Asymmetric Reactions
and Processes in Chemistry

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Ernest L. Eliel, EDITOR
University of North Carolina at Chapel Hill

Sei Otsuka, EDITOR
Osaka University

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FOREWORD

The ACS SYMPOSIUM SERIES was founded in 1974 to provide
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and reports of research are acceptable since symposia may
embrace both types of presentation.

PREFACE

The possibility of an asymmetric synthesis was foreseen in Le Bel's pioneering 1874 paper on the asymmetric carbon atom and the idea was reduced to practice by Emil Fischer, W. Marckwald, and A. McKenzie around the turn of the century. Although there seems to have been a long lasting air of mystery about asymmetric induction, the process was put on a firm mechanistic basis by the classical studies of W. Doering, L. M. Jackman, H. S. Mosher, V. Prelog, and D. J. Cram around 1950. However, it was only in 1961 that a practical asymmetric synthesis proceeding in high optical yield—the hydroboration–oxidation of *cis*-2-butene by tetrapinanyldiborane—was achieved by H. C. Brown and G. Zweifel. By 1971, when the definitive book in the area, *Asymmetric Organic Reactions* by J. D. Morrison and H. S. Mosher appeared, innumerable asymmetric reactions were on record and the mechanism of a number of them was quite well understood, but optical yields much in excess of 40–50 percent were surprisingly rare.

Perhaps as a result of the publication of the Morrison–Mosher book or simply because the time was ripe, the situation has changed drastically in the last ten years. Recent reviews by H. B. Kagan and J. C. Fiaud, D. Valentine and J. W. Scott, and J. W. ApSimon and R. P. Seguin, as well as the current literature indicate large numbers of methods, probably now well over a hundred, by which chiral products may be obtained with enantiomeric excess in the 80- to 90-percent region. Although such methods have been reported from all over the chemically active world, a substantial number have originated either in Japan or in the United States.

It therefore seemed timely to arrange a joint U.S.–Japan Seminar on the topic of asymmetric reactions and processes—the title including not only asymmetric syntheses, both conventional chemical and enzymatic, but also certain separation methods involving the same kind of diastereomeric interactions that are involved in asymmetric synthesis. The seminar was held July 7–11, 1981, at Stanford University with the editors and Professor Harry S. Mosher as co-organizers. It was supported jointly by the Japan Society for the Promotion of Science and the National Science Foundation and featured 19 plenary speakers: nine from Japan and ten from the United States. The names and brief biographies of all but one of these speakers are given on pp. xi–xiii, and their subjects are listed in the Table of Contents.

Approximately half the chapters (1–10) deal with what might be termed "classical asymmetric synthesis": a chiral adjuvant is combined with a prochiral reagent, thus producing diastereotropic ligands or faces. Stereoselective replacement of the ligands or addition to the faces followed by removal of the chiral adjuvant leads to chiral products. The second largest block of chapters (11–13 plus parts of 7 and 8) deals with asymmetric catalysis, involving, in several instances, chiral organometallic reagents. It is remarkable that, not only in the stoichiometric but also in the catalytic reactions presented, optical yields frequently exceed 90%. Chapters 14 and 15 are concerned with large-scale commercial applications of asymmetric enzymatic synthesis and Chapters 16 and 17 deal with biochemical applications of enzyme chemistry.

Despite the fascination of asymmetric synthesis, separation methods for enantiomers even today compete, often successfully, with direct synthetic routes. Thus it is appropriate that the topic of separation was included in the seminar. Chapter 18 is concerned with this topic, as was a paper presented by D. J. Cram on host–guest complexation [J. Am. Chem. Soc., *103*, 3929 (1981); J. Org. Chem., *46*, 393 (1981); and J. Chem. Soc., Chem. Comm., 625 (1981)]. Substantial parts of Chapters 1 and 10 also deal with the role of resolution and separation methods in the synthesis of chiral compounds, including enantioconvergent syntheses.

In addition to the 19 main papers, two short papers and nine posters (preceded by short oral presentations) were featured at the Seminar. Nine of these eleven short communications are summarized in the form of abstracts on pages 261–286. The titles of these communications are listed in the Table of Contents. Abstracts of two communications are not included: that of D. Valentine, Jr. (Catalytica Associates, Inc.) on phosphines having both chiral phosphorus and chiral ligands has been published in J. Org. Chem., *45*, 3691 (1980) and that by B. Sharpless (MIT), on kinetic resolution, has appeared in J. Am. Chem. Soc., *103*, 6237 (1981).

By the judgement of most of the participants, the Seminar was a success in that it brought together information on a wide variety of diverse, although often fundamentally related, methods for efficient synthesis of chiral organic compounds. We hope that this written record will prove of equal interest to the reader.

ERNEST L. ELIEL
University of North Carolina
Department of Chemistry
Chapel Hill, North Carolina 17514

SEI OTSUKA
Osaka University
Department of Chemistry
Toyonaka, Osaka, Japan 560

CONTRIBUTING AUTHORS

ICHIRO CHIBATA is Director of the Research Laboratory of Applied Biochemistry, Tanabe Seiyaku, Co., Ltd. Born Osaka, Japan, 1926; B.S., 1948, Ph.D, 1959, Kyoto University. With Research Laboratories, Tanabe Seiyaku, Co., Ltd. since 1948, Director since 1971.

ERNEST L. ELIEL is W. R. Kenan, Jr. Professor of Chemistry, University of North Carolina, Chapel Hill. Born Cologne, Germany, 1921, D.Phys.-Chem.Sci., University of Havana, Cuba, 1946; Ph.D. University of Illinois, 1948. University of Notre Dame, 1948–72; University of North Carolina since 1972.

HEINZ G. FLOSS is Lilly Professor of Medicinal Chemistry at Purdue University, West Lafayette, Indiana. Born Berlin, Germany, 1934. Diplom., Technical University, Berlin, 1959; Ph.D., Technical University, Munich, 1961; Postdoctoral, University of California at Davis (Conn) 1964–65. At Purdue University since 1966.

KAORU HARADA is Professor of Chemistry, University of Tsukuba, Ibarati. Born Toyonaka, Osaka, Japan, 1927, B.S., 1952, Ph.D., 1961, Osaka University. Research Associate, Florida State University, 1956–64. University of Miami, 1964–74; The University of Tsukuba since 1974.

TAMIO HAYASHI is Instructor, Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University. Born Gifu, Japan, 1948. B.Eng., 1970, Ph.D., 1975, Kyoto University; Postdoctoral, Colorado State University (Hegedus), 1976–77. At Kyoto University since 1975.

CLAYTON HEATHCOCK is Professor of Chemistry, University of California at Berkeley. Born San Antonio, Texas, 1936. B.S. Abilene Christian College, 1958; Ph.D., University of Colorado, 1963; Postdoctoral, Columbia University (Stork), 1963–64. At University of California at Berkeley since 1964.

KENJI KOGA is Professor, Faculty of Pharmaceutical Sciences, University of Tokyo. Born Aichi, Japan, 1938; B.S., 1960, Ph.D., 1966, University of Tokyo; Postdoctoral, University of California at Los Angeles (Cram), 1971–73. At University of Tokyo since 1976.

ALBERT I. MEYERS is Professor of Chemistry, Colorado State University, Fort Collins. Born New York City, New York, 1937. A.B., 1954, Ph.D., 1957, New York University. With Cities Service Research & Development, 1957–58; Louisiana State University, 1958–70; Wayne State University, 1970–72; Colorado State University since 1972.

TERUAKI MUKAIYAMA is Professor, Department of Chemistry, University of Tokyo. Born Nagano prefecture, Japan, 1927. B.S., Tokyo Institute of Technology, 1948; D.Sc., University of Tokyo, 1956. Assistant Professor, Gakushuin University, 1952–58; Professor, Tokyo Institute of Technology, 1962–73; University of Tokyo since 1974.

HITOSI NOZAKI is Professor, Department of Industrial Chemistry, Kyoto University. Born Okayama prefecture, Japan, 1922. B.Eng., 1943, Dr.Eng., 1949, Kyoto University; Postdoctoral, Cornell University (Meinwald), 1956–57. At Kyoto University since 1963.

ATSUYOSHI OHNO is Associate Professor, Institute for Chemical Research, Kyoto University. Born Kure, Hiroshima, Japan, 1936. B.S., Kyoto University, 1958; Ph.D., Osaka City University, 1963; Postdoctoral, Massachusetts Institute of Technology (Swain), 1963–65; Purdue University (Davis) 1965–66. At Kyoto University since 1974.

IWAO OJIMA is Senior Research Fellow and Group Leader, Sagami Chemical Research Center, Sagamihara. Born Yokohama, Japan, 1945. B.S., 1968, M.S., 1970, Ph.D., 1973, University of Tokyo. At Sagami Research Laboratories since 1970.

SEI OTSUKA is Professor, Department of Chemistry, Osaka University. Born Tchingtao, China, 1918. B.S., 1941, D.Sc., 1955, Osaka University; Postdoctoral, Ohio State University (Newman), 1955–57; Max–Planck Institut für Kohleforschung, Mülheim (Wilke), 1958. With Japan Synthetic Rubber, Co. Ltd, 1957–1964. At Osaka University since 1964.

WILLIAM H. PIRKLE is Professor, School of Chemical Sciences, University of Illinois, Urbana. Born Shreeveport, Louisiana, 1934. B.S., University of California, Berkeley, 1959; Ph.D., University of Rochester, 1963; Postdoctoral, Harvard University (Corey), 1964. At University of Illinois since 1964.

GARY H. POSNER is Professor, Department of Chemistry, Johns Hopkins University. Born New York City, New York, 1943; B.S., Brandeis University, 1965; Ph.D., Harvard University, 1968; Postdoctoral, University of California at Berkeley (Dauben), 1969. At Johns Hopkins since 1969.

GABRIEL SAUCY is Associate Director, Chemical Research Department, Hoffmann–La Roche, Incorporated, Nutley, New Jersey. Born Schaffhausen, Switzerland, 1927; Diplom, 1951; Ph.D., 1954, Federal Institute of Technology, Zurich, Switzerland. With Hoffmann–La Roche, Basle, 1954–64, Nutley since 1964.

BARRY M. TROST is Evan P. and Marion Helfaer Professor of Chemistry, University of Wisconsin, Madison. Born Philadelphia, Pennsylvania, 1941. B.A., University of Pennsylvania, 1962; Ph.D., Massachusetts Institute of Technology, 1965. At University of Wisconsin since 1965.

GEORGE M. WHITESIDES is Professor of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts. Born Louisville, Kentucky, 1939. A.B., Harvard University, 1960; Ph.D., California Institute of Technology, 1964. At Massachusetts Institute of Technology since 1963.

Approaches for Asymmetric Synthesis as Directed Toward Natural Products

BARRY M. TROST

University of Wisconsin, Department of Chemistry, McElvain Laboratories of Organic Chemistry, Madison, WI 53706

Asymmetric synthesis of natural products embraces one of four different strategies - 1) resolution of a convenient intermediate or final product, 2) utilization of enantiomerically pure starting materials, 3) asymmetric induction at the stage of an achiral intermediate, and 4) enantioconvergency. Each of these is illustrated. A new type of enantioconvergency embodying a [3.3] sigmatropic rearrangement is employed for the synthesis of prostanoids. Asymmetric induction strategy is examined in the context of a model for asymmetric induction in the Diels-Alder reaction. The enantiomerically pure and partially pure adducts are employed in the synthesis of iboga alkaloids and pillaromycinone. Erythrynolides are the framework for strategies embodying resolution and enantiomerically pure building blocks. For the former, both enantiomers of a key building block are utilized to synthesize different halves of the molecule. In the latter, a single enantiomerically pure intermediate is utilized for the synthesis of the two halves of the molecule in a convergent approach. Emphasis is placed on the general utility of O-methylmandelic acid as 1) an enantiomeric inducing agent, 2) a resolution agent via HPLC, 3) an analytical tool to determine % ee, and 4) a tool for deducing absolute configuration.

The total synthesis of complex natural products offers challenges in the construction of the carbon framework, adjustment of the oxidation pattern, control of relative stereochemistry and control of absolute stereochemistry. While all of these areas offer exciting opportunities, the last remains the least considered and most perplexing in developing particular synthetic strategy. To a very large extent, total synthesis of natural products still implies the synthesis of a racemate which, by definition, contains only 50% of the natural product and may be resolved at the end or along the way.

  In attempting to specifically consider the problem of absolute stereochemistry in developing strategy, four options emerge. First and most common is the resolution of some convenient intermediate or final product. Second and increasingly popular is the utilization of optically pure starting materials. Third is the dissection of the target molecule into an achiral intermediate in which asymmetry can be induced in a subsequent step. Fourth is the design of an intermediate which allows easy interconversion of two enantiomers (enantioconvergency). In this presentation, I wish to consider some aspects of each of these strategies in the context of several problems in the total synthesis of natural products.

Enantioconvergence Strategy

  The concept of enantioconvergent synthesis has heretofore been virtually restricted to cases in which the chiral center is directly epimerizable such as in α-amino acids. In an alternative view, the separate transformation of two enantiomers via stereochemically complementary pathways into a single enantiomeric series represents a case of enantioconvergence.(1) For example, conversion of the enantiomeric alcohols 1a and 1b to 1c via the Z and E olefins respectively converge to the same enantiomer of the product derived via a Claisen ortho ester rearrangement (equation 1). (2,3)

(1)
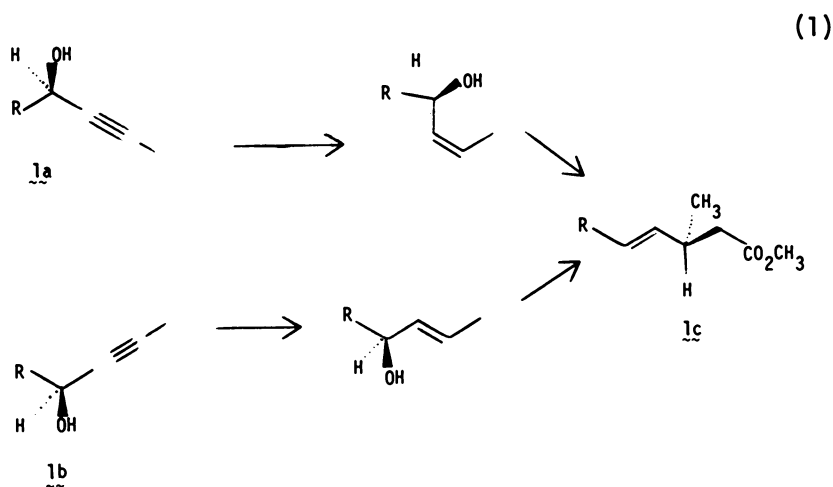
  An alternative conceptual approach to enantioconvergent synthesis involves intermediates whose enantiomers may be readily interconverted by simple chemical reactions. Compound 2 potentially represents such a species since it can be reasoned that a [3.3] sigmatropic rearrangement commutes the S,S isomer 2a into

the R,R isomer 2b (equation 2). (1) Attempts to equilibrate 2a

(2)
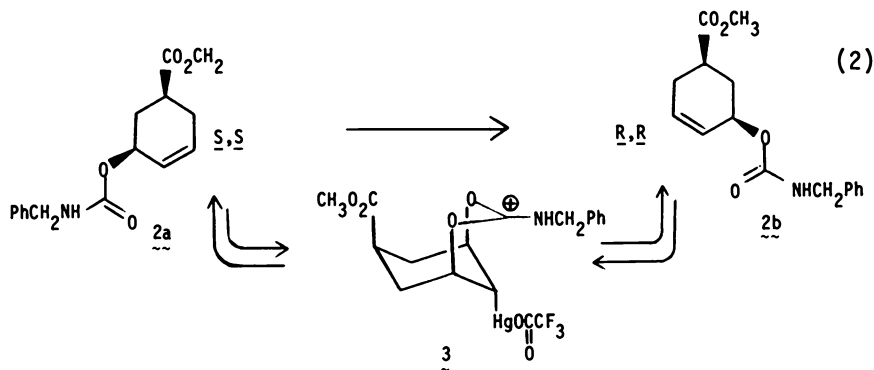
(56% ee, $[\alpha]_D^{25}$ + 16.3° (c 5.25 (CHCl$_3$)) thermally led to recovered
2a with no change in rotation. However, addition of 0.2 equiv.
of mercuric trifluoroacetate to a refluxing dioxane or THF
solution of 2a for 6-10 hours leads to complete racemization and
no competing cis-trans isomerization. A mechanism invoking the
intermediacy of 3 rationalizes this observation.
     Although in its simplest form this process would seem merely
to lead to racemization, it can, in fact, be adapted to optical
enrichment. Thus, use of an optically active urethane such as 4
combined with fractional crystallization of one diastereomer
creates a "resolving machine." Not only optical rotation, but
NMR analysis as well allows determination of optical purity with
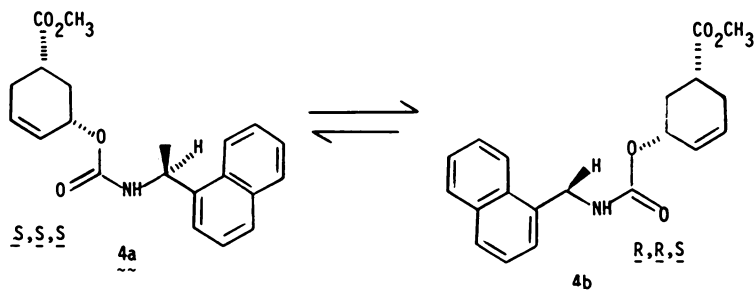
the S,S,S isomer 4a showing the methyl ester absorption upfield
(δ3.58 to that in the R,R,S isomer 4b (δ3.68)). Indeed, reacting
the racemate of the hydroxy ester with the isocyanate derived
from S-α-naphthethylamine gave the urethane 4 as a 1:1 mixture of
4a and 4b with $[\alpha]_{436}^{25}$ -13.2° (c 2.46, PhH) and two singlets of
equal intensity in the NMR spectrum at δ3.68 and 3.58. Mercury
catalyzed equilibration converts this mixture to an approximately
1:2 ratio of 4a to 4b as determined by the NMR spectrum, with the
signal at δ3.68 larger than that at δ3.58, and a rotation

$[\alpha]_{436}^{25}$ -11.8° (c 1.95, PhH). To verify that the urethanes could
be succesfully employed in synthesis, their conversion to the
corresponding hydroxy esters without racemization must be demon-
strated. In fact, treatment with trichlorosilane in hot benzene
containing triethylamine converts optically active 4a back to its
hydroxy ester with no loss of optical activity.

