a similar coupling reaction was carried out. Here, the β-amino ester component **29** contained a residue formed by the coupling of a *p*-bromocinnamic acid residue with the oxyanion of the β-amino ester derived from isovanillin. As in the *O*-methylorantine synthesis, the coupling of **29** with the imino ether was achieved (Scheme 14) by heating the two reactants in chlorobenzene to form the bicyclic 4-oxotetrahydropyrimidine (**30**) containing the macrocyclic fused ring and the diaryl ether side chain at the 6-position. The acetyl group was then introduced by removal of the BOC group, followed by reaction with acetyl chloride, and the bicyclic product opened to the 17-membered lactam **31** in 95% yield under the conditions

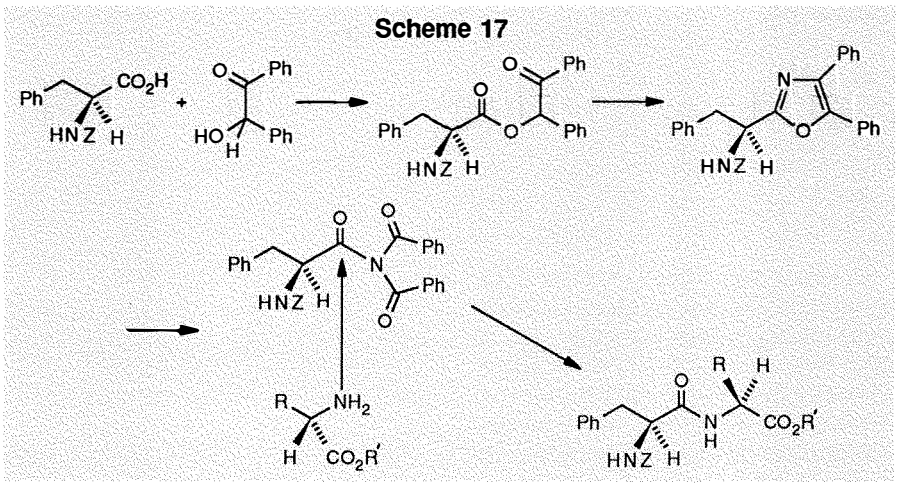
developed earlier. The last phase of the synthesis required activation of the carboxyl group by hydrolysis of the methyl ester with dilute sodium hydroxide followed by esterification with pentafluorophenol. Reductive removal of the TROC group and cyclization of the activated ester took place in dioxane containing DMAP and pyridine, yielding a synthetic product **24** identical in all respects with authentic chaenorhine.[31]

Examination of *O*-methylorantine and chaenorhine in the forms represented by structures **23** and **24**, reveals these alkaloids as cage-like structures in which the bicyclic macrocyclic rings represent a type of cryptate. Unlike conventional methods for the synthesis of such cryptates, which involve the coupling of dibasic acids with diols in symmetrical fashion, our synthesis of these polyamine alkaloids illustrates a method for the construction of macrocyclic bicyclic systems with heteroatoms disposed in an unsymmetrical array. We are investigating the possibility that our β-lactam coupling reaction may be applied to the formation of simpler cryptate-like systems of structure **A** which would be formed by the procedures outlined in Scheme 15. Here, the residue attached to the 4-position of the β-lactam would be a polyether carboxylate which, at a later stage in the synthesis, could be coupled with one of the amino groups in the amino lactam. The sequence resulting in the formation of an unsymmetrically substituted cryptate is shown.

Scheme 15



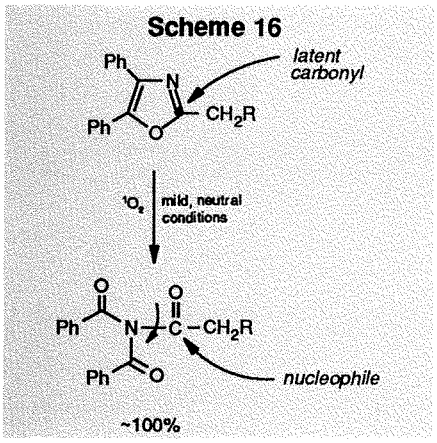
Scheme 17



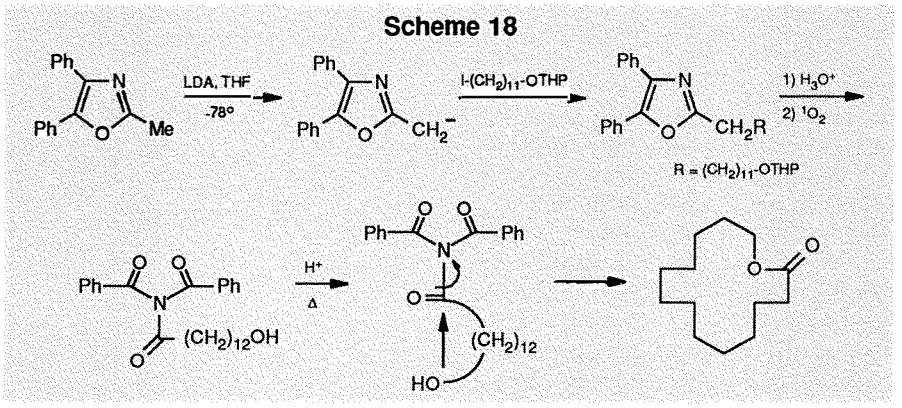
Oxazoles as Protecting-Activating Groups in Synthesis

In earlier work,[32] we observed that photooxidation of substituted oxazoles under mild conditions leads to a complex rearrangement with the formation of triamides in nearly quantitative yields. The triamides represent activated forms of each of the carbonyl groups, since nucleophilic attack at such sites generates good leaving groups, as shown in Scheme 16. We have also found that in the reaction of the triamide with nucleophiles, the acyl carbonyl usually reacts more readily than the aroyl carbonyl, thus permitting selectivity in the use of the triamide as an activated form of the acyl carboxylate.

Scheme 16



Scheme 18

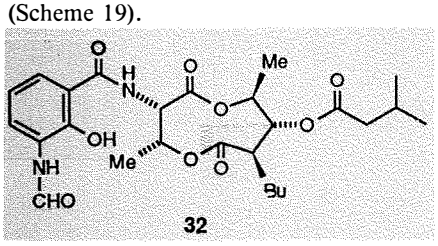


One of the applications which we have explored involves the protection/activation of carboxylates in the syntheses of dipeptides.[33] Thus, the carboxyl group of a *Z*-amino acid can be protected as the C-2 atom of an oxazole to which it is converted by reaction with benzoin in DMAP followed by ammonium acetate treatment of the ester thus formed. Regeneration-activation takes place by singlet-oxygen oxidation to the triamide which reacts with an amino acid or an amino ester to form a dipeptide without racemization (Scheme 17).

Another very useful application of the oxazole-to-triamide conversion lies in the

use of the oxazole as a template for macrolide formation.[34] For example, starting with 2-methyl-4,5-diphenyloxazole, an ω-hydroxyl group may be introduced at the 2-position by a suitable alkylation procedure, and the active form of the carboxylate generated for intramolecular cyclization. This sequence is illustrated in the formation of tetradecanolide (Scheme 18) and in the formation of a series of naturally occurring macrolides (Table 5).

The method was also shown to be applicable to the formation of polyether lactones. *N*-Bromosuccinimide (NBS) bromination of the 2-methyl-4,5-diphenyloxazole permitted introduction of the polyether alcohol side chain using pentaethylene glycol in base. Photooxidation generated the triamide which underwent acid-catalyzed cyclization in dilute benzene (Scheme 19).

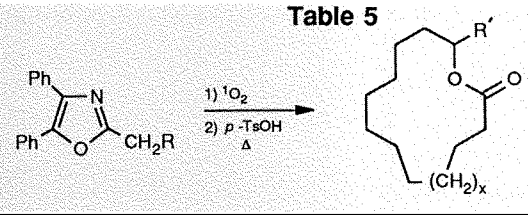


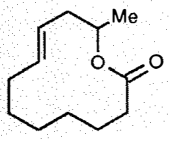
32

An outstanding example of the use of the oxazole in protection-activation functions is found in the synthesis of antimycin A-3 (**32**).[35] Here, the 2-methyl-4,5-diphenyloxazole was used as a scaffolding for the construction of the entire carbon-oxygen framework of the macrolide antibiotic. As illustrated in Scheme 20, the oxazole ring served to protect the latent carbonyl group at the C-2 position during a series of six operations: 1) alkylation of the methyl group with butyllithium and butyl iodide, 2) reaction of the 2-methylene group with optically active methoxymethoxymethylpropanal, 3) acylation of the newly formed hydroxyl group with isovaleryl chloride, 4) deprotection of the secondary alcohol by cleavage of the methoxymethyl ether, 5) coupling of the alcohol with a protected derivative of optically active threonine and 6) deprotection of the alcohol in the threonine residue by fluoride-promoted cleavage of the *tert*-butyldimethylsilyl group. The final release of the activated carboxylate from the oxazole took place by singlet-oxygen oxidation, generating the triamide, which then underwent cyclization to form the macrocyclic nucleus. The details of this process are shown in Schemes 21-23.

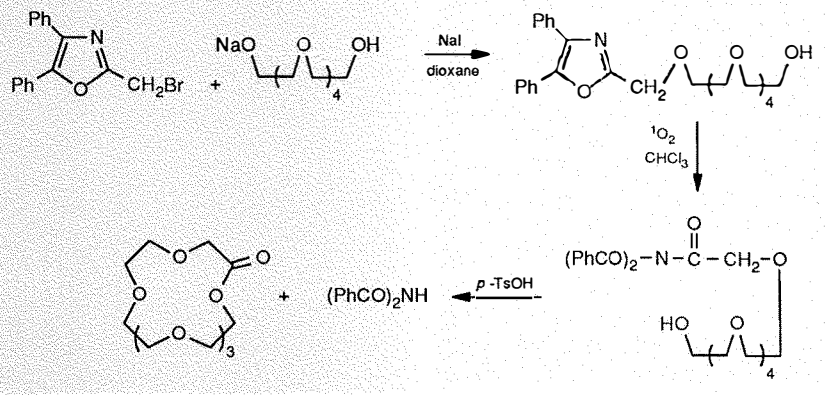
It is interesting that the acylation step (**33** → **34**) (Scheme 21) produces a mixture of diastereomers in the ratio of 4:3:2:1. We were fortunate in that the desired isomer

Table 5

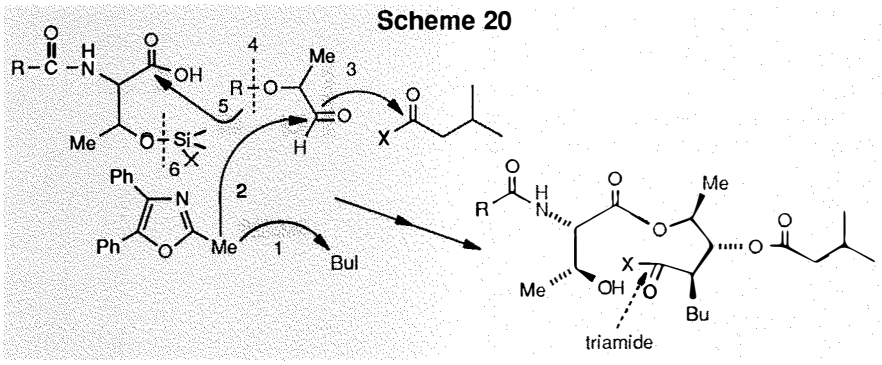


R	lactone	% yield
$-(CH_2)_{11}OH$	x = 2, R′ = H	75
$-(CH_2)_{12}OH$	x = 3, R′ = H	76
$-(CH_2)_{11}CH(Me)OH$	x = 3, R′ = Me	64
$-(CH_2)_5CH{=}CHCH_2CH(Me)OH$		55