With the phenomenon established, a strategy for prostanoid
synthesis emerges as shown in equation 3. In the major simplifi-

(3)
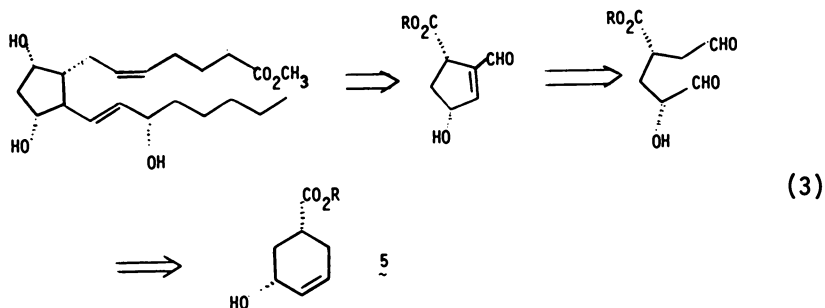
cation, two key points must be recognized 1) the ability of an α,β-
unsaturated aldehyde to lead to introduction of both side chains
and 2) the ability of a carboxy group to serve as a precursor to
an alcohol by a carboxy inversion procedure. The ready accessi-
bility of a cyclopentene-1-carboxaldehyde by a directed aldol
condensation and the generation of a dialdehyde by the oxidative
cleavage of an olefin leads to the alcohol 5 which relates to 4.
This approach also intrinsically differentiates the C(9) and C(11)
oxygens to provide an entry into a number of PG compounds.
Scheme 1 illustrates the utilization of this strategy for an
analogue.

Asymmetric Induction Strategy

While a great deal of emphasis has been placed upon search-
ing for asymmetric induction, strikingly successful results
remained elusive until very recently. One of the most powerful
approaches for the synthesis of natural products has been the
Diels-Alder reaction but asymmetric induction in this reaction
remained disappointing. (4) This reaction is particularly impor-
tant since the cycloaddition normally creates chiral products
from achiral reactants. A working model for inducing chirality
could greatly enhance the power of the approach.

Although the mechanism of the Diels-Alder reaction is still
controversial, it is practically useful to envision a relation-
ship between its transition state (t.s.) and a charge transfer
complex. (5) In its simplest version, the two enantiomeric t.s.'s
6a and 6b become diastereomeric t.s.'s if a chiral "solvator" is
present. Preferential solvation of one of the two enantiotopic

SCHEME 1. An Enantioconvergent Approach to Prostanoids
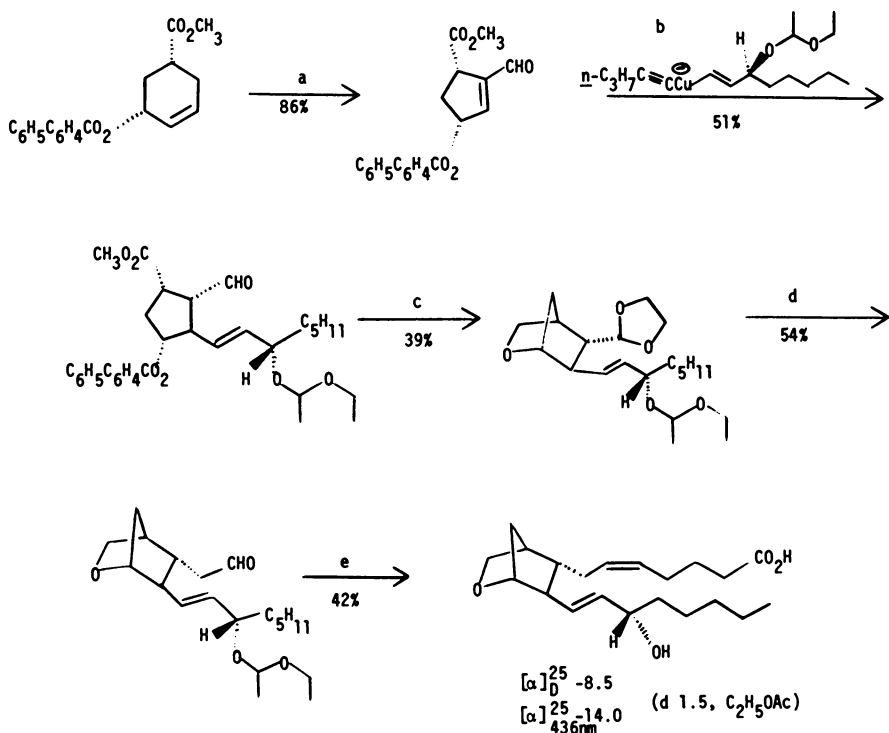
(a) i) 1 mol% OsO_4, $NaClO_3$, H_2O; ii) $NaIO_4$, THF, H_2O;
iii) $C_5H_9NH_2OAc$, PhH, 50°.

(b) HMPA, THF, ether, -78° (1 h), -20° (3h).

(c) i) [structure] $N(CH_3)_2$, HOAc, CH_3CN; ii) LAH, THF, 0°; iii) TsCl,
C_5H_5N, 0°; iv) NaH, DMF, rt.

(d) i) CH_3COCO_2H, THF, $BF_3\cdot$ether; ii) $C_2H_5OCH=CH_2$, $POCl_3$, $(C_3H_5)_3N$;
iii) $Ph_3PCH_2OCH_3Cl$, $\underline{t}$-C_4H_9Li, THF, 0°; iv) $Hg(OAc)_2$, THF, H_2O
then KI, H_2O.

(e) i) $Ph_3\overset{+}{P}CH_2(CH_2)_3CO_2^-$, CH_3SOCH_2Na, DMSO; ii) HOAc, THF, H_2O.

faces of the diene will then lead to preferential reaction via
6a or 6b, i.e. to asymmetric induction. Reasoning that a π-stack-
ing type of interaction might be an effective "solvator," that
such an interaction would be more favorable with the diene than
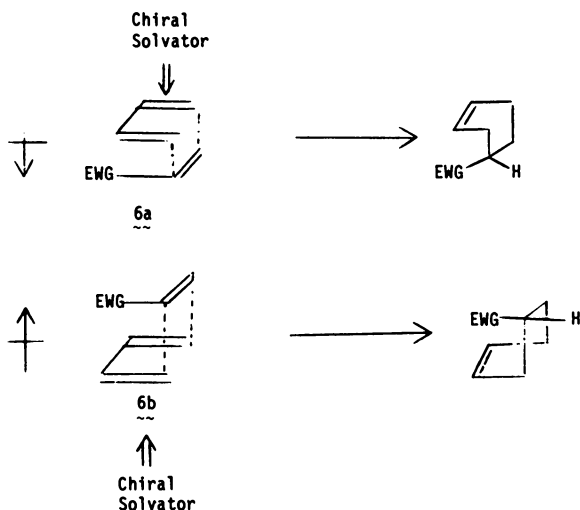
the dienophile (for electronic reasons), and that internal
solvation would be more favorable than external solvation led us
to explore incorporation of a mandelic acid group into the diene.
In such a mandelate system, a large substituent L either projects
toward (i.e. 7a) or away (i.e. 7b) from the diene and would thus
bias the sense of stacking of the system to want the latter inter-

action. Choice of L=OCH$_3$ and S=H has the advantages that the
chiral inducing agent is readily available in optically pure
form and offers a direct method for analyzing the degree of
asymmetric induction by NMR spectroscopy. In addition, it offers
a method for the direct determination of absolute configuration.
Mosher suggested a model, represented in 8a and 8b, in which the
extended dihedral angle of 0° between R' and Ph in 8a and R and
Ph in 8b leads to shielding of R' in 8a and R in 8b (in these
extended Newman projections, the circle represents the CO$_2$ group)
(6). An alternative model depicted in 9a and 9b suggests a
dihedral angle of about 60° between R and Ph in 9a and R' and Ph
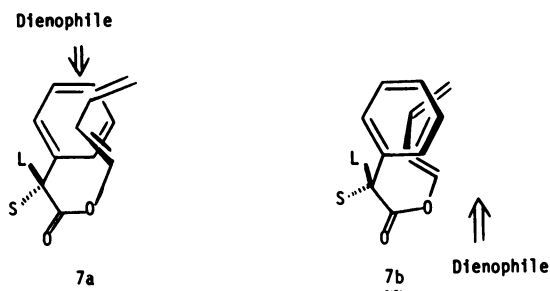
8a   8b

9a   9b
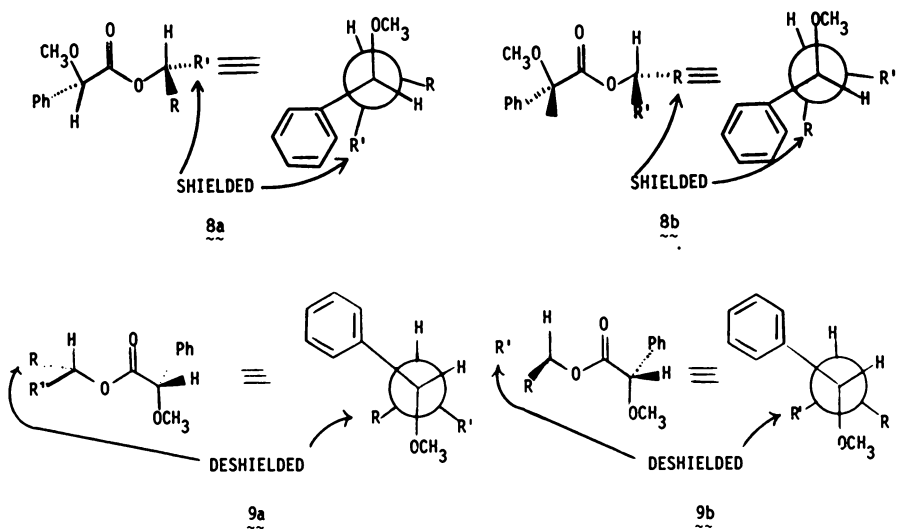
in 9b which should lead to <u>deshielding</u> of R in 9a and of R' in 9b due to the anisotropy of the phenyl ring. Dipolar effects and extended eclipsing interactions tend to favor conformations 9a and 9b while eclipsing interactions around the carboxylate func- tion tend to favor 8a and 8b. <u>Fortunately, both conformational models predict the same trend</u> - the S-mandelate ester of enantio- mer 10a should exhibit the NMR signal for R downfield of the corresponding signal for the S-mandelate ester of enantiomer 10b

10a   10b

and the converse situation holds for the signals for R'. We have found that this little used method has correctly predicted every absolute configuration we were able to verify independently. Chart 1 exemplifies some of the molecules with key NMR absorp- tions.

Diels-Alder condensation of diene 11 with acrolein and juglone, catalyzed by BF$_3$·ether and B(OAc)$_3$ respectively, led to adducts 12 and 13 (5). For 12, the ratio of the absorptions for the aldehydic protons at δ9.65 and 9.20 of 82:18 represents the degree of asymmetric induction and assigns the 1R,2R configura- tion to the major product - an interpretation confirmed by cor- relation with the known 1R,2R-2-hydroxymethylcyclohexanol.
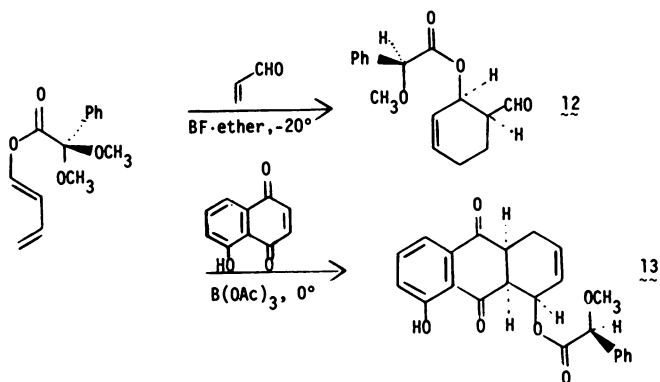
The 64% ee rises to ∿100% ee for the juglone adduct 13 whose
enantiomeric purity and absolute stereochemistry were assigned
by the NMR method (see Chart 1). Both results agree with a t.s.
invoking folding as represented in 7b - in good accord with the
model. Most interesting is the enhancement of the ee as a
function of dienophile. Again the model presented accommodates
this observation. For juglone, charge transfer interactions in
the t.s. for cycloaddition should be more important than for
acrolein - a fact that should lead to tighter complex formation
at the t.s. and thus enhanced chiral recognition.

A strategy for synthesis of iboga alkaloids evolves from
the acrolein cycloaddition (9,11). Focusing on the simplest con-
ceptual approach to iboga alkaloids via Diels-Alder chemistry,
a double bond must be introduced into the existing cyclohexyl
ring. Such a retrosynthetic analysis, represented in equation 4,
rapidly dissects the problem to the cycloaddition of acrolein to
a 1-acyloxy-1,3-hexadiene. Scheme 2 summarizes the synthesis to

$$(4)$$
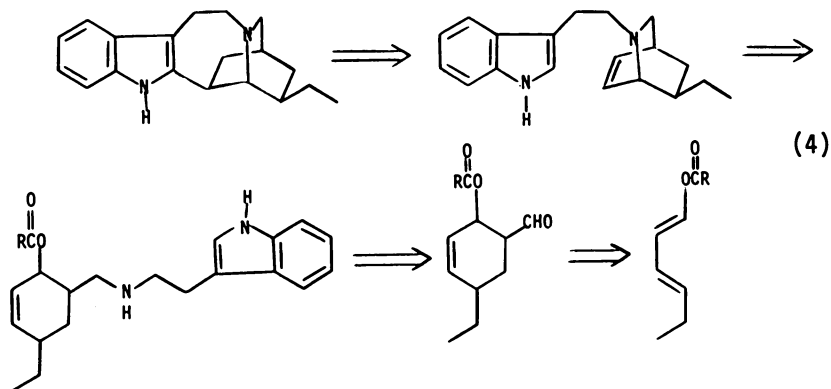
give 80% of 3R,4S,6R-ibogamine and 20% of the 3S,4R,6S isomer(9).

A

δ5.55

CH$_3$ •••• H O Ph H / O / OCH$_3$
δ1.35 H δ5.32
S

H CH$_3$ H O Ph H / O / OCH$_3$
δ1.20
R

B

CH$_3$ H O Ph H / CH$_3$O$_2$C O / OCH$_3$
δ1.21 δ3.59
S

δ3.74 CH$_3$O$_2$C •••• H O Ph H / O / OCH$_3$ CH$_3$
δ1.12
R

C

δ9.10 CHO H ← δ5.96 O O Ph OCH$_3$ H
S

δ9.56 CHO H O O Ph OCH$_3$ H
δ5.80
R

Chart 1.   Determination of absolute configuration using mandelate esters. Con-figurations denoted refer only to carbinol carbon atom. Key: A, Ref. 7; B, Ref. 8; C, Ref. 9; D, Ref. 10; and E, Ref. 5. Continued on next page.
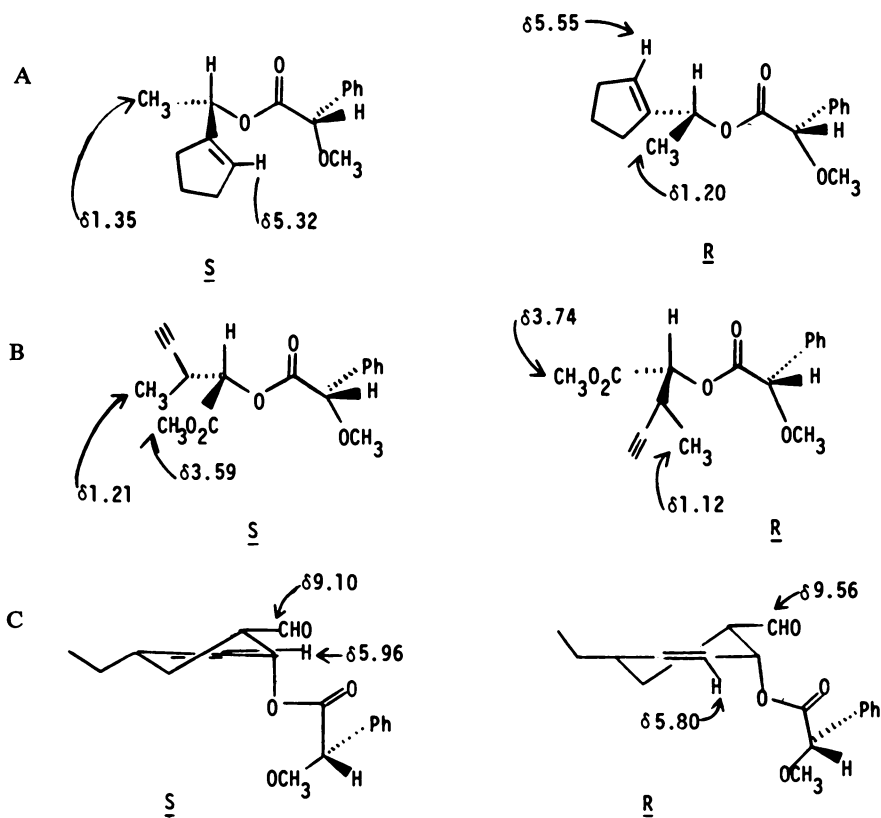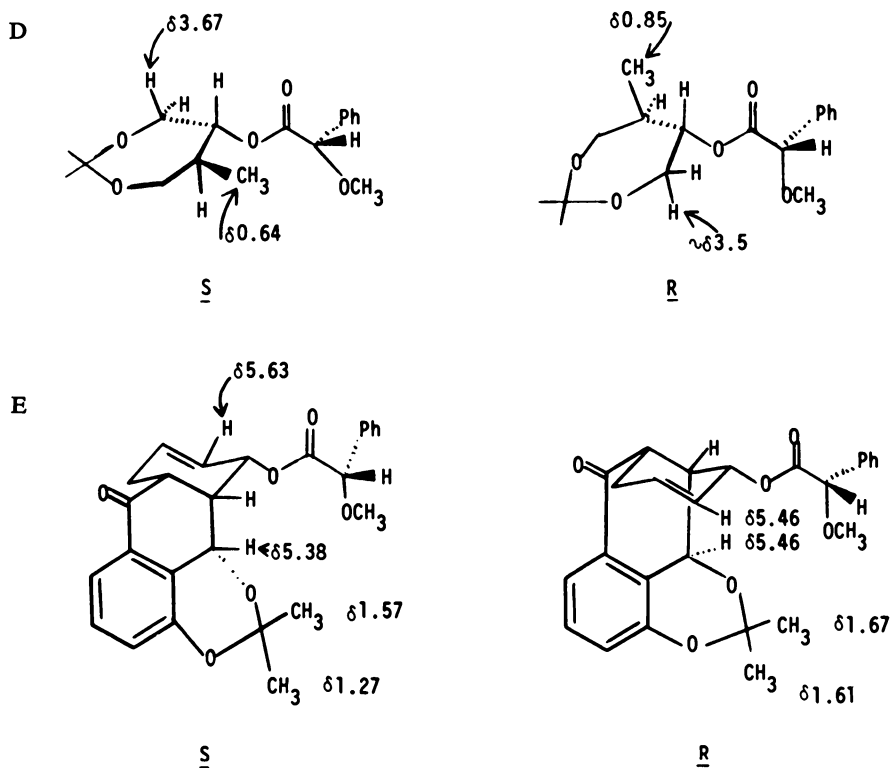
D

S

R

E

S

R

Chart 1. Continued. Determination of absolute configuration using mandelate esters. Configurations denoted refer only to carbinol carbon atom. Key: see page 11.