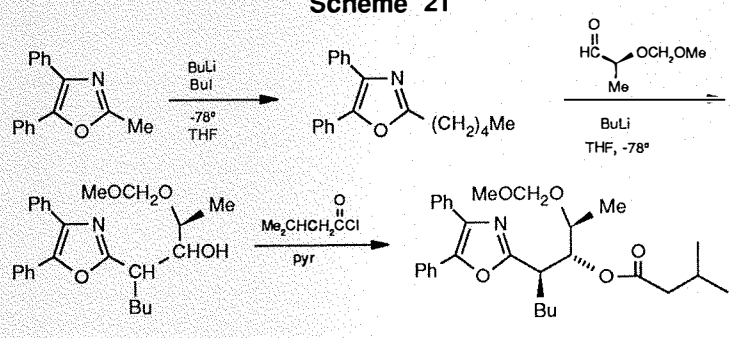
Scheme 19



Scheme 20



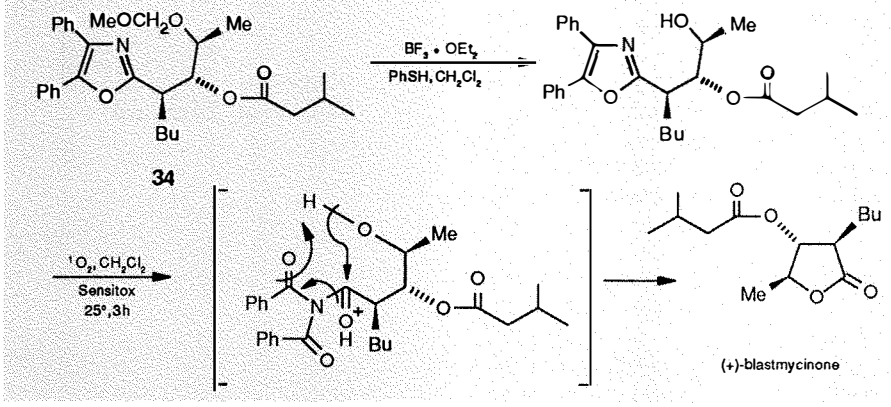
Scheme 21



33 **34**

34 was the predominant product, and we were able to prove its stereochemistry after removal of the methoxymethyl group by photooxidation to blastmycinone, a natural product of known configuration[36] (Scheme 22).

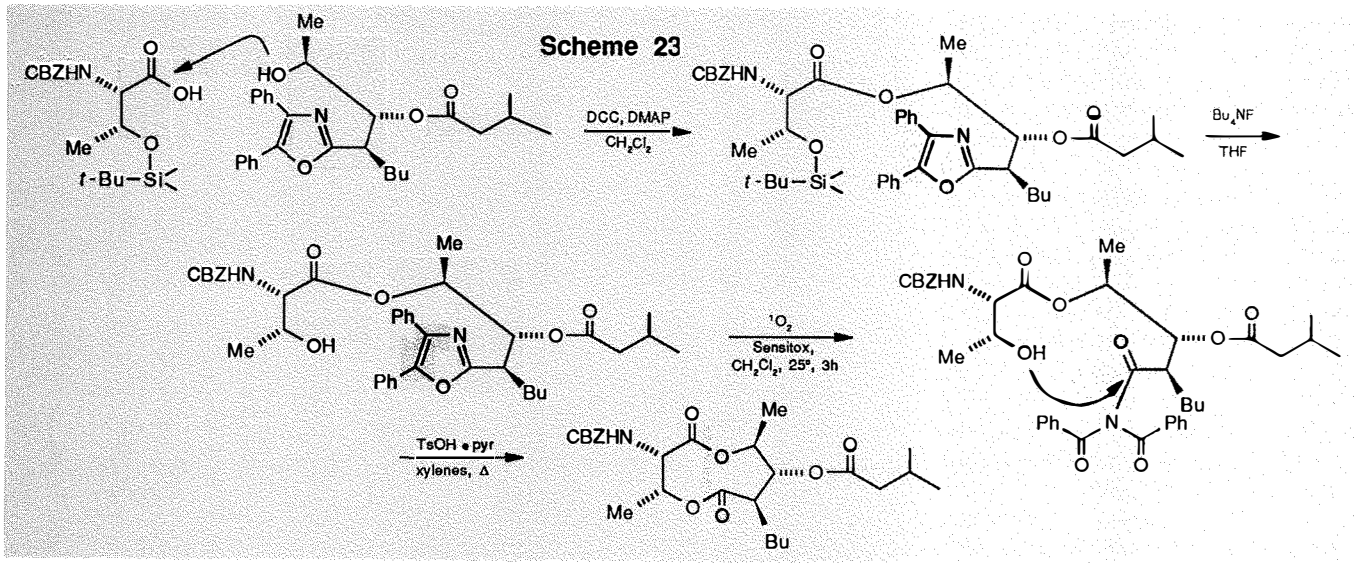
Scheme 22



Vicinal Tricarbonyl Functions in Organic Synthesis

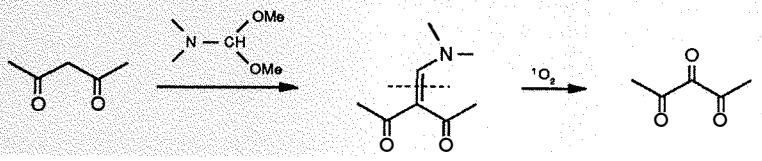
During the course of our earlier work on the reactions of singlet oxygen with enamines, we were able to show that enamine cleavage is a mild and efficient way of cleaving carbon-carbon bonds in olefins which are substituted with electron-rich groups. This type of cleavage was utilized effectively in our procedure for oxidative decarboxylation whereby an azetidinecarboxylic ester could be converted through the enol silylate to the corresponding β-lactam (Scheme 1).