SCHEME 2. A Synthesis of Optically Active

Ibogamine
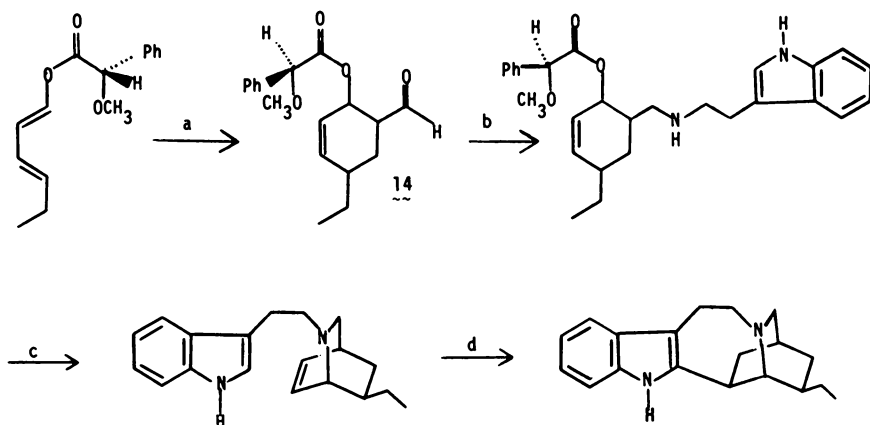
(a) acrolein, $BF_3 \cdot$ether. (b) tryptamine, $MgSO_4$, $PhCH_3$ then add
(c) 3%$(Ph_3P)_4Pd$, CH_3CN. $NaBH_4$, CH_3OH.
(d) $(CH_3CN)_2PdCl_2$, $AgBF_4$, $(C_2H_5)_3N$, CH_3CN then add $NaBH_4$.

The ee and absolute configuration of the initial adduct 14
assigned by the NMR method (see Chart 1) was verified by compari-
son of the final product with an authentic sample. A similar
strategy was employed for the synthesis of catharanthine 15 (11).

15
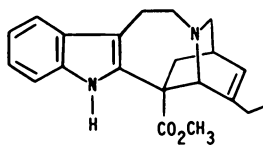
An approach toward anthracyclinone antitumor agents emerges
from the juglone adduct 13 (12). Pillaromycinone 16 has all of
its chiral centers in ring D, and they can emanate from a cyclo-
hexenone 17 in which the cis ring juncture would direct the
stereochemical introduction of the remaining substituents (see
equation 5). The cis ring juncture of 17 can readily derive from
a Diels-Alder reaction starting from a cyclohexenone 18. This
requires partial saturation of the B ring but in such a manner as
to facilitate rearomatization, thus utilizing the presence of the
two oxygen substituents. Furthermore, the cis B/C ring juncture
of 18 will direct an incoming diene so as to create the correct

(5)
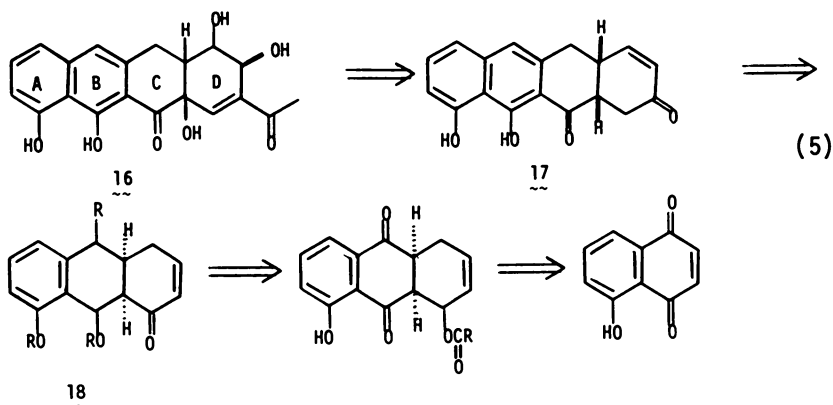
stereochemistry of 17. The stereochemistry of 18 and, by extrapolation, that of 16 is established in the first step of synthesis, the Diels-Alder reaction, even though the pertinent chiral centers (in ring B) disappear in the final product. They represent stereochemical relay centers which are to be discharged once they served their function. Scheme 3 outlines the approach. Preliminary experiments suggest that treatment of 19 with BF₃· ether in methanol does produce the acetonide of deoxypillaromy-cinone.

Resolution Strategy

The mandelate esters serve yet an additional role in chiral synthesis - facilitation of resolution by hplc. The diastereo-mers in entries 1,2, and 4 of Chart 1 are all readily resolved on a Waters Prep 500 column utilizing 2-10% ethyl acetate in hexane (7,8,10,13). The diastereomer labelled S of entry 2, Chart 1, may be used for a synthesis of verrucarinic acid 21 as outlined in equation 6; the acid is produced as its bis t-butyl-dimethylsilyl ether for incorporation into verrucarin A (8).

(6)
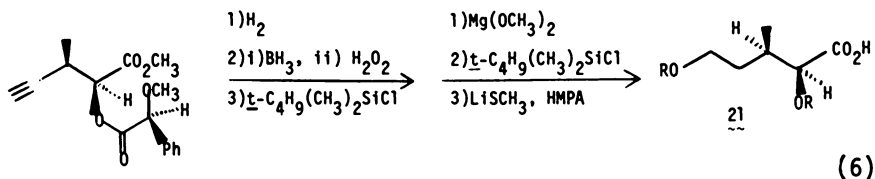
The macrolide erythrynolide B, 22, offers a particularly striking strategy utilizing this type of resolution (equation 7). In particular utilizing 23 as a key intermediate which focuses on an allylic alkylation for the crucial ring formation, the alcohol 24 and acid 25 become simple precursors containing all the critical centers. Straightforward analysis rapidly converts

SCHEME 3. An Approach to Pillaromycinone
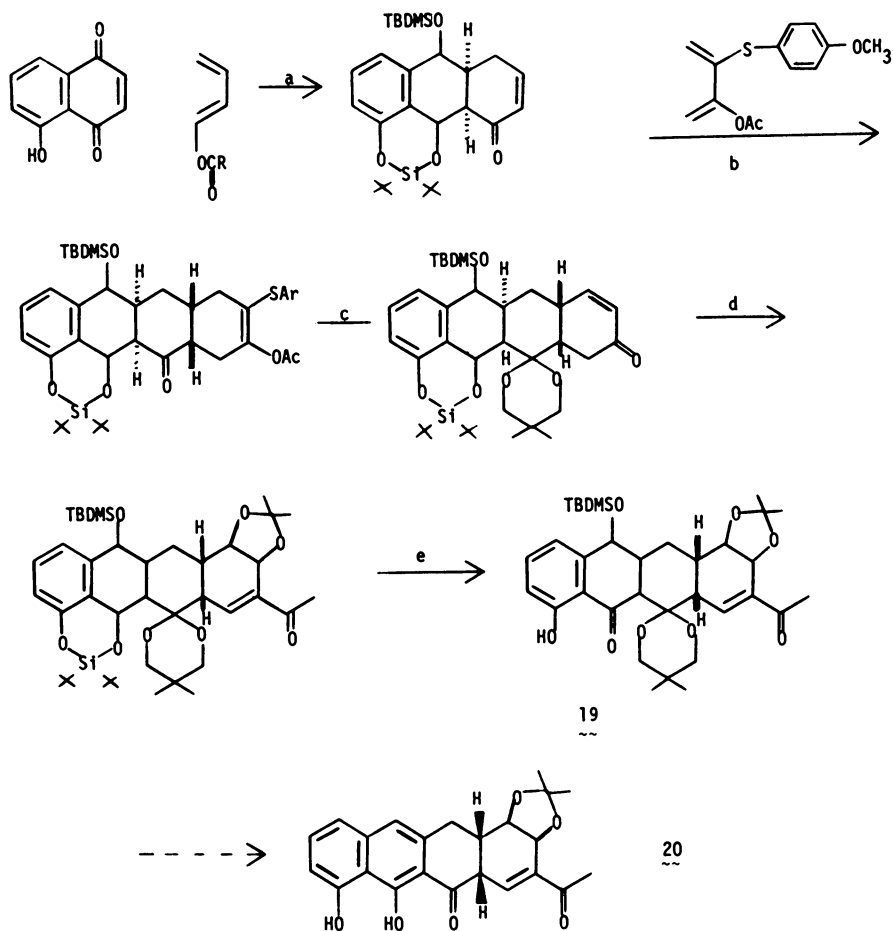
(a) i)BF₃·ether, CHCl₃, 25°; ii) NaBH₄, CH₃OH, PhCH₃;
iii) (t-C₄H₉)₂SiCl₂, 1-hydroxybenztriazole, (C₂H₅)₃N, CH₃CN;
iv) LiBH₄, THF, 0°; v) t-C₄H₉(CH₃)₂SiCl, imidazole, DMF, 50°;
vi) DIBAL-H, PhCH₃, -78°; vii) Ac₂O, DMSO, PhCH₃.
(b) BCl₃, CH₂Cl₂, 0°. (c) i) (CH₃)₂C(CH₂OH)₂, TsOH, PhH;
ii) MCPBA, CH₂Cl₂, -78°; iii) CH₃Li, ether; iv) PhCH₃, reflux.
(d)   O CH₃
         ‖ /
    Ph₂PCHOCH₃, n-C₄H₉Li, THF, -78°; ii) O₂,hν, sensitizer,
    CH₂Cl₂.
(e) i) C₅H₅N(HF)ₓ, C₅H₅N, THF; ii) MnO₂, (CH₃)₂CO.
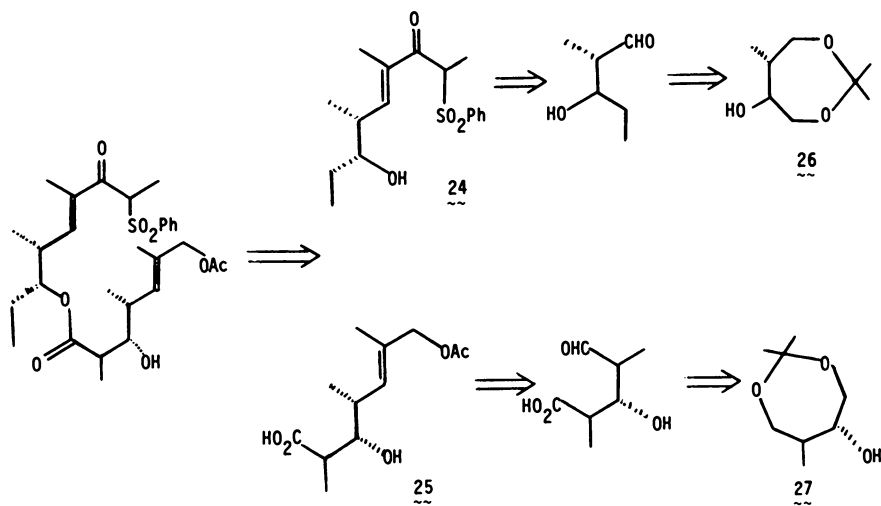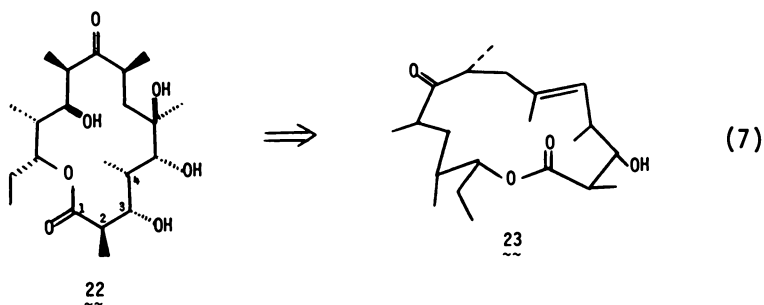
hydroxyketone 24 to alcohol 26 and acid 25 to alcohol 27. However, 26 and 27 are simply mirror images. Thus, in this strategy, both enantiomers are needed - the 5R,6R isomer 26 for the northwestern half and the 5S,6S isomer 27 for the southeastern half. Preparative hplc of the mandelate ester of the racemate readily leads to their epimerically pure diastereomers whose optical purities and configurations were assigned by NMR spectroscopy (see Chart 1, entry 4) and confirmed by potassium carbonate hydrolysis to enantiomerically pure 26 and 27 ; the configurations so deduced were in agreement with the literature assignment (10). The recovered O-methylmandelic acid was suitable for recycling. Equations 8 and 9 show the approaches to 24 (10) and 25 (14) respectively.

(8)
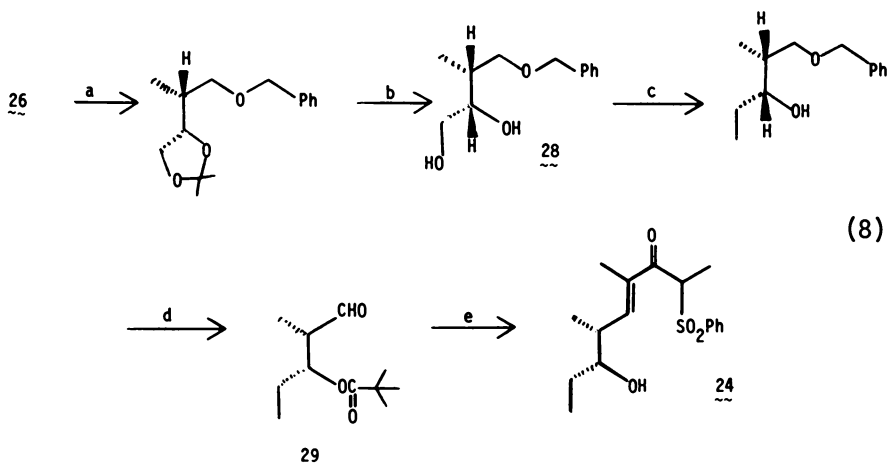
(a) i) conc HCl, Δ; ii) NaH, PhCH₂Br, DMF, rt.   (b) HCl, H₂O,
CH₃CN, rt.   (c) i) 2,4,6-(i-C₃H₇)₃C₆H₂SO₂Cl, C₅H₅N, rt;
iii) Li(CH₃)₂Cu, ether, -78°.   (d) i) t-C₄H₉COCl, C₅H₅N;
ii) 10% Pd/C, C₂H₅OAc, rt; iii) (COCl)₂, DMSO, (C₂H₅)₃N, CH₂Cl,
-60°.   (e) i) LDA, CH₃CH₂C(O)CH(CH₃)SO₂Ph, THF, -78°; ii) SOCl₂,
C₅H₅N, -50°.

(9)
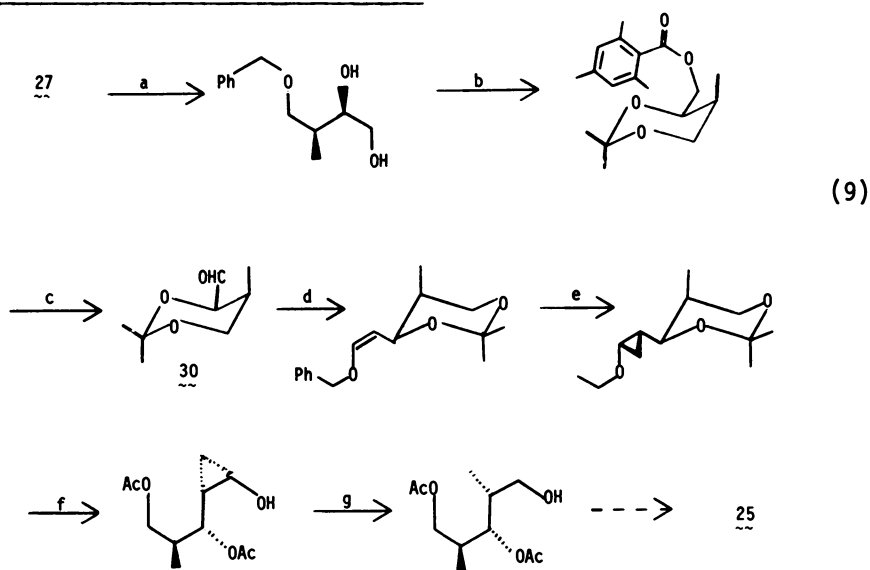
(a) Steps a and b in equation 8.   (b) i) 2,4,6(CH₃)₃C₆H₂COCl,
C₅H₅N, -40°; ii) H₂, 10% Pd/C, CH₃OH, HOAc, rt; iii) (CH₃)₂C(OCH₃)₂
TsOH, rt.   (c) i) NaOCH₃, CH₃OH, 65°; ii) DMSO, (COCl)₂, CH₂Cl₂,

Optically Active Building Blocks

An even more efficient strategy might be based upon the utilization of the same chiral building block for all the asymmetric centers provided such a building block is readily available in enantiomerically pure form. The benzyl ether of $\underset{\sim}{31}$ (see equation 10) is the intermediate in the cuprate coupling of $\underset{\sim}{28}$

$$(10)$$
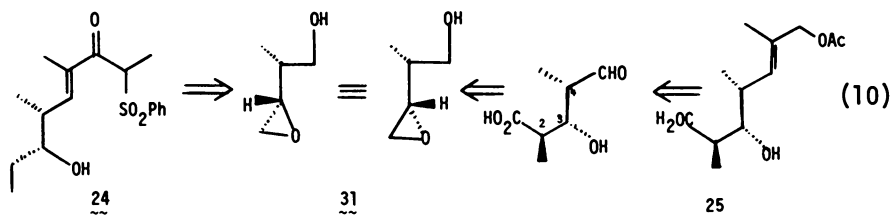
in equation 8, step c. Thus, the relationship of $\underset{\sim}{31}$ to $\underset{\sim}{24}$ is apparent. On the other hand, whereas the two original chiral centers of $\underset{\sim}{27}$ (equation 7) correspond to C(2) and C(3) of erythrynolide B, the two chiral centers of $\underset{\sim}{31}$ correspond to C(3) and C(4) (equation 10). In this approach, these two centers assume responsibility for creating C(2) of an appropriate configuration. Thus, $\underset{\sim}{31}$ represents a single enantiomer from which all the chiral centers of erythrynolide B will spring.

The fact that $\underset{\sim}{31}$ is a four carbon chain in which every carbon bears a substituent, three of them oxygen and one a methyl group, suggests R,R-tartaric acid as a logical precursor (15,16). Scheme 4 outlines an extraordinarily efficient route from R,R-tartaric acid to $\underset{\sim}{31}$ in an overall yield of 64%. Correlation of $\underset{\sim}{31}$ via cuprate coupling and selective formation of the pivalate at the secondary alcohol gives $\underset{\sim}{32}$ which was previously derived from $\underset{\sim}{29}$.
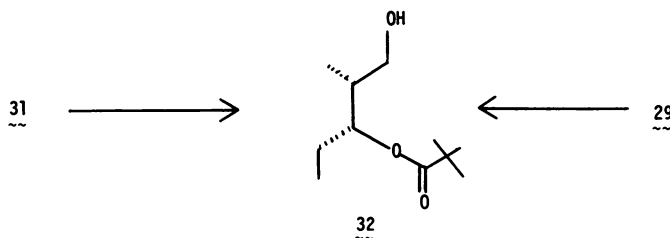
footnotes to equation 9 contd...
$(C_2H_5)_3N$, $-60°$.   (d) $PhCH_2OCH_2\overset{+}{P}Ph_3Cl^-$, t-$C_4H_9OK$, THF, $-78°$.
(e) CH_2I_2, $Zn(Ag)$, DME, rt.   (f) i) $HOAc$, CH_3OH, rt; ii) Ac_2O, C_5H_5N, rt; iii) H_2, Pd, CH_3OH.   (g) i) $Hg(OAc)_2$, rt; ii) $NaBH_4$, CH_3OH.

SCHEME 4. Synthesis of a Key Synthon for Erythrynolide B

$$[\alpha]_D^{21} \ -4° \ (c \ 1.14, \ CHCl_3)$$

31
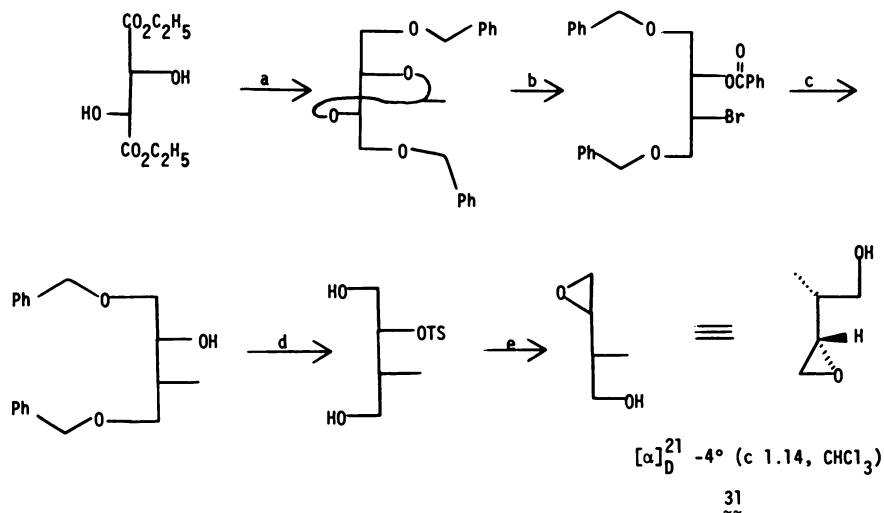
(a) i) PhCHO, HC(OC$_2$H$_5$)$_3$, TsOH, rt; ii) LAH, ether, Δ;
iii) NaH, PhCH$_2$Br, THF. (b) NBS, CCl$_4$, Δ. (c) Li(CH$_3$)$_2$Cu,
ether, 0°. (d) i) TsCl, C$_5$H$_5$N, rt; ii) H , 10%Pd/C,
CH$_3$OH, HOAc. (e) NaOH, CH$_3$OH.

This correlation also provides unambiguous confirmation of the
absolute stereochemistry of 29. Furthermore, 31 can be converted
to aldehydes 33 and 34 which are related to 30 (equation 9) as
shown in equation 11.

(11)
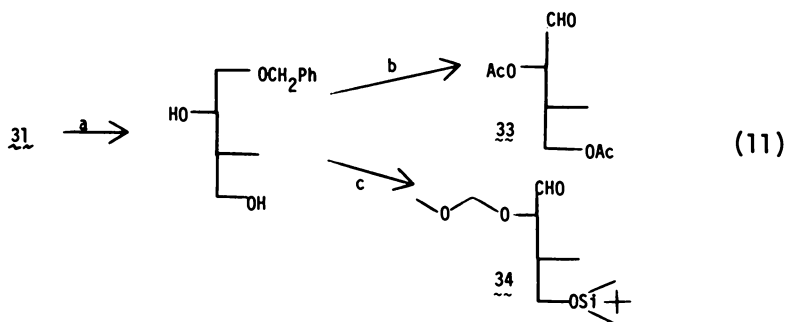
(a) PhCH$_2$ONa, PhCH$_2$OH, rt. (b) i) Ac$_2$O, C$_5$H$_5$N, rt; ii) H$_2$,
10% Pd/C, CH$_3$OH, HOAc; iii) PCC, CH$_2$Cl$_2$, 0°.
(c) i) t-C$_4$H$_9$(CH$_3$)$_2$SiCl, imidazole, DMF, rt; ii) MEM-Cl,
(i-C$_3$H$_7$)$_2$NC$_2$H$_5$, CH$_2$Cl$_2$; iii) step ii and iii of b.

The creation of the final chiral center can be envisioned
analogous to equation 9 but remains yet to be accomplished.
     While the completion of the synthesis awaits the outcome of
the above studies, the critical macrocyclization step has been
demonstrated in a model. Thus, this approach provides much
promise of efficiently creating the macrolide antibiotics.

Acknowledgment

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Synthetic Control Leading to Natural Products

TERUAKI MUKAIYAMA

University of Tokyo, Department of Chemistry, Faculty of Science, Tokyo, Japan 113

New and useful asymmetric reactions have been
developed based on the concept of "Synthetic
Control". The concept of "Synthetic Control" is
characterized by the utilization of common metal
chelates for inter-or intramolecular interactions
leading to highly stereospecific or entropically
advantageous reactions. A variety of optically
active compounds are obtained in much higher
enantiomeric purities, compared with conventional
methods, by utilizing chiral heterocyclic compounds
such as chiral pyrrolidine or oxazepine derivatives,
which have strong interactions with organometallic
compounds to form tight complexes as intermediates.
Similarly, asymmetric intramolecular Diels-Alder
reactions are realized by the utilization of effective
intramolecular metal chelation. Various natural
products are successfully synthesized by the appli-
cation of these reactions.

In this article, we summarize a variety of asymmetric synthe-
ses guided by the principle of "Synthetic Control" described in
the abstract.

   <u>Asymmetric syntheses based on chiral diamines</u>. Optically
active secondary alcohols are obtained by reduction of prochiral
ketones with the chiral hydride reagent <u>1</u> prepared from lithium
aluminium hydride and (<u>S</u>)-2-(N-substituted aminomethyl)-
pyrrolidines, derived easily in four steps from commercially
available (<u>S</u>)-proline.[1]

PhCOEt   96% ee

α-Tetralone   86% ee
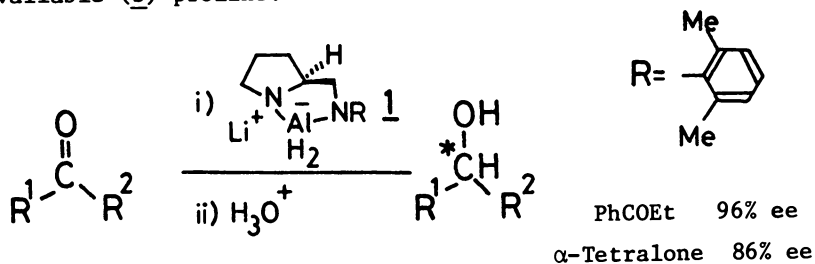
   The diamine <u>2</u> (R=Ph) was also applied to the synthesis of
optically active α-hydroxyaldehydes. Treatment of the aminal,
prepared from the chiral diamine and phenylglyoxal, with Grignard
reagents affords hydroxyanimals,which, in turn, are hydrolyzed
to yield α-alkyl-α-hydroxyphenylacetaldehydes.[2a]

>94% ee
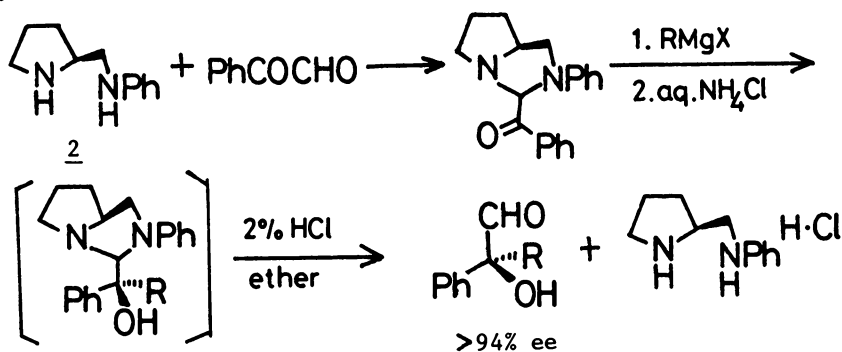
   A more general and versatile method for the preparation of
α-hydroxyaldehydes was also developed.[2b] Such aldehydes, in the
desired configuration, are obtained by the following reaction
sequence: i) reaction of one kind of Grignard reagent (RMgX) with
the aminal of methyl glyoxylate, ii) diastereoselective addition
of a second kind of Grignard reagent (R'MgX) to the ketoaminal,
iii) hydrolysis of the resulting α-hydroxyaminal.

The two enantiomers of frontalin, a pheromone of several species of beetles belonging to the genus <u>Dendroctonus</u>, were separately synthesized by applying this asymmetric reaction.[2c]

(−) 84% ee   (+) 100% ee

Frontalin

$$(-): R^1 = -(CH_2)_3C(CH_3)=CH_2, \quad R^2 = Me$$

$$(+): R^1 = Me, \quad R^2 = -(CH_2)_3C(CH_3)=CH_2$$
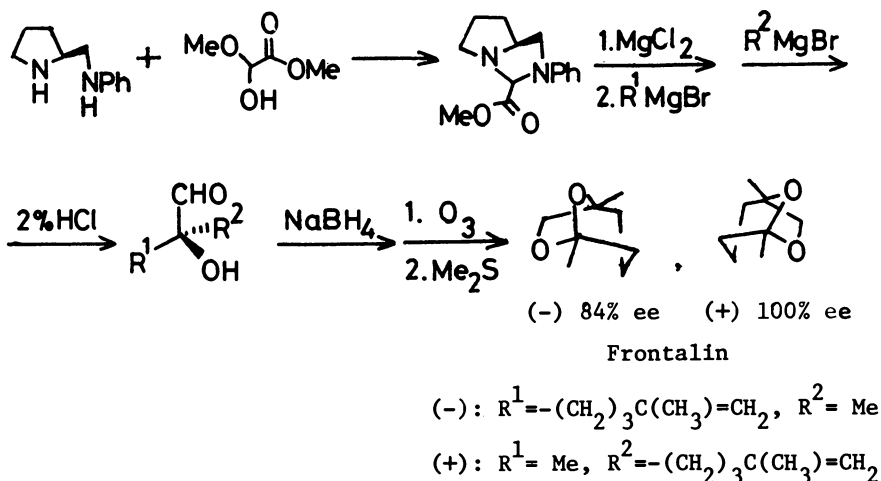
Furthermore a new marine antibiotic, (−)-Malyngolide, discovered in the marine blue green alga <u>Lyngbya majuscula Gomont</u>, was synthesized in high optical yield by way of another application of this asymmetric reaction.[2d] The sequence is outlined in Scheme 1.

Optically active β-formyl-β-hydroxycarboxylic esters are obtained by employing either the lithium or zinc enolate of ethyl acetate in place of Grignard reagents in the above mentioned reaction.[2e]

84−92% ee
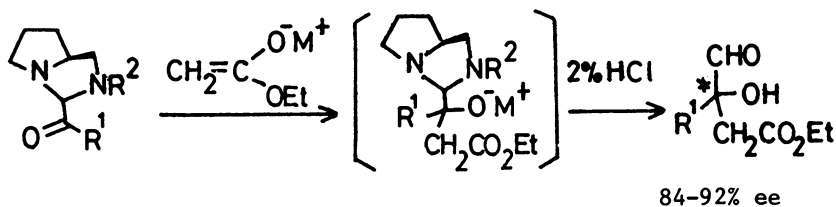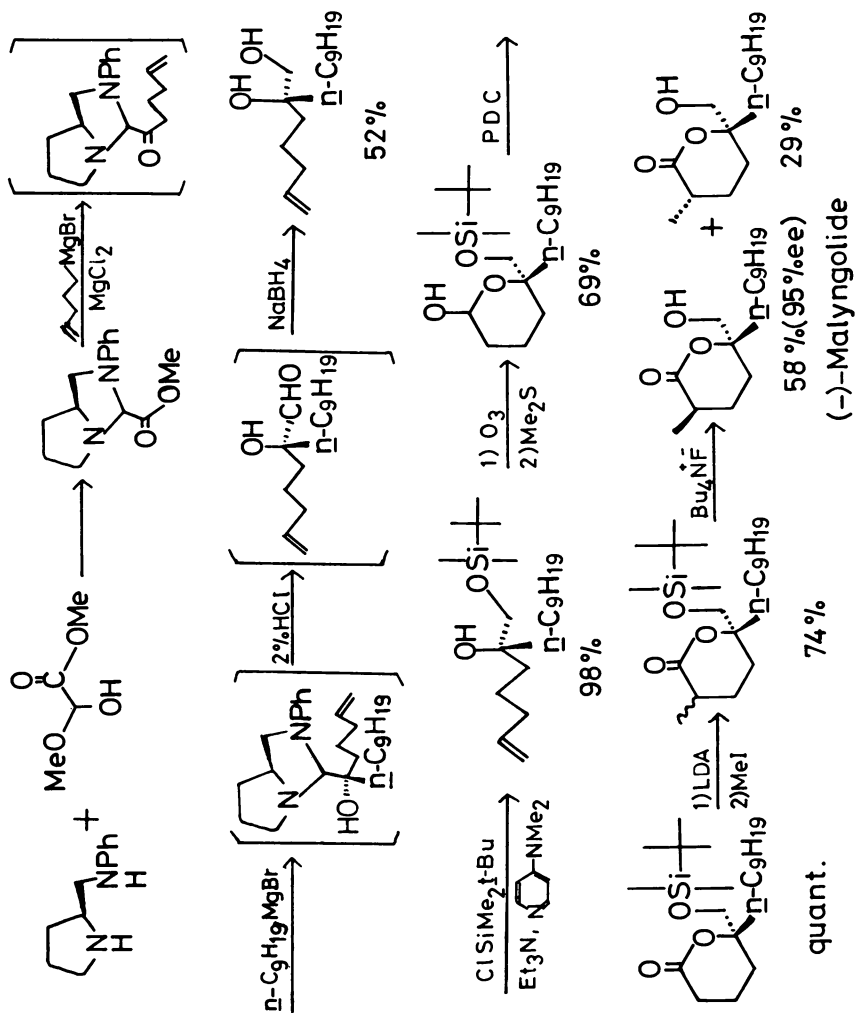
Scheme 1.

Asymmetric syntheses based on chiral aminoalcohols. Various chiral aminoalcohols **3**, **4**, **5**, **6** were synthesized starting from (**S**)-proline, and the enantioselective addition of organometallic compounds to aldehydes in the presence of these aminoalcohols was investigated.

3   **4**   **5**   **6**
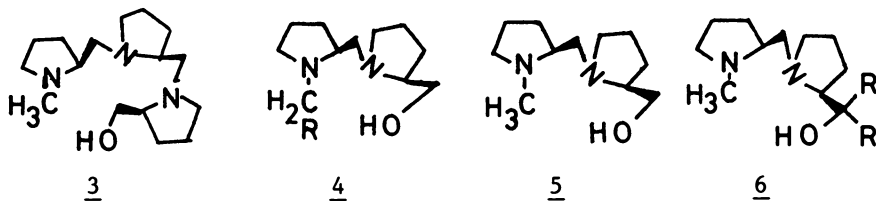
The enantioselective addition of alkyllithium reagents to aldehydes in the presence of the lithium salt of aminoalcohol **5** yields optically active secondary alcohols. High optical yields are achieved when the reaction is carried out in dimethyl ether and dimethoxymethane at low temperature.[3]

$$R^1Li + R^2CHO \longrightarrow$$
1 h

54-94% ee
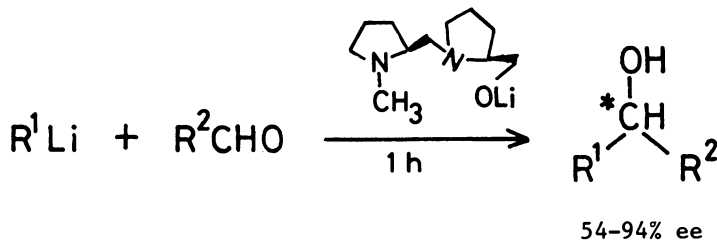
It is of interest that the alcohols which possess the **R** configuration are produced by the reaction of dialkylmagnesiums with aldehydes, whereas the alcohols obtained by the similar reaction of alkyllithiums possess the **S** or **R** configuration, depending on the size of the alkyllithium.[3]

$$R^1_2Mg + R^2CHO$$
toluene, -110°C, 1h

(**R**)-(+) 22-92% ee
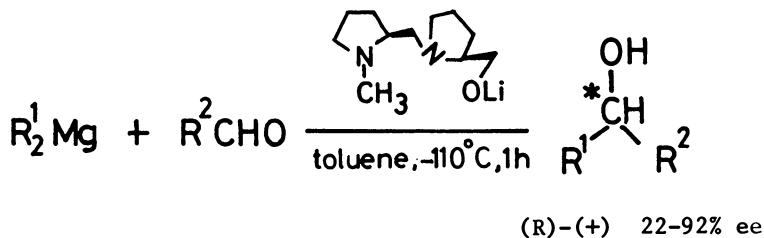
By extending the above mentioned asymmetric addition of alkyllithium to other organolithium reagents such as lithium salts of methyl phenyl sulfide, 2-methylthiothiazoline, acetonitrile, N-nitrosodimethylamine, and trialkylsilylacetylenes, optically active oxiranes, thiiranes, aminoalcohols, and acetylenic alcohols are readily obtained.[4,5]
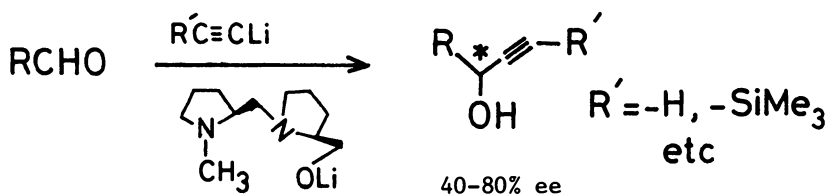
Some of the optically active acetylenic alcohols were successfully converted to, e.g., γ-ethyl-γ-butyrolactone, the insect pheromone of _Trogoderma_, and important intermediates for the synthesis of substances with antibacterial activities.[6]

Trogoderma
insect pheromone   canadensolide   avenaciolide
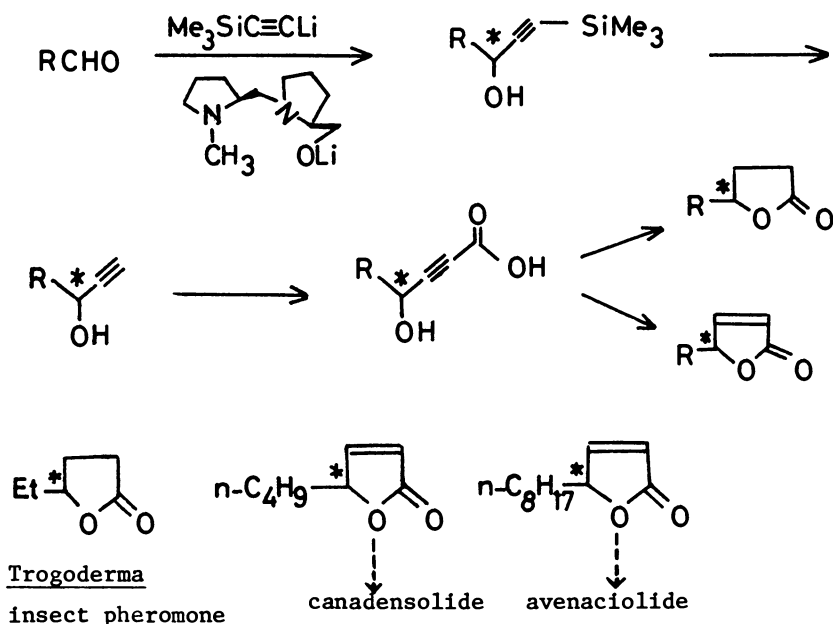
A chiral aminoalcohol 7, derived from *l*-4-hydroxyproline, is found to be a superior catalyst for the enantioselective 1,4-addition of arylthiols to 2-cyclohexen-1-one to yield 3-arylthiocyclohexanones in high optical purities.[7]