Scheme 23

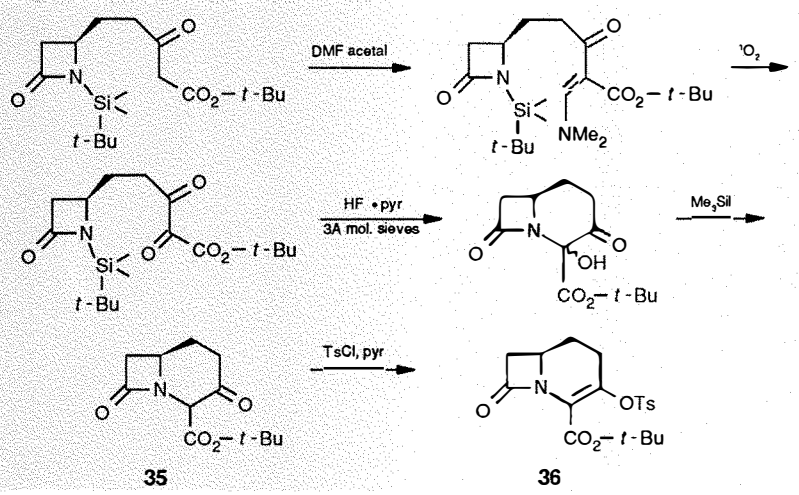


During the course of these studies, we were able to extend the enamine cleavage reaction to the general procedure for the conversion of ketones and other carbonyl groups to 1,2-dicarbonyl groups.[37] This method involved the formation of α-enamino derivatives by the use of Bredereck's Reagent, followed by cleavage of the enamine with singlet oxygen. In a further extension of this work, we found that β-dicarbonyl compounds react readily with dimethylformamide dimethyl acetal under very mild conditions without added catalyst to form enamines susceptible to cleavage by singlet oxygen, leading to 1,2,3-tricarbonyl derivatives (Scheme 24). Such tricarbonyl derivatives represent functional-group aggregates which, hitherto, have not been extensively utilized by organic chemists. Since the central carbonyl of such 1,2,3-tricarbonyls is located adjacent to two electron-deficient carbon atoms, this assembly represents an electrophilic site of

Scheme 24



Scheme 25

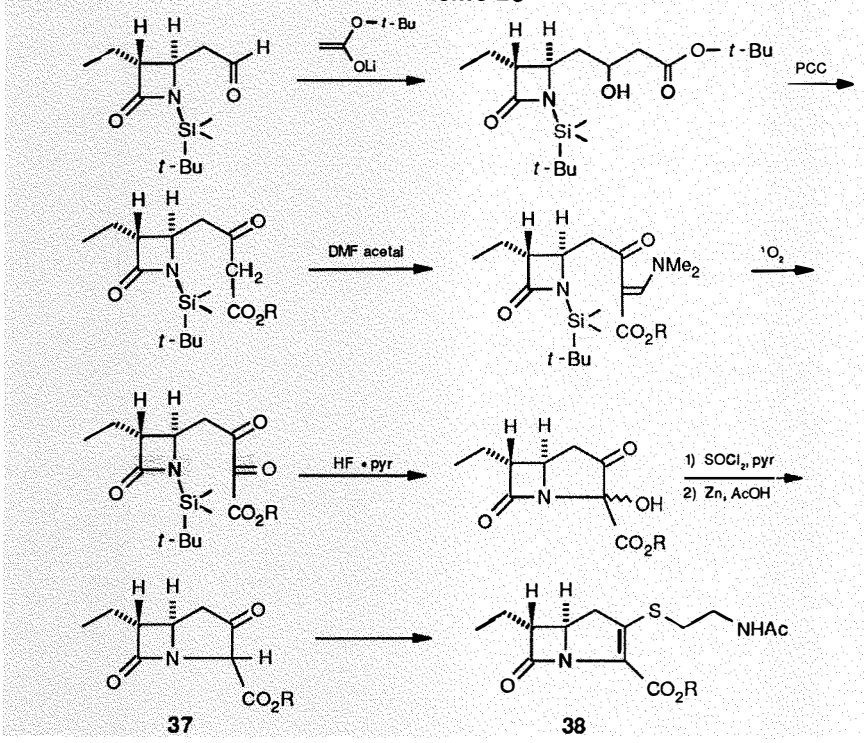


unusual reactivity, ready for bond formation with even weak nucleophiles. To date, such tricarbonyl systems have been observed as hydrates, as in oxomalonic ester, ninhydrin and in oxomalononitriles; but these systems have rarely been incorporated into synthetic plans as sites for special reactivity where a highly electrophilic center is needed for a difficult bond-forming task.

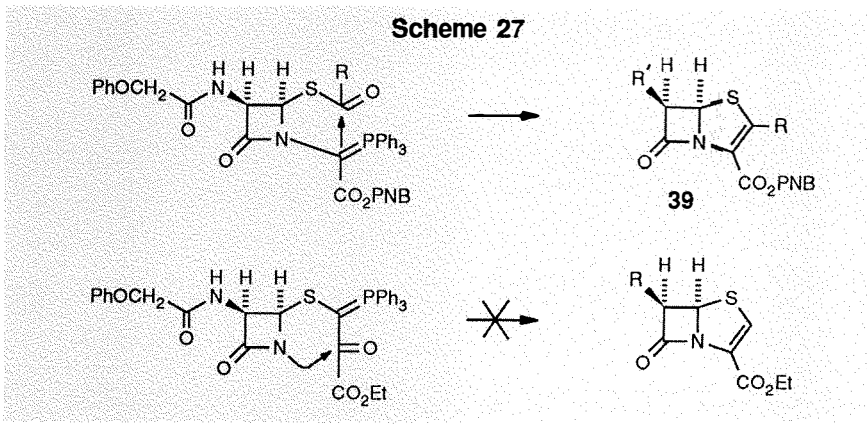
In the course of our studies on the synthesis of β-lactams related to the penicillins and thienamycins, we explored the possibility of using tricarbonyl residues to form fused rings with β-lactams. Such bond formation would permit the synthesis of derivatives of penicillin, cephalosporin, thienamycin and other fused-ring β-lactams of biological interest. Our initial work utilized a known β-dicarbonyl system attached to an azetidinone, as shown in Scheme 25. Here, we were able to convert the β-keto ester to an enamine which could then be cleaved with singlet oxygen to form the intermediate tricarbonyl compound as a partially hydrated product. Addition of 3A molecular sieves removed the water of hydration and permitted cyclization to form the fused **4,6**-membered system **35** which was converted to **36**, a derivative used in the synthesis of homothienamycin.[38] Another application was found in the synthesis of **37**, a precursor to the antibiotic PS-5 **(38)**, related to thienamycin (Scheme 26). Again, formation of a β-keto ester was followed by enamine formation, cleavage and cyclization to form the fused **4,5**-membered ring. The intermediate carbinolamine formed in this way readily underwent reductive removal of the OH group yielding **37**.[39]