88% ee
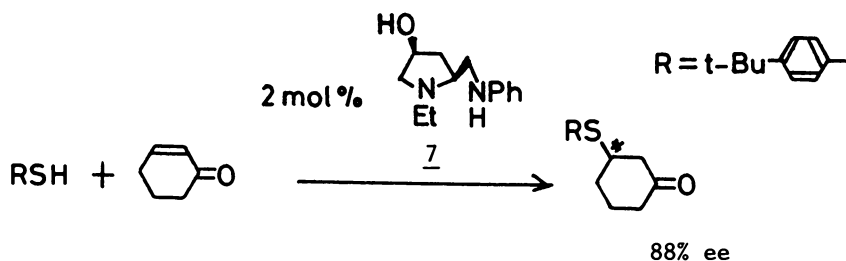
Asymmetric synthesis based on a chiral oxazepine. (2R,3S)-3,4-Dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione (8) was prepared from the half ester of malonic acid and *l*-ephedrine and syntheses of various optically active carboxylic acids starting from this chiral oxazepine 8 were investigated.
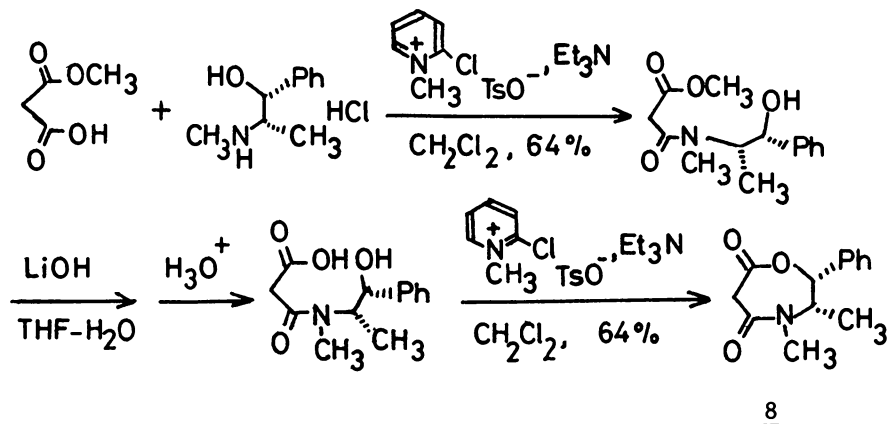
i) Synthesis of β-substituted carboxylic acids.

Optically active β-substituted alkanoic acids are obtained by the reaction of the 6-alkylidene derivatives of 8 (9), which are easily prepared from 8 and aldehydes, with Grignard reagents in the presence of a catalytic amount of nickel chloride, followed by hydrolysis.[8]

RCHO + **8** → (TiCl₄ / PyH-THF) → **9**

76-99%   **9**
(E:Z=100:0-85:15)

R MgX, NiCl₂ / THF, -78°C → H₃O⁺ →

82- >99% ee

The antibiotic indolmycin was synthesized in high optical purity as one application of this chiral reagent (Scheme 2).[9]

ii) Synthesis of optically active cyclopropanedicarboxylic acids.

The reaction of dimethylsulfoxonium methylide with 6-alkylideneoxazepine **9** followed by hydrolysis gives almost optically pure cyclopropanedicarboxylic acids in good yields.[10]

9 → (CH₂S(CH₃)₂ / THF, rt) → (i) OH⁻ ii) CH₂N₂) →

>90% ee

iii) Synthesis of optically active 3-substituted γ-butyrolactones.

Almost optically pure 3-substituted γ-butyrolactones were obtained by the following sequence; i) the reaction of 6-alkylideneoxazepine **9** with phenylthiomethyllithium in the presence of a catalytic amount of nickel chloride, ii) the transformation of the adduct **10** to the dihydrofuran derivatives **11** by trimethyloxonium tetrafluoroborate, iii) acid hydrolysis of the dihydrofuran derivative **11**.[11]

Scheme 2.

Scheme 2. (continued)
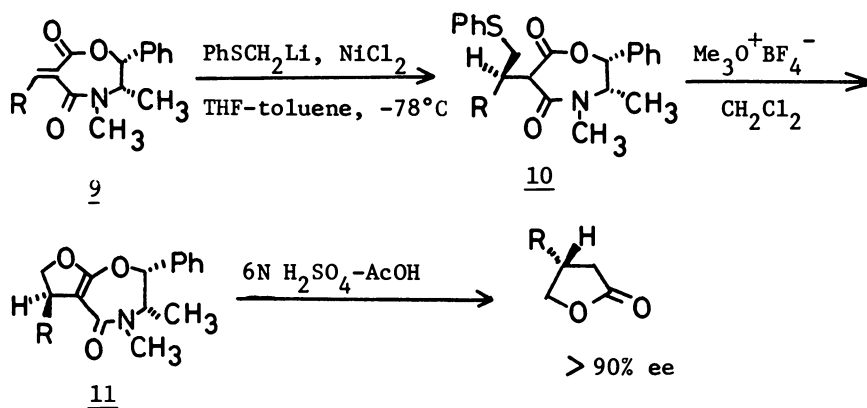
Diels-Alder reaction assisted by intramolecular interactions.

The Diels-Alder reaction is one of the most important reactions in organic synthesis and has been applied to the synthesis of various natural products which possess a six-membered ring system. Unfortunately, however, there are some limitations to the structures of dienes and dienophiles that can be used successfully. For example, the Diels-Alder adducts between furan derivative and β,β-dimethylacrylic acid derivatives have not yet been isolated.

The adducts of some sterically hindered dienophile and furan derivatives are successfully obtained in good yields by the intramolecular Diels-Alder reaction of the diene and dienophile activated by an alkoxymagnesium salt coordinated to the same mole-cule. The acceleration of the reaction is apparently due to the coordination of the dienophile and a proximity effect which makes the reaction entropically advantageous.[12]
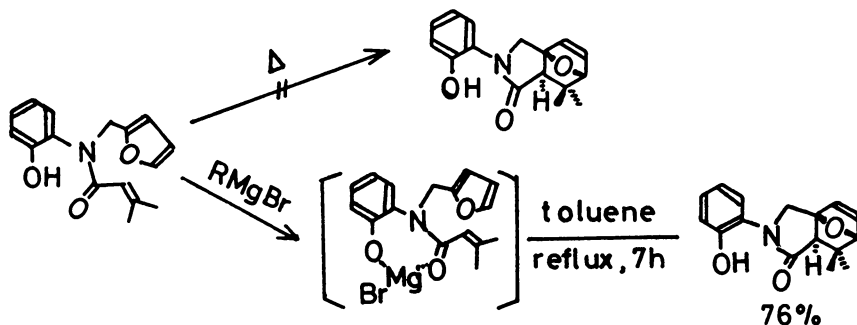
This process was applied to the synthesis of the Karahana ether.[13]
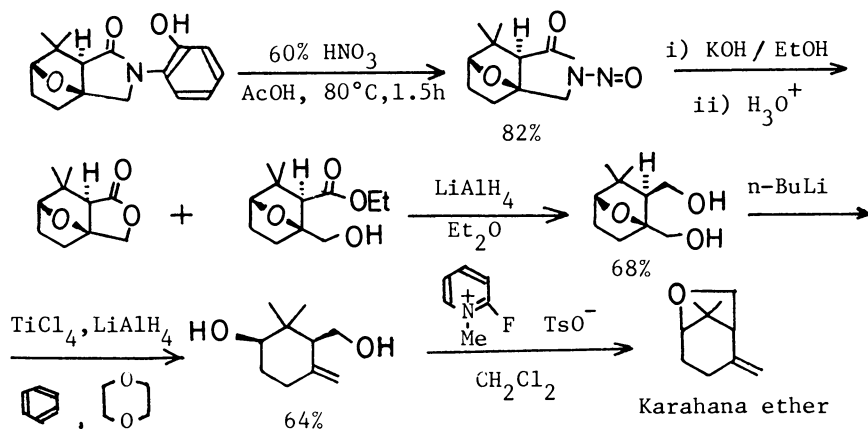
The above sequence was adapted to an asymmetric Diels-Alder reaction. The reaction of β,β-dimethylacrylic acid derivative 12, derived from (R)-2-amino-2-phenylethanol, afforded preferentially one diastereomer 13 in good yield, as did the crotonic acid derivative.
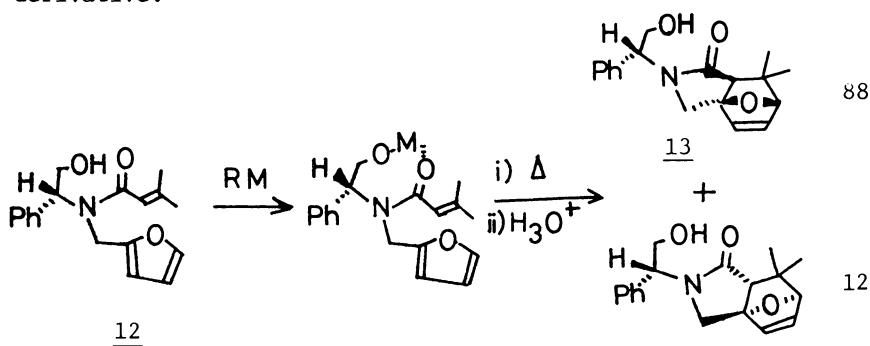
The adduct 13 is transformed into (+)-Farneciferol C.[14]

i)CBr$_4$,PPh$_3$/THF
ii)Ph$_3$SnH,AIBN/
benzene reflux

i)LiAlH$_4$/Et$_2$O
ii)TsCl/pyridine
iii)PhSK/EtOH
iv)MCPBA/CH$_2$Cl$_2$

i) n-BuLi
ii) Cl⟍OTHP

iii) H$_3$O$^+$
iv) 5%Na-Hg
Na$_2$HPO$_4$/MeOH,HMPA

i) CBr$_4$,PPh$_3$/CH$_3$CN
ii) KO⟍⟍O⟍O
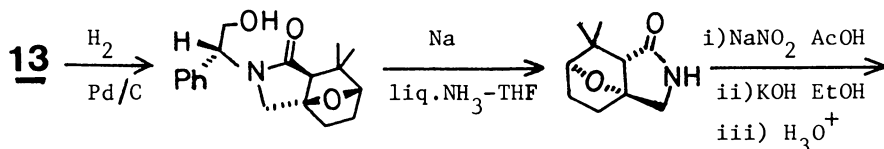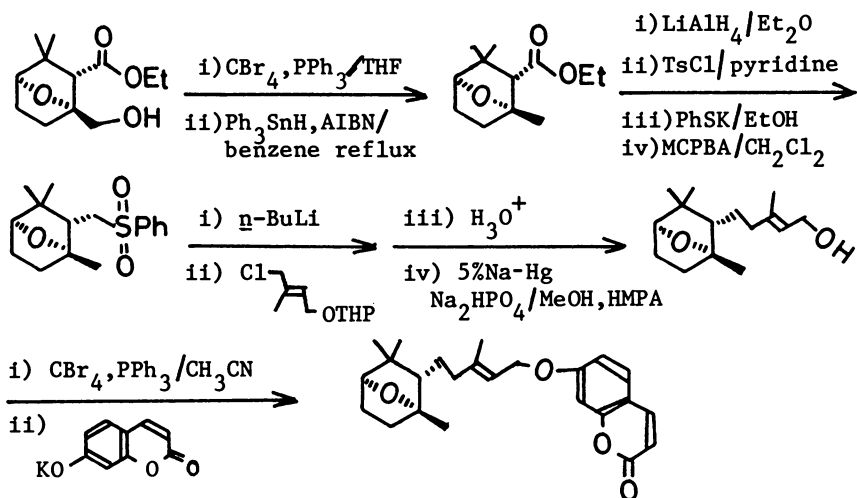
(+)-Farneciferol C

This methodology, i.e., the introduction of an intramolecular chelate effect for highly selective reaction, has been further extended to the asymmetric Michael reaction. The reaction of N-crotylephedrine **14** with Grignard reagents, followed by acid hydrolysis, constitutes a simple procedure for obtaining highly optically pure carboxylic acids.[15]

14

R'MgBr

H$_2$SO$_4$-AcOH

85- >99% ee
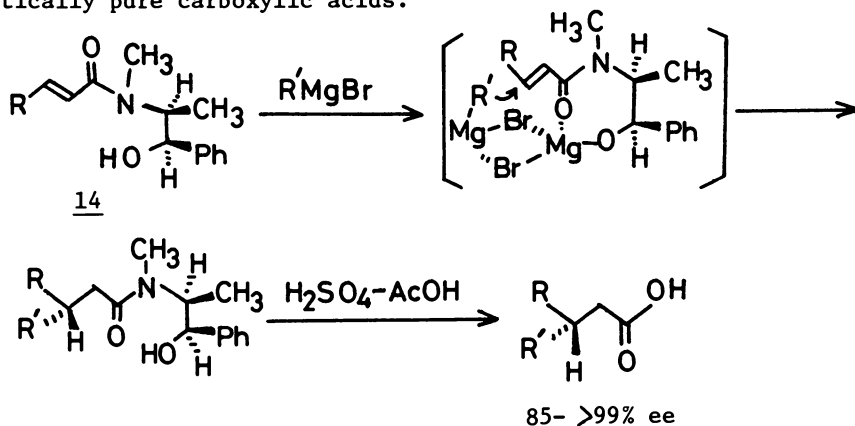
<u>Stereospecific reactions leading to optically active sugar</u>
<u>derivatives</u>. The cadmium salt of the 2-allyloxybenzimidazole
derivative <u>15</u> reacts with various aldehydes to afford adduct <u>16</u>
in high regio- and stereoselectivity. Adducts <u>16</u> are subsequently
transformed into <u>trans</u>-vinyloxirane <u>17</u>.[16]

D- or L-Ribose is synthesized starting from 2,3-<u>O</u>-
isopropylidene-D- or L-glyceraldehyde, respectively, by the appli-
cation of this reaction (Scheme 3).[17]

<u>16</u>   57-98%

(α/γ=75/25-90/10)

<u>17</u>

60-91%

R^2=(CH$_2$CH$_2$O)$_3$Me
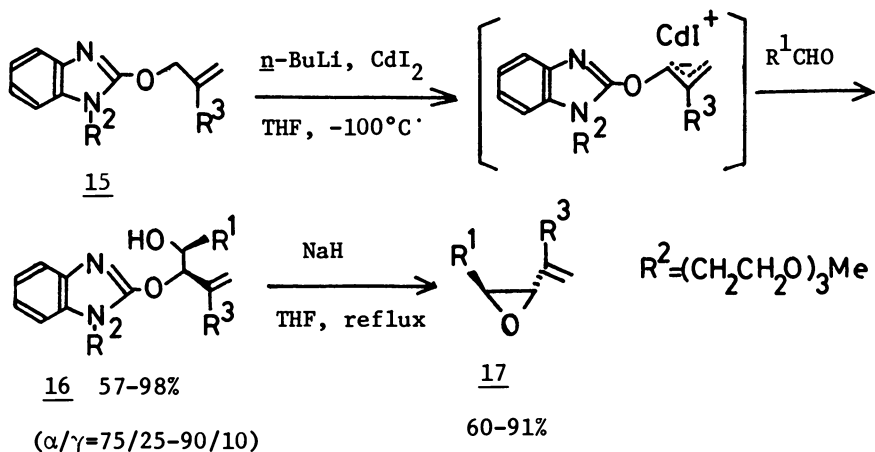
Further, the mild allylation of carbonyl compounds with
allyltin dihaloiodide, formed in situ by the oxidative addition
of stannous fluoride to allyl iodide, has been applied to the
synthesis of 2-deoxy-D-ribose starting from 2,3-<u>O</u>-isopropylidene-
D-glyceraldehyde.[18]

<u>18</u>   74%

(<u>erythro</u>:<u>threo</u>=81:19)

<u>erythro-18</u>   71%   95%   75%

2-deoxy-D-ribose
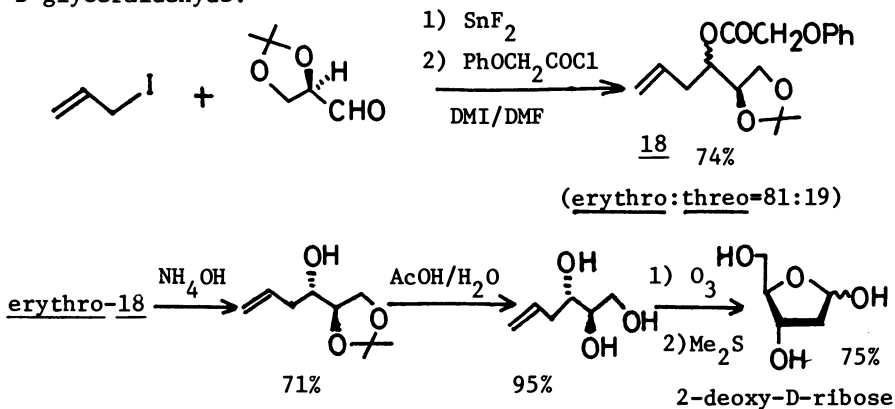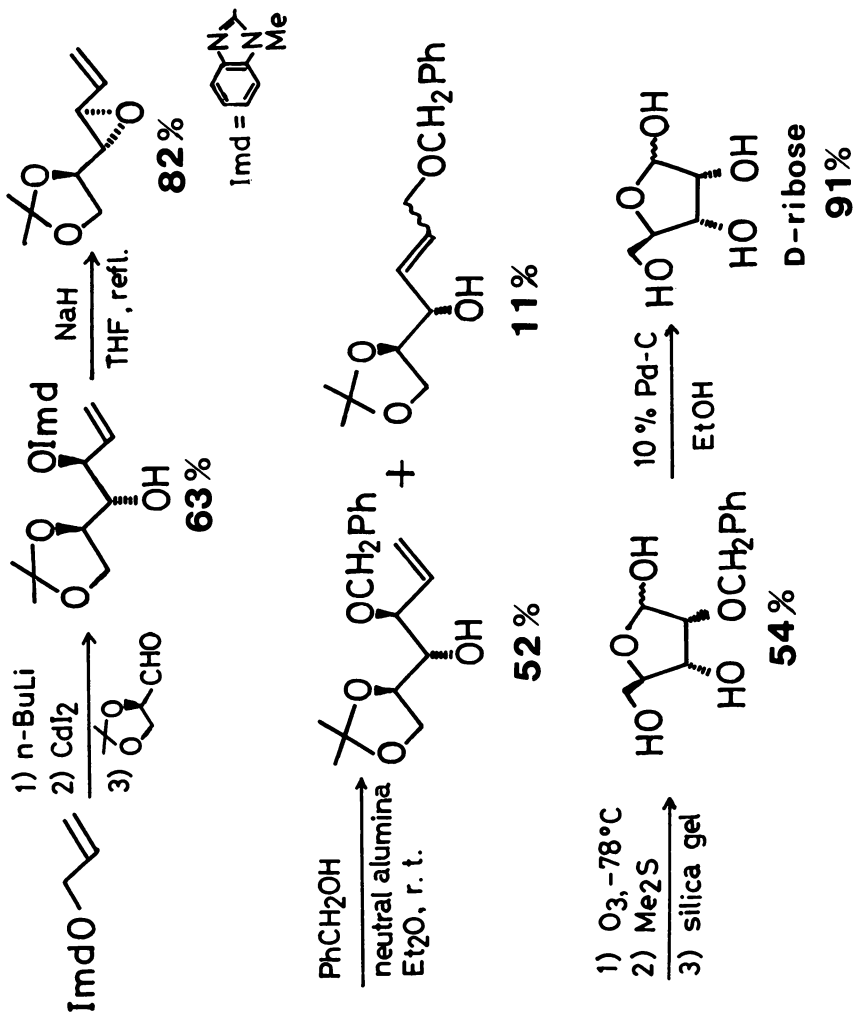
Scheme 3.

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Asymmetric Synthesis of Chiral Tertiary Alcohols in High Enantiomeric Excess

ERNEST L. ELIEL, JORMA K. KOSKIMIES, BRUNO LOHRI, W. JACK FRAZEE, SUSAN MORRIS–NATSCHKE, JOSEPH E. LYNCH, and KENSO SOAI

University of North Carolina, Department of Chemistry, Chapel Hill, NC 27514

Chiral 1,3-oxathianes have been used as adjuvants for highly stereoselective asymmetric syntheses. Acylation (direct or via an intermediate carbinol) proceeds to give exclusively equatorial products in which the chirality has been transferred to C(2) of the 1,3-oxathiane. Reaction of the acyl compounds with Grignard reagents gives predominantly one diastereomer of a 2-oxathianylcarbinol bearing two different alkyl groups on the carbinol carbon, following Cram's rule. Conditions for maximum stereoselectivity have been worked out. Cleavage of the oxathiane (NCS/AgNO$_3$) leads to α-hydroxyaldehydes, RR'C(OH)CHO, from which glycols, RR'C(OH)CH$_2$OH, tertiary alcohols, RR'C(OH)CH$_3$ and other derivatives can be prepared, generally in enantiomeric purity exceeding 90%. Suitable chiral 1,3-oxathianes can be conveniently derived from camphor (either enantiomer) or (+)-pulegone.

In 1971 we discovered ($\underline{1}$) that the reaction of conformationally locked 2-dithianyllithium compounds with electrophiles (Corey-Seebach reaction) proceeds with remarkable stereoselectivity, giving virtually exclusively the equatorial substitution products, as exemplified in Scheme 1 (R=H). The preference for the 1,3-dithianyl-2-carbanion to undergo electrophilic substitution from the equatorial side amounts to over 6 kcal/mol ($\underline{2}$), corresponding to a selectivity factor in excess of 10,000. This high preference was subsequently shown ($\underline{3}$) to be due to stereoelectronic factors, in accord with theoretical predictions ($\underline{4}$, $\underline{5}$, $\underline{6}$).

Stereoselectivities of such magnitudes resemble those found in enzymatic reactions and we resolved to try to apply the high
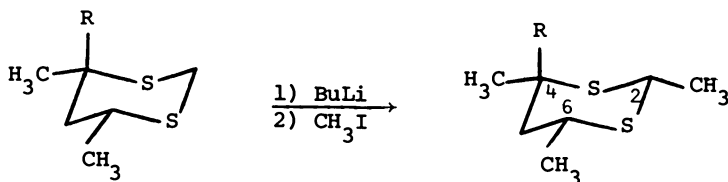
Scheme 1

selectivity to the design of a very efficient asymmetric
synthesis. Before entering into details, we wish to state here
the conditions of an effective asymmetric synthesis in general
terms (7):

1)   The synthesis must be highly stereoselective.

2)   If a chiral adjuvant (chiral auxiliary reagent) is
     built into the starting material, the chiral center
     (or other chiral element) created in the asymmetric
     synthesis must be readily separable from the chiral
     adjuvant without racemization.

3)   The chiral adjuvant itself must be recoverable in
     good yield and without loss of enantiomeric purity.

4)   The chiral adjuvant should be readily (cheaply)
     available in enantiomerically pure form.

In addition, of course, the synthesis must proceed in
acceptable overall chemical yield. Statement 1) is qualitative
and its translation into quantitative terms is a matter of taste.
Syntheses producing 85-90% enantiomeric excess (e.e.) usually
allow purification of the chiral product (or an intermediate on
the way) to enantiomeric purity by simple recrystallization.
However, higher demands may be made in cases of syntheses of
chiral liquids when crystalline intermediates are not accessible.
With respect to statements 2) and 3), these conditions are
particularly easy to fulfill in catalytic asymmetric synthesis
where 2) simply demands separation of the chiral product from the
chiral catalyst and 3) is superseded by a requirement of reason-
able turnover. (A turnover number of 100, modest by the standards
of many catalytic reactions, is equivalent to a 99% recovery of
chiral auxiliary reagent, which is rarely achieved!) Catalytic
asymmetric syntheses are therefore particularly attractive, but,
of course, they are often not available. Statement 3) may not
apply when the chiral auxiliary reagent is very cheap (e.g.
sucrose).
Contemplation of Scheme 1 suggests that its application to
asymmetric synthesis should be facile if R = CH$_3$ and the starting

dithiol is resolved. However, separation of the new chiral center
(C-2) from the original one (C-6) would appear to be unachievable.
We felt that this dilemma could be overcome by the use of 1,3-
oxathianes instead of 1,3-dithianes and, indeed, it was found that
the electrophilic reactions of 2-lithio-1,3-oxathianes are of the
same order of stereoselectivity as those of the corresponding
dithianes (8). However, an asymmetric synthesis based on the
stereoselective cleavage of the C(2)-S bond followed by scission
of the C(6)-O linkage in 2-alkyl-4,6,6-trimethyl-1,3-oxathianes
gave disappointingly low optical yields (9).

   A chance discovery pointed us toward the successful synthetic
approach. 2-Acyl-1,3-oxathianes can be obtained with exclusively
equatorial acyl groups by acylation of conformationally biassed
2-lithio-1,3-oxathianes or (in better yield) by reaction with
aldehydes followed by Swern oxidation (10). We discovered (8)
that reaction of these ketones with Grignard reagents once again
proceeds highly stereoselectively giving one of the two possible
tertiary alcohols in large excess over the other. The sequence
of the two highly stereoselective steps is shown in Scheme 2. It
is clear that starting from a chiral 1,3-oxathiane such as 1,
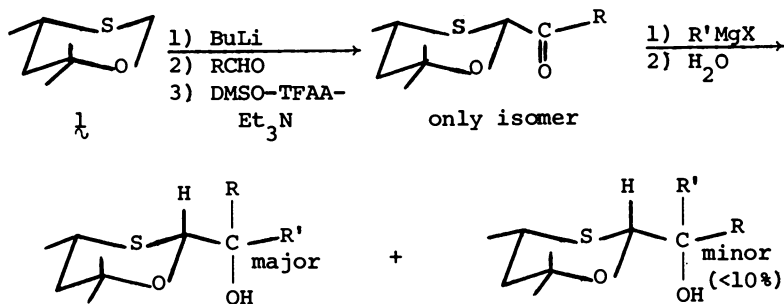
Scheme 2

proceeding as shown in Scheme 2, and hydrolyzing the resulting
product, one should be able to synthesize chiral α-hydroxyalde-
hydes in high optical yields. The process should also allow for
recovery of the hydroxythiol from which the original 1,3-oxathiane
was synthesized. The hydroxyaldehyde products, in turn, might be
converted to chiral α-hydroxyacids, primary-tertiary glycols,
primary-tertiary epoxides and other products bearing a chiral
tertiary carbinol function of the type RR"C(OH)C-. Tertiary
alcohol derivatives of the latter type are not easily available in
high enantiomeric purity by conventional methods. If, in addi-
tion, the chiral oxathiane is readily available in high enantio-
meric purity, all four conditions for a viable asymmetric synthe-
sis previously discussed may be fulfilled.

   Before discussing the experimental details and applications
of the asymmetric synthesis outlined in Scheme 2, we shall take up

its rationale and discuss briefly optimization of experimental conditions to obtain high optical yields.

The two-step synthesis summarized in Scheme 2 proceeds with high stereoselectivity in each step. The stereoelectronic rationale for the selectivity of the first step has already been discussed (2, 3). The second step is based on Cram's rule and, in particular, on the rule involving the rigid model where the metal of the organometallic reagent is complexed to an oxygen or nitrogen atom linked to the chiral center adjacent to the ketone function of the substrate (11). As shown in Scheme 3, application of this rule predicts the stereoselective outcome of the Grignard additions to 2-acyl-1,3-oxathianes if one also considers the fact
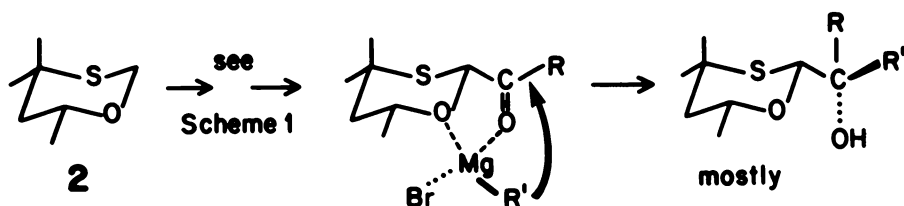
Scheme 3

that magnesium is a hard acid center and will therefore complex to the hard oxygen rather than to the soft sulfur in the oxathiane (12). Indeed, highly stereoselective additions of Grignard reagents involving operation of the rigid-model Cram's rule have been repeatedly observed in the literature (13).

For the success of the projected asymmetric synthesis it is crucial that the stereoselectivity of the Grignard addition be extremely high, with one diastereomer predominating over the other by 95% or more. (A 95% predominance of one diastereomer will translate into a 95% predominance of one enantiomer after hydrolysis, i.e. into a 90% e.e.) We therefore studied (14) variations in the structure of the oxathiane (1, Scheme 2 or 2, Scheme 3), the organometallic reagent (R'MgI, R'MgBr, R'MgCl, R'₂Mg or R'Li), solvent (diethyl ether, tetrahydrofuran or mixtures thereof) and temperature (reflux temperature down to -78°C). We also studied the effect of varying R and R' (Scheme 2). The results of these experiments are summarized in Table 1. It was not necessary to employ optically active starting materials for this preliminary study, since, starting with racemic 2-acyl-1,3-oxathiane, one obtains two diastereomeric carbinols in the Grignard synthesis (Scheme 2) whose ratio is equal (or nearly so) to the ratio of enantiomers attainable when one starts with completely resolved 1 or 2 and subsequently hydrolyzes the tertiary carbinol product

to a chiral α-hydroxyaldehyde. Analysis of the mixture of diastereomeric tertiary alcohols (Scheme 2) was generally performed by NMR spectroscopy: either the ratio of the areas of the C(2) protons (distinct in the two isomers) or the ratio of C-13 signals of carbon nuclei adjacent to the exocyclic chiral center [notably C(2), C(OH) or the carbon nuclei in R and R' adjacent to the carbinol function] could be employed to this end. Authentic mixtures of the diastereomers expected in each reaction were synthesized (for NMR comparison) from the lithio derivative of $\underset{\sim}{1}$ or $\underset{\sim}{2}$ and a ketone RR'C=O.

Perusal of Table 1 indicates the following features: a) Oxathiane $\underset{\sim}{2}$ (Scheme 3) is somewhat superior to oxathiane $\underset{\sim}{1}$ (Scheme 2), notably with alkyl (as distinct from phenyl) ketones. We ascribe this to the more ready accessibility of the oxygen atom in $\underset{\sim}{2}$ (as compared to $\underset{\sim}{1}$) for complexation. b) High stereoselectivity is easier to achieve with phenyl ketones than with alkyl ketones. This is a common feature in asymmetric synthesis; we ascribe it to the lesser reactivity of phenyl compared to alkyl ketones caused by conjugation of the C=O double bond. (Other things being equal, reactions with higher activation energies have a better chance of being selective than those with lower activation energies; when the activation energies for reaction of both enantiomers are low, their difference must of necessity be small - the difference between two small numbers cannot be a large number - and so selectivity must also of necessity be low. Unfortunately the converse does not follow: If the activation energies for both enantiomers are high, their difference may or may not be large and selectivity may or may not be satisfactory.) c) Stereo-selectivity is increased by lowering the temperature; this is particularly important for aliphatic ketones whose stereo-selectivity is not satisfactory at room temperature but often becomes so at -78°C. The enhancement of stereoselectivity with temperature is a fairly general phenomenon based on the kinetic equation $k_R/k_S = e^{\Delta\Delta S^{\ddagger}/R} \, e^{-\Delta\Delta H^{\ddagger}/RT}$; as T decreases (and assuming that $\Delta\Delta H^{\ddagger}$ is negative, i.e. that predominance of the $\underline{R}$-isomer is activation enthalpy controlled) k_R/k_S (i.e. selectivity) increases. d) Grignard reagents are superior to alkyllithium or dialkylmagnesium reagents. This may be due to better complexation of the metal in the former (cf. Scheme 3). e) Alkylmagnesium iodides are marginally superior to alkylmagnesium bromides which are appreciably better than alkylmagnesium chlorides. This order came as somewhat of a surprise since we had expected the chlorides to be better coordinating species. Earlier literature on this particularly point (13) is not clear-cut. f) In some instances, a mixture of ether and tetrahydrofuran is superior to diethyl ether itself, but the effect is marginal. Again this order was unexpected, since we had expected the better coordinating THF to interfere more with the formation of the complex postulated (Scheme 3) to be responsible for the stereoselectivity. Clearly

Table 1

Reactions of 2-Acyl-1,3-Oxathianes with Grignard and Other Organometallic Reagents (cf. Scheme 2)

Oxathiane	Acyl Group	Organometallic	Solvent	Temp.°C	% e.e.
1	C_6H_5CO	CH_3MgI	ether–THF (5:1)	reflux	98
1	C_6H_5CO	CH_3Li	ether	R.T.	50
1	CH_3CO	C_6H_5MgBr	THF	reflux	70
1	CH_3CO	C_6H_5MgBr	ether	reflux	28
1	CH_3CO	C_6H_5Li	ether–benzene (30:1)	0	44
2	C_6H_5CO	CH_3MgI	ether–THF (3:1) ·	reflux	96
2	C_6H_5CO	CH_3Li	ether	R.T.	72
2	CH_3CO	C_6H_5MgBr	ether	reflux	78
2	CH_3CO	C_6H_5MgBr	ether	–40	86
2	CH_3CO	C_6H_5Li	ether–benzene (30:1)	0	76
2	CH_3CO	$(C_6H_5)_2Mg$	dioxane–ether (1:10)	reflux	56
2	C_6H_5CO	C_2H_5MgI	ether	reflux	>99
2	C_2H_5CO	C_6H_5MgBr	ether	reflux	60
2	C_2H_5CO	C_6H_5MgBr	ether	–78	92
1	C_6H_5CO	C_2H_5MgI	ether–THF (4:1)	reflux	>99

$\mathscr{R}$	C_6H_5CO	$(CH_3)_2CHMgI$	ether	reflux	98
$\mathscr{R}$	$(CH_3)_2CHCO$	C_6H_5MgBr	ether	reflux	70
$\mathscr{R}$	$(CH_3)_2CHCO$	C_6H_5MgBr	ether	-78	99
$\mathscr{R}$	CH_3CO	C_2H_5MgI	ether	-78	94
$\mathscr{R}$	C_2H_5CO	CH_3MgI	ether	reflux	60
$\mathscr{R}$	CH_3CO	$\underline{n}-C_3H_7MgI$	ether	reflux	80
$\mathscr{R}$	CH_3CO	$\underline{n}-C_3H_7MgBr$	ether	reflux	68
$\mathscr{R}$	CH_3CO	$\underline{n}-C_3H_7MgCl$	ether	reflux	54
$\mathscr{R}$	CH_3CO	$\underline{n}-C_4H_9MgBr$	ether	reflux	74
$\mathscr{R}$	CH_3CO	$(\underline{n}-C_4H_9)_2Mg$	ether-hexane	reflux	52
$\mathscr{R}$	$(CH_3)_2CHCO$	CH_3MgI	ether	-78	54[a]
$\mathscr{R}$	$(CH_3)_3CO$	CH_3MgI	ether	-78	92
$\mathscr{R}$	CH_3CO	$H_2C=CHMgBr$	ether-THF (3:1)	-78	80
$\mathscr{R}$	$CH_2=CHCO$	CH_3MgI	ether	-78	90
$\mathscr{R}$	CH_3CO	$HC\equiv CMgBr$	THF	R.T.	88

[a] The reverse procedure (addition of isopropylmagnesium iodide to the methyl ketone at -78°) gave no addition product.

this is not the only effect of THF in the transition state. Similar observations had been made earlier (13).

    In general, under appropriate conditions, the stereo-selectivity of the reaction is remarkably high with ratios of 95:5 or more leading, eventually, to enantiomeric excesses above 90%. Similarly high stereoselectivity had been observed in a number of earlier examples involving Cram's rule in the rigid model (13).