In recent studies, we have used tricarbonyl chemistry in the formation of the penem nucleus, a system first studied by Woodward and co-workers at the Ciba Research Institute.[40] Woodward was able to synthesize a penem derivative **(39)** (Scheme 27) by an elegant procedure involving an intramolecular Wittig reaction employing cyclization at the C-2 and C-3 positions. When he attempted to use the same type of coupling for the formation of the N-to-C-3 bond the reaction failed, presumably because the anion of the ylide served to reduce the electrophilic reactivity of the α-keto carbonyl. Other attempts to form penems by N-to-C-3 closure also met with failure (Scheme 28). DiNinno at Merck attempted the cyclization of the bromo thioether derivative **40** using a complex organometallic catalyst,[41] but his product

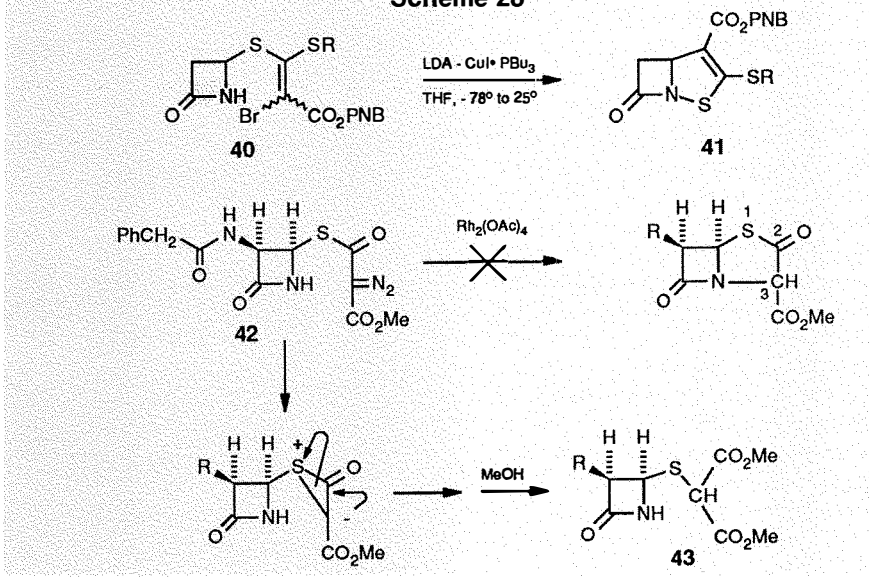
Scheme 26



Scheme 27



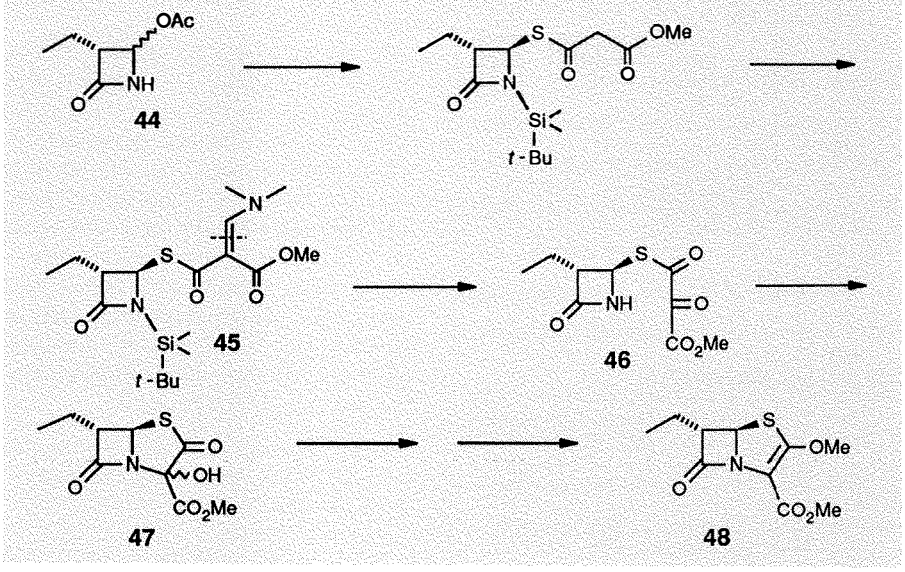
Scheme 28



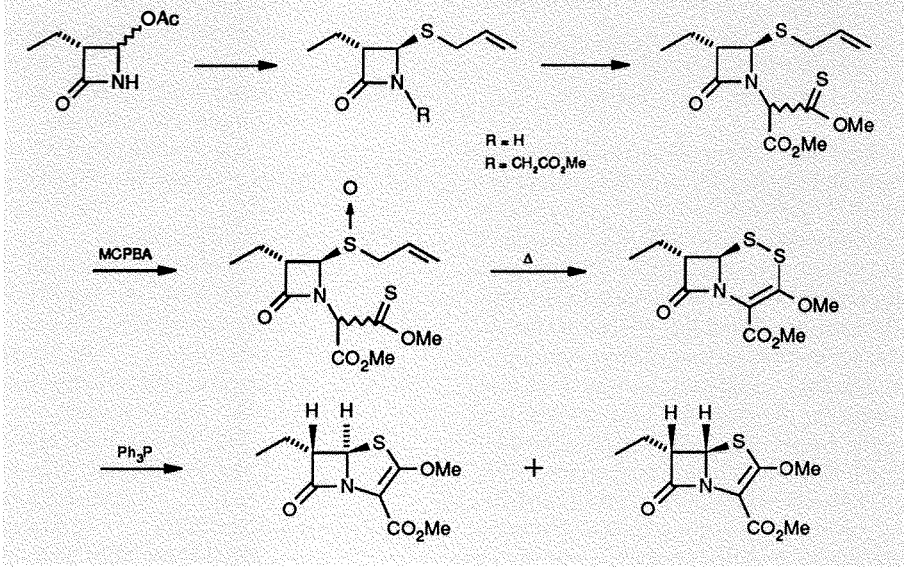
was shown to be an isopenem (**41**) by the X-ray studies of Oida.[42] A third attempt at formation of the penem by N-to-C-3 bond closure utilized a method analogous to that developed for the synthesis of thienamycin, *i.e.*, the rhodium acetate-catalyzed decomposition of diazo derivative **42**. While this reaction worked well in the formation of carbapenems, a complication developed when applied to **42**. Here, the sulfur atom interacted with the intermediate carbene, generating an ylide which then decomposed through a ketene to produce **43**.[43]

In our investigation, as outlined in Scheme 29, we began with the acetoxy β-lactam **44** and introduced the thiomalonate residue. Subsequent conversion to the enamine **45** and cleavage with singlet oxygen formed the tricarbonyl derivative **46**. Here, the weakly nucleophilic NH of the β-lactam, formed after desilylation, was able to add to the central carbonyl to generate the desired fused-ring system without interference from the neighboring sulfur atom. The product **47** could be reduced with thionyl chloride/zinc-acetic acid to form the desoxy intermediate which, on reaction with diazomethane, formed the penem **48** in the form of an enol ether.[44] While NMR and mass spectroscopic evidence served to establish this structure, we obtained confirmation by the preparation of the same material through an independent synthesis utilizing the method of Cooke,[45] as shown in Scheme 30.

Scheme 29



Scheme 30



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References:

1) Wasserman, H.H.; Glazer, E. *J. Org. Chem.* **1975,** *40,* 1505 and references cited therein.
2) Wasserman, H.H.; Hlasta, D.J.; Tremper, A.W.; Wu, J.S. *Tetrahedron Lett.* **1979,** 549.
3) Wassserman, H.H.; Lipshutz, B.H.; Tremper, A.W.; Wu, J.S. *J. Org. Chem.* **1981,** *46,* 2991.
4) Wasserman, H.H.; Lipshutz, B.H. *Tetrahedron Lett.* **1976,** 4613.
5) Wasserman, H.H.; Tremper, A.W. *ibid.* **1977,** 1449.
6) Wasserman, H.H.; Lipshutz, B.H.; Wu, J.S. *Heterocycles* **1977,** *7,* 321.
7) Wasserman, H.H.; Hlasta, D.J.; Tremper, A.W.; Wu, J.S. *J. Org. Chem.* **1981,** *46,* 2999.
8) Kamiya, T. *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Cambridge University Press: London, 1976.
9) Manhas, M.S.; Amin, S.G.; Bose, A.K. *Heterocycles* **1976,** *5,* 669.
10) Nicolaus, B.J.R. *et al. Helv. Chim. Acta* **1965,** *48,* 1867.
11) Ojima, I.; Shimizu, N. *J. Am. Chem. Soc.* **1986,** *108,* 3100.
12) Kupchan, S.M. *et al. Chem. Commun.* **1974,** 329; Kupchan, S.M. *et al. J. Org. Chem.* **1977,** *42,* 3660.
13) Pais, M.; Sarfati, R.; Jarreau, F.-X.; Goutarel, R. *Tetrahedron* **1973,** *29,* 1001.
14) Hocquemiller, R. *et al. Compt. Rend. C.* **1974,** *278,* 525.
15) McManis, J.S.; Ganem, B. *J. Org. Chem.* **1980,** *45.* 2041.
16) Tabor, C.W.; Tabor, H.; Bachrach, U. *J. Biol. Chem.* **1964,** *239,* 2194.
17) Bormann, D. *Chem. Ber.* **1970,** *103,* 1797.
18) Kemp, D.S.; Sidell, M.D.; Shortridge, T.J. *J. Org. Chem.* **1979,** *44,* 4473.
19) Wasserman, H.H.; Robinson, R.P.; Matsuyama, H. *Tetrahedron Lett.* **1980,** 3493.
20) Seifert, K.; Johne, S.; Hesse, M. *Helv. Chim. Acta* **1982,** *65,* 2540.
21) Wasserman, H.H.; Robinson, R.P. *Tetrahedron Lett.* **1983,** *24,* 3669.
22) Lotter, H.L. *et al. Tetrahedron Lett.* **1975,** 2815; Turner, C.E. *et al. J. Pharm. Sci.* **1976,** *65,* 1084; Elsohly, M.A. *et al. ibid.* **1978,** *67,* 124; Slatkin, D.J. *et al. Photochemistry* **1975,** *14,* 580.
23) Bouffard, F.-A.; Johnston, D.B.R.; Christensen, B.G. *J. Org. Chem.* **1980,** *45,* 1130.
24) Wasserman, H.H.; Pearce, B.C. *Tetrahedron Lett.* **1985,** *26,* 2241.
25) Martin, V.S. *et al. J. Am. Chem. Soc.* **1981,** *103,* 6237.
26) Wasserman, H.H.; Leadbetter, M. *Tetrahedron Lett.* **1985,** *26,* 18.
27) Hikino, H.; Ogata, M.; Konno, C. *Heterocycles* **1982,** *17,* 155.
28) Kompis, I.; Hesse, M.; Schmidt, H. *Chimia* **1970,** *24,* 450; Bernhard, H.O. *et al. Helv. Chim. Acta* **1973,** *56,* 1266; Bosshardt, H. *et al. Pharm. Acta Helv.* **1976,** *51,* 371.