    With the information given in Table 1 as background, we proceeded to design an asymmetric synthesis involving a highly stereoselective 1,3-oxathiane alkylation (Scheme 2) followed by an almost equally selective Grignard step (Schemes 2, 3). The target compound chosen was atrolactic acid methyl ether and the chiral adjuvant was the resolved oxathiane 1, obtained as shown in Scheme 4. Complete resolution of 3-benzylthiobutyric acid

$$CH_3CHCH_2CO_2H \quad \underset{3)\ Na,NH_3}{\overset{1)\ esterification}{\underset{2)\ CH_3MgI}{\longrightarrow}}} \quad CH_3CHCH_2-C(CH_3)_2 \quad \underset{H_2SO_4}{\overset{(CH_2O)_x}{\longrightarrow}}$$

with $SCH_2C_6H_5$ group and $[\alpha]_D^{25} - 8.31°$ on the left; SH and OH groups with $[\alpha]_D^{25} + 16.6°$ on the right

44% e.e.
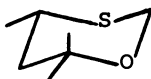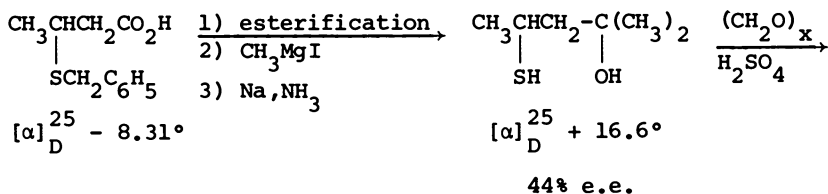
$[\alpha]_D^{25} - 30.4°$

1

62% overall yield

Scheme 4

(from crotonic acid and benzyl mercaptan (15)) with brucine has been described in the literature (16) but is tedious, requiring seven recrystallizations. We employed cinchonidine for this task and contented ourselves with using starting material of 44% enantiomeric purity. (Actually, according to optical rotation values of our acid and of that in the literature, ours should have been 48% enantiomerically pure; however, the hydroxythiol obtained (Scheme 4) showed only 44% e.e. by a chiral shift reagent determination. Either the rotation of the "completely resolved" acid reported in the literature (16) is too low - i.e. the acid was not, in fact, completely resolved - or some

racemization - by elimination-addition of benzyl mercaptan -
occurred at the ester stage of the synthesis. If the former
explanation is correct, this represents one of many failures we
have encountered in trying to derive accurate enantiomeric excess
data from optical rotations.) This may have been fortunate,
since it is much easier to determine, with accuracy, e.e.'s of
44% than e.e.'s of 95% or more! Since reaction of lithio-
oxathiane 1 (Scheme 4) with ethyl benzoate proceeded poorly, we
carried out, instead, reaction with benzaldehyde followed by
selective oxidation (Scheme 5) employing dimethyl sulfoxide -
trifluoroacetic anhydride (or oxalyl chloride) - triethylamine
(10). (Other oxidants tend to oxidize the sulfur as well as the
carbinol.) Reaction of the ketone so obtained with methyl-
magnesium iodide gave the corresponding carbinol (Scheme 5) in
virtually complete diastereomeric purity.

$[\alpha]_D^{25}$ - 42.3°, 44% e.e.

$[\alpha]_D^{25}$ - 40.9°   3

68% overall yield
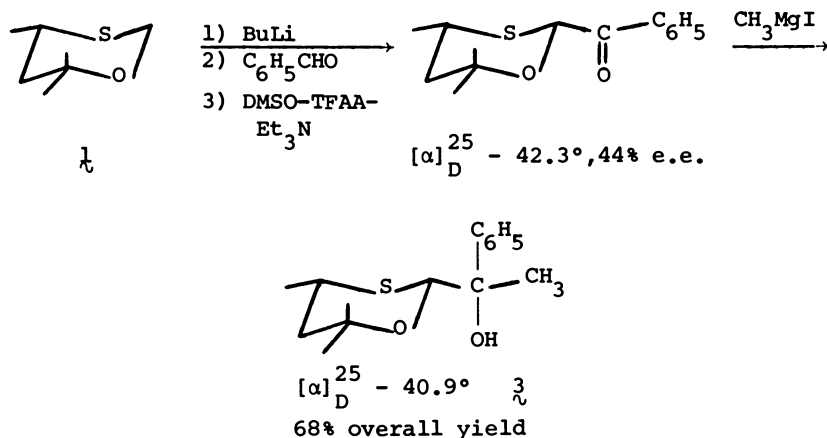
Scheme 5

     The hydrolysis of oxathianes (17) is not as simple a
reaction as one might surmise, especially in the present case
where the molecule bears an acid-sensitive tertiary alcohol group.
We finally carried out this step in good yield using methyl
iodide/water/acetonitrile/calcium carbonate (18). Since the
resulting α-hydroxyaldehyde could not readily be characterized
and suffered extensive cleavage upon oxidation, we preceded the
cleavage step by O-methylation and followed it by oxidation of
the α-methoxyaldehyde to atrolactic acid methyl ether (4, Scheme
6). The optical purity of this acid was inferred from its
rotation (19) to be 44% but for further confirmation the acid
was converted (with diazomethane) to the methyl ester whose
enantiomeric purity was found to be 44% by NMR analysis employing

$$3$$

$$[\alpha]_D^{25} \ -44.5°$$

$$4, \ [\alpha]_D^{25} \ + 13.9° \ (MeOH)$$

59% overall yield
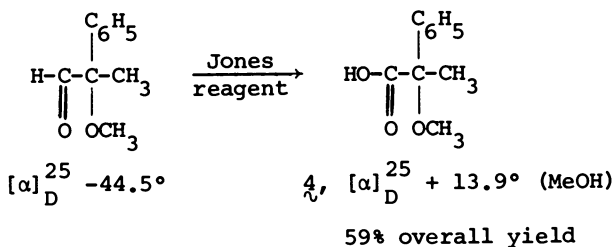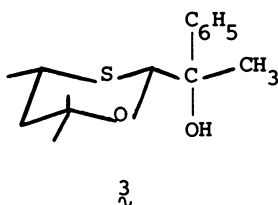
Scheme 6

a chiral shift reagent. The "optical yield" (= 100 x e.e. of product/e.e. of starting material) was thus quantitative. Using reasonable confidence limits for the chiral shift reagent determination, the enantiomeric purity of the product is 44±1% (and likewise for the starting material) giving an optical yield of 97-100%. Configurational correlation (9) of starting material 1 and product indicates the stereochemistry of the reaction to be compatible with the operation of Cram's (rigid model) rule. A similar synthesis based on 2 gave 92% optical yield (9).

Although both optical and chemical yield in these syntheses (reported (9) in 1978) are satisfactory, they are subject to criticism on two grounds, related to the conditions for a viable asymmetric synthesis laid down above: 1) The methyl iodide cleavage of the oxathianylcarbinol 3, while producing the α-hydroxyaldehyde in good yield, does not permit recovery of the chiral oxathiane (or hydroxythiol) moiety and thus falls afoul of condition 3. 2) The chiral oxathiane adjuvant is not enantio-merically pure and while, in principle, it can be obtained in enantiomerically pure form, this would be far from facile. Thus condition 4, relating to easy availability of the chiral adjuvant in optically pure form, is not fulfilled either.

It would appear that the easiest way of preparing an optically pure chiral 1,3-oxathiane might be from a chiral (and enantiomerically pure) natural product. In principle, all that is required is the existence of an S-C-C-C-O moiety, with the

linking C-C*-C unit being chiral. We have synthesized two perti-
nent oxathianes, one (5) derived from (+)- or (-)-camphor-10-
sulfonic acid (20) (Scheme 7) and the other (6) derived from
(+)-pulegone (21) (Scheme 8).

Both (+)- and (-)-camphorsulfonic acids are available
commercially, the latter in form of its ammonium salt. While the
free acid (a hemihydrate) is difficult to characterize, the
ammonium salt is easily recrystallized to enantiomeric purity and
characterized by specific rotation. Treatment of either acid or
salt with thionyl chloride followed by lithium aluminum hydride
reduction of the resulting sulfonyl chloride gives the exo alcohol
10-mercaptoisoborneol. Unfortunately the yield is only 50-55%,
partly because the reduction of the sulfonyl chloride function to
mercaptan is not clean, and partly because the reduction of the
ketone function is not entirely stereoselective: about 10% of
10-mercaptoborneol (endo) is also formed and the isomer must be
purified by column chromatography. Once pure, the hydroxythiol
is converted to the corresponding oxathiane (5, Scheme 7) and the
rest of the synthesis (20) proceeds in analogous fashion as that
captioned in Schemes 5 and 6, except that conversion of oxathiane
5 to the lithium derivative required sec-butyllithium in this case
and that the methyl iodide cleavage did not proceed as well as for
the trimethyloxathiane case summarized in Schemes 5 and 6. Using
(+)-camphorsulfonic acid as chiral adjuvant, we were able to
obtain (+)-atrolactic acid methyl ether (2-phenyl-2-methoxy-
propionic acid, cf. Scheme 6) in 97±2% enantiomeric purity (20),
as determined by NMR spectroscopy of the ester in presence of a
chiral shift reagent.

Although this synthesis produces an essentially enantio-
merically pure product, it has several drawbacks: the difficulty
of purifying the starting material, the need for sec-butyllithium
to make the lithio derivative of 5 and difficulties we encountered
(22) at times in the methyl iodide cleavage. We decided therefore
to look for yet another chiral oxathiane adjuvant - preferably one
which would closely resemble the 4,4,6-trimethyloxathiane used in
most of the preliminary experiments shown in Table 1 - and for a
better method of cleavage.

The oxathiane which we now prefer is the one derived from
pulegone as shown in Scheme 8 (21). Enantiomerically pure (+)-
pulegone is a cheaply available perfume chemical. 1,4-Addition of
benzyl mercaptan in the presence of base gives predominantly the
more stable trans isomer 7-benzylthiomenthone which, upon
reduction with sodium in liquid ammonia in presence of a proton
donor, yields the more stable equatorial alcohol with simultaneous
cleavage of the benzyl group, thus leading to 7-mercaptomenthol as
the predominant isomer. This material can readily be freed of
diastereoisomers by high pressure liquid chromatography.
Alternatively, the crude material may be converted to the
corresponding oxathiane (6, Scheme 8) which crystallizes and can
thus be freed of diastereomeric impurities. (The major side

product 7, derived from 7-mercaptoneomenthol, has found use as a chiral adjuvant in its own right; it can be isolated in pure form from the mother liquor by hplc.) The overall yield of the pure oxathiane from (+)-pulegone is about 30% (Scheme 8).


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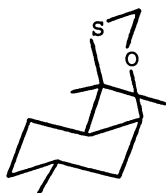
The oxathiane 6 shown in Scheme 8 can be used as discussed earlier (Schemes 5, 6). We shall describe here three syntheses undertaken with oxathiane 6: that of (+)-ethylmethylpropyl-carbinol (21) (93% e.e., Scheme 9), that of (-)-ethylmethylphenyl-carbinol (23) (100% e.e., Scheme 9) and that of mevalolactone (24) (87-97% e.e., Scheme 10).

Synthesis of carbinols 7a and 7b (Scheme 9) is entirely analogous to the syntheses described earlier. However, cleavage in the case of 7a and 7b was carried out by means of N-chloro-succinimide (NCS) - silver nitrate (25). This cleavage produces not only the chiral α-hydroxyaldehydes in good yields but also returns the hydroxythiol chiral adjuvant in form of the pair of diastereomeric sultines 8. (Lithium aluminum hydride reduction of 8 yields the hydroxythiol which, upon treatment with para-formaldehyde and acid, regenerates oxathiane 6.) In this way condition 3 for a viable asymmetric synthesis (vide supra), namely recovery of the chiral adjuvant, is finally fulfilled. Reduction of the rather sensitive hydroxyaldehydes with sodium borohydride gives glycols 9a and 9b whose enantiomeric purity was determined by either Mosher's acid or chiral shift reagents and NMR spectro-scopy to be 94% in the case of 9a and 99% in the case of 9b (26). Conversion of the glycols to monotosylates followed by hydride reduction gives the tertiary carbinols 10a and 10b in 93% and 100% enantiomeric purity, respectively (27). (The increase from 99% to 100% e.e. in going from 9b to 10b if indeed significant, is probably due to the fact that the intermediate tosylate was crystallized.) The enantiomer of 9b was synthesized similarly using oxathiane 7 (Scheme 9) as a chiral template; the enantio-meric excess of the product was 97%. Tertiary alcohols such as 10 have in the past been accessible in enantiomerically pure form only with difficulty, though recently alternative means of asymmetric synthesis have been disclosed (27, 28).
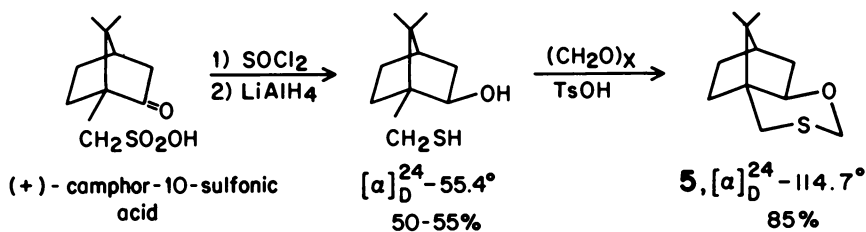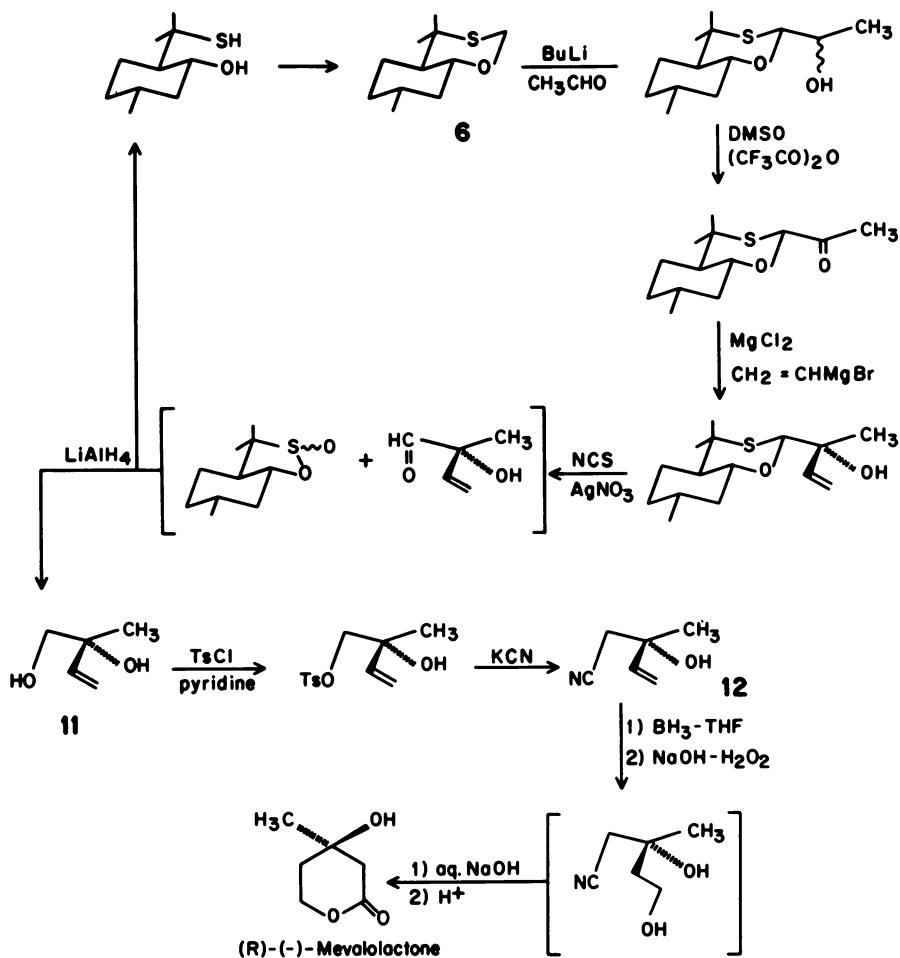
Scheme 7
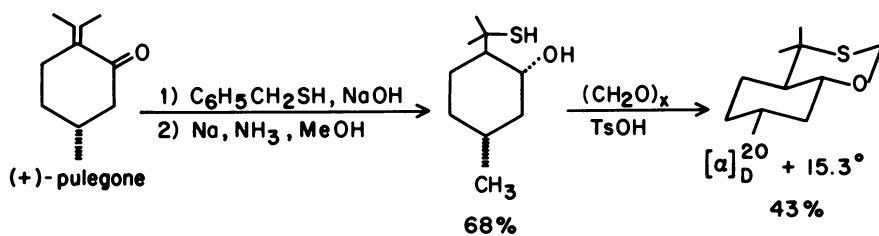
Scheme 8
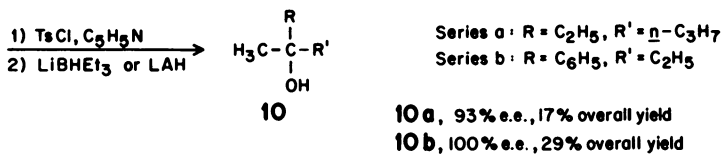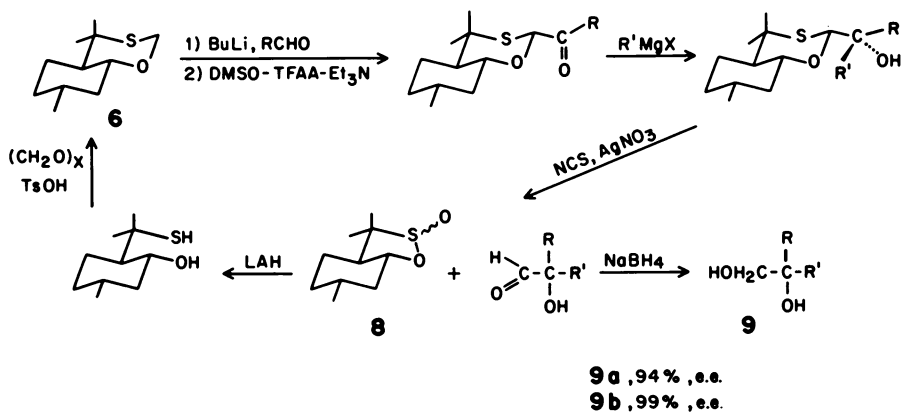
Scheme 9

Experiments presently in progress suggest that the monotosylate precursors of the tertiary alcohols can alternatively be converted, by base, to primary-tertiary epoxides which in turn may be opened at the primary site by a variety of nucleophiles, thus greatly amplifying the opportunities for synthesis of compounds bearing chiral tertiary carbinol moieties. It has also proved possible (23, 30) to oxidize the α-hydroxyaldehydes to α-hydroxy-esters which, in turn, may be saponified to α-hydroxyacids.

Our synthesis of (R)-(-)-mevalolactone (24) is shown in Scheme 10. The crucial intermediate, synthesized by the earlier described method, is (+)-2-methyl-3-butene-1,2-diol, 11. Its oxathiane precursor was obtained in 90% diastereomer excess, increased to 97% by one recrystallization. Diol 11 was then converted to the monotosylate which yielded chiral 3-hydroxy-3-methyl-4-pentenonitrile, 12, when heated with KCN/EtOH. Hydroboration-oxidation was attended with in situ hydrolysis and lactonization to give directly (R)-(-)-mevalolactone. Its optical purity was estimated to be at least 87% as judged from optical rotation; the upper limit, of course, is 97%, the diastereomer excess of the precursor. Unfortunately an attempted determination of enantiomeric purity by NMR using a chiral shift reagent with the benzhydrylamide gave only a single signal for the benzhydrylic hydrogen, though this proton was clearly doubled in an analogous experiment with racemic mevalolactone. This failure is but a demonstration of the general difficulty of determining enantiomeric purities in excess of 90% by NMR with chiral shift reagents, given that the peak of the minor enantiomer, amounting to 5% or less, becomes hard to quantify and even hard to detect. Better methods (e.g. chromatographic ones (31)) are urgently needed for the determination of such high enantiomeric purities.