29) Stoessl, A. *Tetrahedron Lett.* **1966,** 2287; Stoessl, A. *Can. J. Chem.* **1967,** *45,* 1745.
30) Wasserman, H.H.; Brunner, R.K.; Buynak, J.D.; Carter, C.G.; Oku, T.; Robinson, R.P. *J. Am. Chem. Soc.* **1985,** *107,* 519.
31) Wasserman, H.H.; Robinson, R.P.; Carter, C.G. *ibid.* **1983,** *105,* 1697.
32) Wasserman, H.H.; McCarthy, K.E.; Prowse, K.S. *Chem. Rev.* **1986,** *86,* 845.
33) Wasserman, H.H.; Lu, T.-J. *Tetrahedron Lett.* **1982,** *37,* 3831.
34) Wasserman, H.H.; Gambale, R.J.; Pulwer, M.J. *Tetrahedron* **1981,** *37,* 4059.
35) Wasserman, H.H.; Gambale, R.J. *J. Am. Chem. Soc.* **1985,** *107,* 1423.
36) Aburaki, S.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1979,** *52,* 198.
37) Wasserman, H.H.; Ives, J.L. *J. Org. Chem.* **1985,** *50,* 3573.
38) Wasserman, H.H.; Han, W.T. *Tetrahedron Lett.* **1984,** *25,* 3743.
39) *Idem ibid.* **1984,** *25,* 3747.
40) Woodward, R.B. *Spec. Publ.-Chem. Soc.* **1977,** *28,* 167; Pfaendler, H.R.; Gosteli, J.; Woodward, R.B. *J. Am. Chem. Soc.* **1980,** *102,* 2039; Lang, M.; Prasad, K.; Gosteli, J.T.; Woodward, R.B. *Helv. Chim. Acta* **1980,** *63,* 1093 and references cited therein.
41) DiNinno, R.; Linek, E.V.; Christensen, B.G. *J. Am. Chem. Soc.* **1979,** *101,* 2210.
42) Oida, S. *et al. Tetrahedron Lett.* **1980,** *21,* 619.
43) Marchand-Brynaert, J.; Ghosez, L.; Cossement, E. *ibid.* **1980,** *21,* 3085; Marchand-Brynaert, J.; Vekemans, J.; Bogdan, S.; Cossement, E. *Spec. Publ.-Chem. Soc.* **1981,** *38,* 269.
44) Wasserman, H.H.; Han, W.T. *J. Am. Chem. Soc.* **1985,** *107,* 1444.
45) Cooke, M.D.; Moore, K.W.; Ross, B.C.; Turner, S.E. *Tetrahedron Lett.* **1983,** *24,* 3373.

About the Author

Professor Harry H. Wasserman was born in Boston, MA, in 1920. He received the B.S. degree at M.I.T. in 1941 and then began graduate study with R.B. Woodward at Harvard. The years 1942-1945 were spent in military service in Africa and the Middle East as a Chemical Officer in the Air Force. In 1945, he returned to Harvard as a Research Assistant on the O.S.R.D. Penicillin Project. In 1946 he resumed study for the Ph.D., which he received in 1949. Since 1948, he has been on the faculty of Yale University with research interests in the field of natural products and in the development of new synthetic methods. He has been particularly interested in the chemistry of reactive intermediates such as ethoxyacetylene, cyclopropanone, β-lactams, singlet oxygen and vicinal tricarbonyl derivatives. He was Chairman of the Chemistry Department, 1962-1965, and Director of the Division of Physical Sciences at Yale, 1972-1974. He is presently Eugene Higgins Professor of Chemistry.

Professor Wasserman was a Guggenheim Fellow at the University of California, Berkeley from 1959-1960, Chairman of the Organic Division of the American Chemical Society in 1965, and a member of the N.I.H. Medicinal Chemistry Study Section. He lectured in the Japanese Society for the Promotion of Science Program in 1978 and was Visiting Distinguished Professor at Texas A & M University in 1982. This year, he gave the Max Hoffer Memorial Lecture at Hoffmann LaRoche.

He received Yale's Devane Medal for excellence in teaching in 1978, the Yale Teaching Prize in 1985, and the Catalyst Medal from the Chemical Manufacturers Association the same year. He has been American Editor of *Tetrahedron Letters* since 1960 and currently serves as Consultant to the Ortho Pharmaceutical Corporation. In 1987, he received the ACS Aldrich Award for Creative Research in Organic Synthesis. He is a Fellow of the American Academy of Sciences and a Member of the National Academy of Sciences.

Professor Wasserman's chemistry employs many important Aldrich reagents, some of which are listed below.

Award-Winning Chemistry
1987 - Professor Harry H. Wasserman

Dr. Harry H. Wasserman, Professor of Chemistry at Yale University, is the recipient of the 1987 A.C.S. Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich.

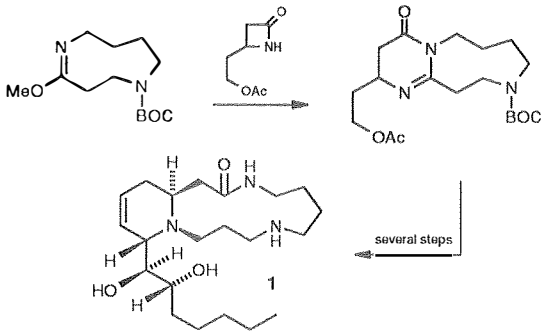
During recent years, Professor Wasserman's interest has focused on the utilization of azetidinones, oxazoles and vicinal tricarbonyl derivatives of β-lactams as building blocks or as protecting-activating groups in natural-product synthesis. Singlet-oxygen chemistry, the hallmark of his research, was elegantly applied in methods based on these building blocks.

We extend our congratulations to Professor Wasserman, and herein acknowledge some of his work.[1]

Total synthesis of (±)-cannabisativine

During the synthesis and purification of 3-aminocardicinic acid, the azetidinone nucleus underwent facile rearrangement to the ring-expanded product.[2]

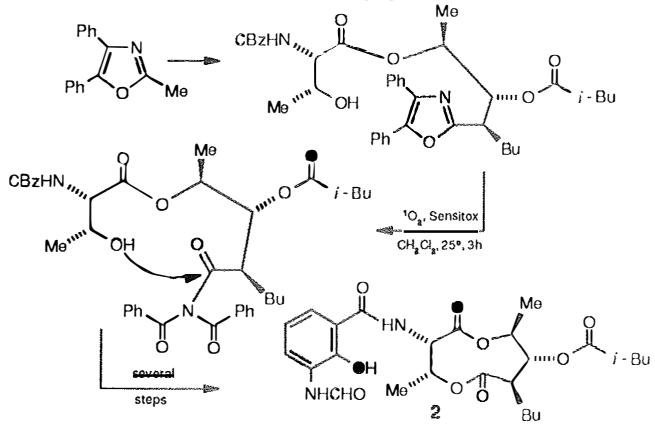
The potential of this reaction prompted Prof. Wasserman to develop a new synthetic method involving the construction of azetidinone-containing precursors and their subsequent rearrangement to ring-expanded products. The successful completion of the syntheses of celacinnine, homaline, verbascenine and other macrocyclic polyamine alkaloids amply demonstrates the power of his idea. The synthesis of cannabisativine (**1**)[3] exemplifies this method.



Antimycin A-3 synthesis

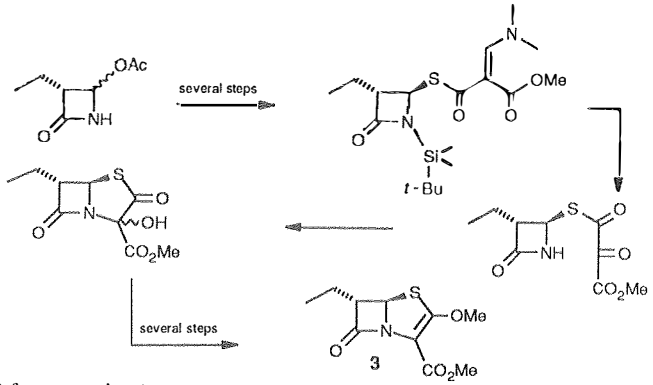
The synthesis of antimycin A-3 (**2**) represents an elegant application of the singlet-oxygen-mediated oxazole-triamide rearrangement[4] and the use of oxazole in protection-activation functions in the syntheses of macrocyclic lactones and polyethers.[5]

The oxazole-triamide photooxidation-rearrangement has also been utilized in the syntheses of dipeptides and macrolides.



Penem synthesis with vicinal tricarbonyl derivatives of β-lactams

The 1,2,3-tricarbonyl compounds derived from the enamine of β-dicarbonyls by singlet-oxygen cleavage possess a highly reactive electrophilic site (C-2). Wasserman's group developed a method based on this chemistry which involved conversion of vicinal tricarbonyl derivatives of β-lactams to thienamycin and penem derivatives. The synthesis of enol-ether **3** by a *difficult-to-achieve N-to-C₃ ring closure* illustrates this method.[6]



References and notes:

(1) For a review of Prof. Wasserman's work in this area, see *Aldrichim. Acta* **1987**, *20*(3), 63 (this *Acta*). (2) Wasserman, H.H.; Hlasta, D.J.; Tremper, A.W.; Wu, J.S. *J. Org. Chem.* **1981**, *46*, 2999. (3) Wasserman, H.H.; Leadbetter, M. *Tetrahedron Lett.* **1985**, *26*, 2241. (4) Wasserman, H.H.; McCarthy, K.E.; Prowse, K.S. *Chem. Rev.* **1986**, *86*, 845. (5) a) Wasserman, H.H.; Gambale, R.J.; *J. Am. Chem. Soc.* **1985**, *107*, 1423. b) Wasserman, H.H.; Gambale, R.J.; Pulwer, M.J. *Tetrahedron* **1981**, *37*, 4059. (6) Wasserman, H.H.; Han, W.T. *J. Am. Chem. Soc.* **1985**, *107*, 1444.

Here are just a few of the important reagents utilized by Prof. Wasserman. For a more detailed list, see p 74 of this *Acta*.

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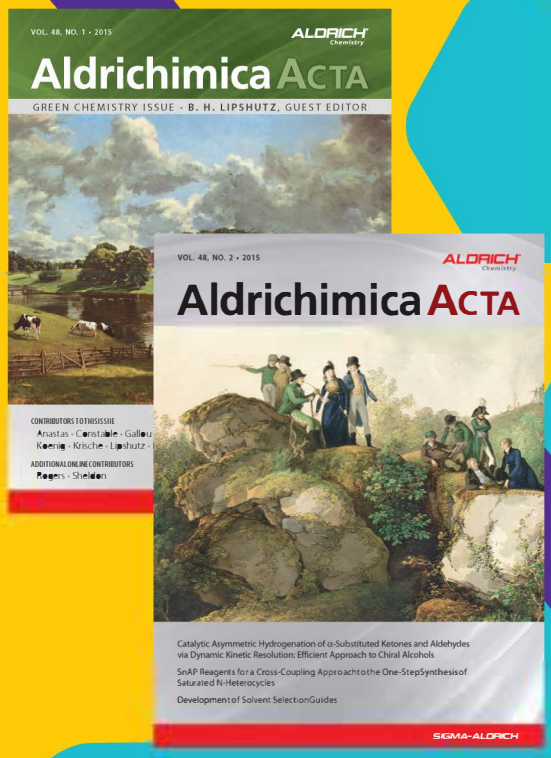

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