It should be mentioned here that the highest previously attained enantiomeric excess in the synthesis of mevalolactone was 17% (32). Although the reported (24) overall chemical yield in the synthesis summarized in Scheme 10 is low, recent improvements (use of $NaBH_4$ instead of $LiAlH_4$ in reduction to glycol 11 followed by efficient continuous extraction) have increased this yield by about a factor of five and the possibility of further improvement is under investigation (33).

Scheme 10

Acknowledgement

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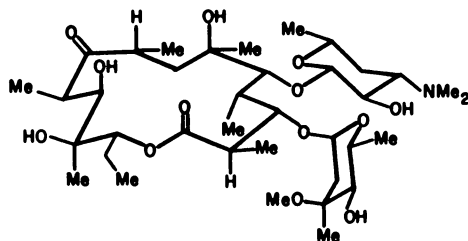33. Kogure, T.; Eliel, E.L. unpublished observations.

molecule and the above mentioned quote from the master of organic
synthesis which planted the seed of the project which is discussed
in this article. In casting about for a method which might be used
to attack the synthetic problem posed by erythromycin, I came
across a statement by another master -- of the field of biosyn-
thesis. In fact, it was also in "Perspectives in Organic Chemis-
try" that J.W. Cornforth wrote: "Nature, it seems, is an organic
chemist having some predilection for the aldol and related conden-
sations..." (3) Thus, the erythromycin aglycone is presumably con-
structed by Nature by a series of aldol-type condensations of pro-
pionate units:
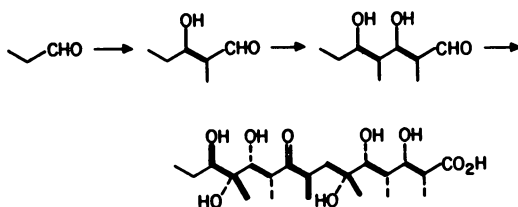
In 1976 we began an investigation of the aldol condensation with
the ultimate goal of learning enough about its stereochemistry to
use it as the sole method for constructing the aglycone of
erythromycin-A and, at the same time, controlling the relative
stereochemistry of its ten centers of chirality. Here, following a
brief review of our early work, I shall discuss some recent unpub-
lished experiments that pertain to the coordination chemistry of
the enolate counterion and how that can influence the stereochemis-
try of the aldol condensation.

In evaluating the aldol condensation as a method for building
acyclic molecules containing many stereocenters, such as
erythronolide-A, there are two types of diastereoselection which
must be considered. The first is referred to as simple diastereo-

selection and arises from the fact that two newly-created chiral
centers may be formed with either the erythro or threo relative
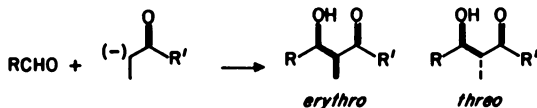
configuration.* It is now clear that simple diastereoselection is controlled by two factors -- the configuration (E or Z) of the eno-late and the orientation of the enolate and aldehyde in the transi-tion state of the aldol reaction itself. Deprotonation of an ethyl carbonyl compound can give either a trans-or a cis-enolate:*

trans-enolate   *cis*-enolate
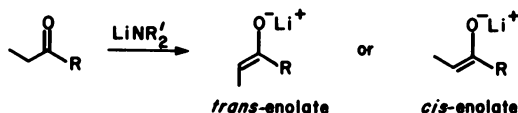
Since the aldehyde and enolate both have enantiotopic faces, there are two relative ways they can approach one another. That is, the Si face of the aldehyde can become bonded to the Re face of the enolate (giving the erythro diastereomer) or the Re face of the aldehyde can be attacked by the Re face of the enolate (giving the threo diastereomer):

Re   Re

Si   Si   Si-Re   Re-Re
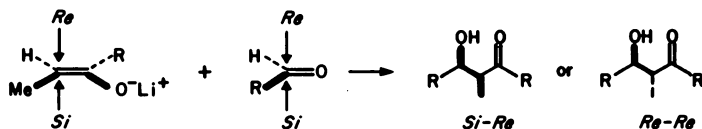
It has now been fairly well established what factors control enolate configuration. Deprotonation of ethyl carbonyl compounds in which the other group attached to the carbonyl is small gives predominately the trans - enolate. As the R group becomes larger, more cis-enolate is produced. With very large R groups, the cis-enolate is the overwhelming diastereomer produced (Table 1).**

It has also been established what factors control the orienta-tion of the two reactants in the transition state for the aldol

---

*The stereochemical descriptors erythro and threo are used in the following sense. When the aldol is written so that its main chain is in an extended (zig-zag) arrangement, an erythro isomer is one in which the bonds to the α-alkyl group and the β-hydroxy group both project toward (bold bonds) or away from (dashed bonds) the viewer.

*I shall use the configurational descriptors cis and trans with the O⁻ or O⁻M⁺ group always being the point of reference. In the E-Z system, depending on the nature of R, either OM (O⁻) or R may be fiducial, which is confusing.

**"Large" and "small" require definition at this point. What is im-portant is the size of the group from the standpoint of the sub-stituent attached to the α position relative to the carbonyl group. Thus, in propionate esters, all alkoxy groups are "small," since the methyl senses only the oxygen part of the group.

Table I
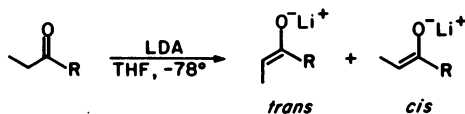
R	trans	cis	
-OCH₃	97%	3%	small
-OC(CH₃)₃	97%	3%	
-CH₂CH₃	70%	30%	medium
-CH(CH₃)₂	44%	56%	
-C₆H₅	0%	100%	large
-C(CH₃)₃	0%	100%	

reaction. When the R group is small, neither _cis_- nor _trans_- eno-
lates show any simple diastereoselection. Thus, the _cis_-enolate
from propionaldehyde and the _trans_-enolate from methyl propionate
both react with aldehydes to afford essentially 1:1 mixtures of
erythro and _threo_ isomers.
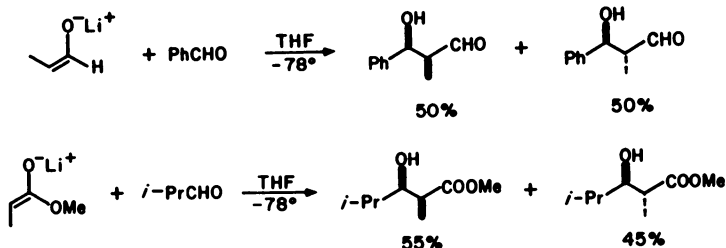
However, when the R group is large, both _cis_- and _trans_- enolates
show substantial stereoselectivity, giving rise to opposite
diastereomers. Thus, the _cis_- enolate from ethyl _t_-butyl ketone
gives almost entirely erythro aldols while the trans enolate from
2,6-dimethyl propionate gives _threo_-aldols with good stereoselec-
tivity. (4,5) This behavior is readily interpreted in terms of a
transition state model first put forth by Zimmerman and Traxler for
the Ivanov condensation in 1957. (6) In the Zimmerman model (Figure
1) it is assumed that there is carbon-carbon bonding in the transi-
tion state of the reaction, and that the two oxygens of the react-
ing array are both disposed in the general direction of the cation.
This leads to six-center arrangements in which the R group of the
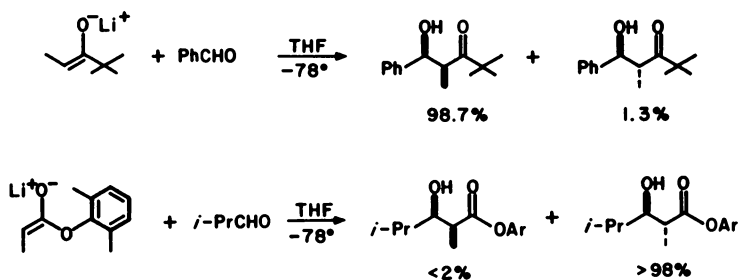
aldehyde and the R' group of the enolate are either close to one another or remote from one another. The argument goes that, if the interaction of R with R' is large, the top transition state (R's remote) will be favored. Thus, a cis-enolate will lead to an erythro-aldol and, similarly, a trans-enolate to a threo-aldol.
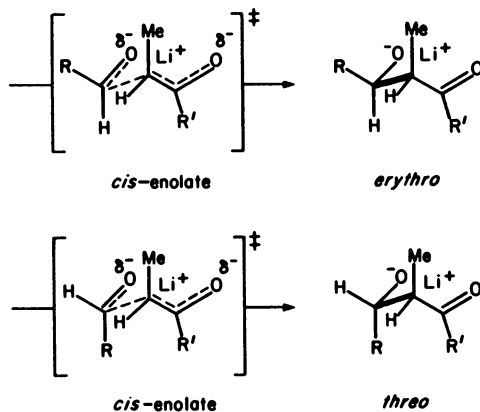
Figure 1.   Zimmerman-Traxler transition state (6) showing the transformation of a cis-enolate to erythro- and threo-aldols.

The other aspect of the aldol condensation to be considered in using this reaction for the construction of compounds such as erythronolide-A is diastereoface selection. That is, in many cases one will want to carry out aldol condensations on aldehydes already having one or more chiral centers. The carbonyl faces in these molecules are diastereotopic, rather than enantiotopic, and there

are four relative ways such aldehydes can react with achiral eno-
lates:
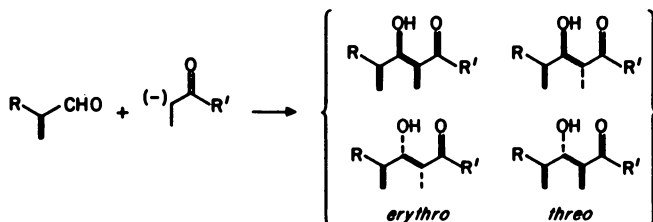
erythro   *threo*

Of course, this is no more than the problem of relative asymmetric
induction which was first examined systematically by Cram (7) and
Prelog (8) nearly thirty years ago. Using various erythro or threo
selective reagents, even though one can reasonably control simple
diastereoselection, one still obtains mixtures of "Cram" and
"anti-Cram" diastereomers:

86%   14%

erythro,"Cram"   *erythro,"anti-Cram"*
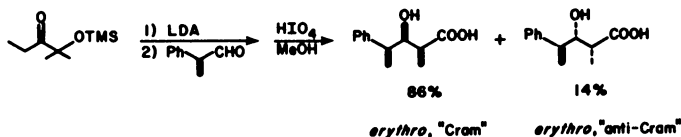
Although a diastereomer ratio of 6:1 is not bad, it is not nearly
high enough for the purpose at hand. That is, if one is to use the
aldol condensation as a method for the repetitive addition of
propionaldehyde synthons to build up large molecules having many
centers of chirality, one will soon be defeated by the effects of a
geometric progression unless each condensation proceeds with very
high stereoselectivity. Thus, five condensations, each proceeding
with 80% stereoselectivity, will lead to an overall stereochemical
yield of only 33%.

     We have examined a purely logical way in which the "Cram's
rule problem" can be attacked -- double stereodifferentiation.* For
example, either reactant in an aldol condensation can be chiral and
exhibit diastereoface selectivity. Suppose we have an aldehyde
which reacts with achiral enolates to give the two possible erythro
adducts in a 10:1 ratio:

---

*The phenomenon has also been referred to as "double asymmetric in-
duction." (9) We have used the term double stereodifferentiation,
first introduced by Izumi and Tai (10) in order to avoid confusion
in cases involving racemates.

RCHO + (−) [structure] → [structure] + [structure]

(10/1)
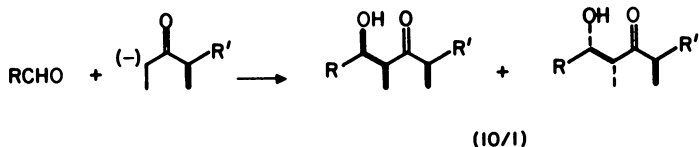
Also suppose that we have a chiral enolate which reacts with achiral aldehydes to give the two _erythro_-aldols in a 10:1 ratio:

[structure] + (−) [structure] → [structure] + [structure]

(10/1)
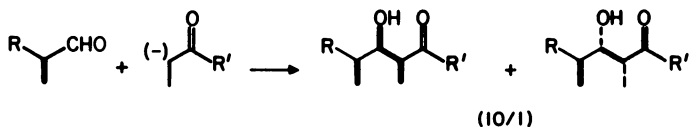
Now suppose that we allow one enantiomer of the chiral aldehyde to react in turn with the two enantiomers of the chiral enolate. In one case the two reactants will both promote the same absolute configuration (chirality) at the two new chiral centers. In this case, the effective "Cram's rule selectivity" shown by the aldehyde will be greater than in its reactions with representative achiral enolates. For the selectivities chosen in this example, the "Cram:anti-Cram ratio" should be on the order of 100:1.

[structure] + [structure] → [structure] + [structure]

good   good   bad   bad

10 × 10 = 100   1 × 1 = 1
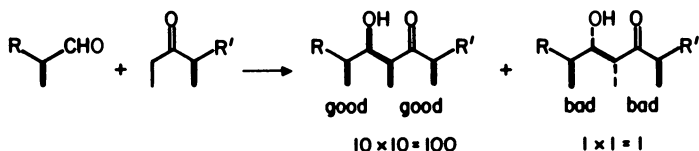
Of course, in the other combination, neither reactant gets its way. In this case, the effective diastereoface selectivity shown by the aldehyde should be poorer than is seen in reactions of the same aldehyde with representative achiral enolates.

[structure] + [structure] → [structure] + [structure]

good   bad   bad   good

10 × 1 = 10   1 × 10 = 10
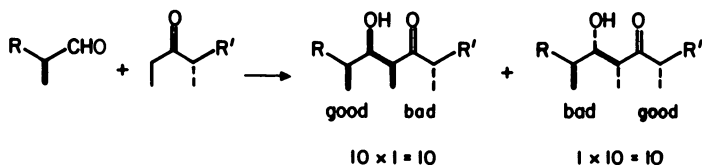
In order to test this concept as a way of controlling the problem of diastereoface selectivity in aldol condensations involving chiral aldehydes, we prepared the chiral ethyl ketone shown below, which is available in four straightforward steps from D-fructose. This compound shows modest inherent diastereoface

selectivity, reacting with benzaldehyde to give the two <u>erythro</u>-aldols in a ratio of 4:1, with the <u>R,R</u> diastereomer predominating. As a reaction partner, we chose the acetonide of glyceraldehyde, since both enantiomers are readily available. This aldehyde also shows modest inherent diastereoface selectivity in its reactions with achiral enolates -- on the order of 4.5:1. The sense of the stereoselectivity is such that <u>R</u>-glyceraldehyde acetonide gives predominantly the aldol with the <u>S,S</u> configuration at the two new
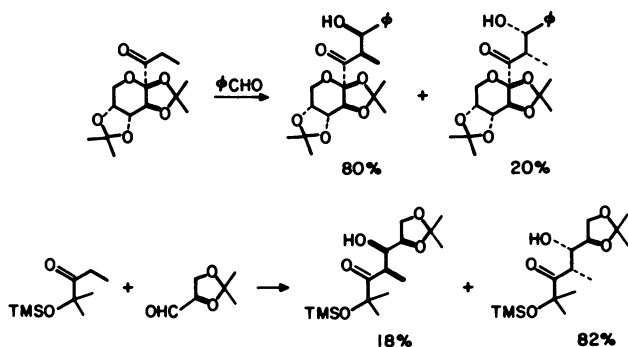
centers. Thus, the fructose-derived ketone and the acetonide of <u>R</u>-glyceraldehyde show unproductive double stereodifferentiation and give an almost equal mixture of the two <u>erythro</u>-aldols. However, the other combination is reinforcing, and only a single <u>erythro</u>-aldol results. (11)
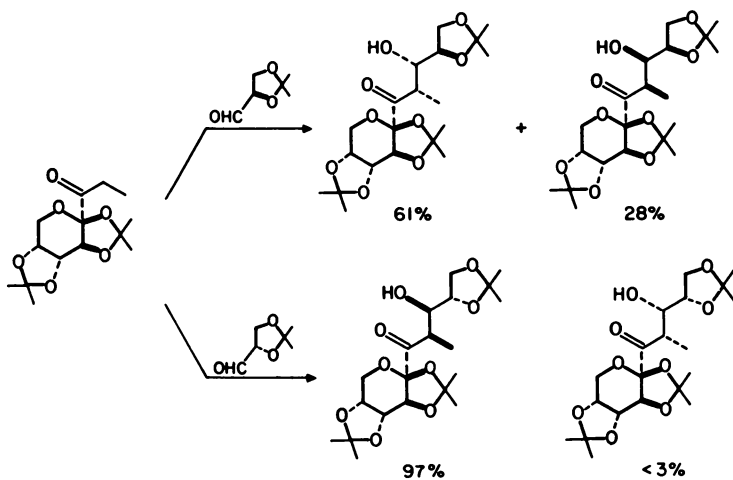
We have also observed double stereodifferentiation when one of the chiral elements is a reactant and the other is the solvent. One example of this phenomenon is shown below for the condensation

of the indicated achiral ethyl ketone with the acetonide of R-glyceraldehyde. Although the magnitude of the effect is small, it is significant. (11)
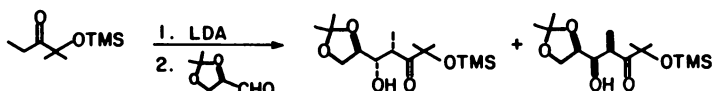
solvent	ratio
THF	4.3:1
MeO–[OMe, OMe, OMe structure]–OMe	5.0:1
MeO–[OMe, OMe structure]–OMe	3.6:1

To capitalize on the concept of double stereodifferentiation as a method for enhancing mediocre diastereoface selectivity in aldol condensations of chiral aldehydes, we synthesized the chiral ethyl ketone shown below. This compound shows good to excellent inherent diastereoface selectivity with achiral aldehydes. The selectivity appears to increase dramatically with the steric demand of the group attached to the aldehyde carbonyl. Thus, with pivaldehyde and diacetaldehyde, only one aldol is produced. The diastereoface selectivity in these two cases is at least 19:1 and 10:1, respectively. (12)

R = C_6H_5–	75%	25%
= i-C_3H_7–	75%	25%
= t-C_4H_9–	>95%	<5%
= $C_6H_5CH_2$–	87%	13%
= $(C_6H_5)_2CH$–	>90%	<10%
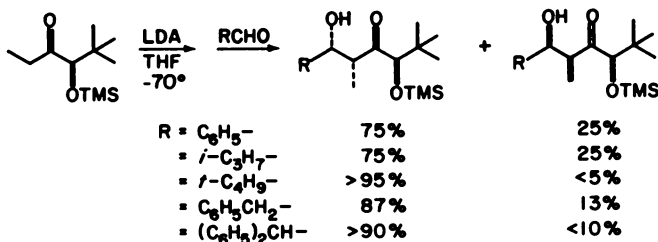
What was surprising was the discovery that condensation of the racemic ketone with racemic α-phenylpropionaldehyde gives a single racemic aldol! In order for this to be observed, the R enantiomer of the aldehyde must react selectively with the R enantiomer of the ketone, and not with the S enantiomer. That is, the reaction must show kinetic resolution. Since the racemates of both reactants are
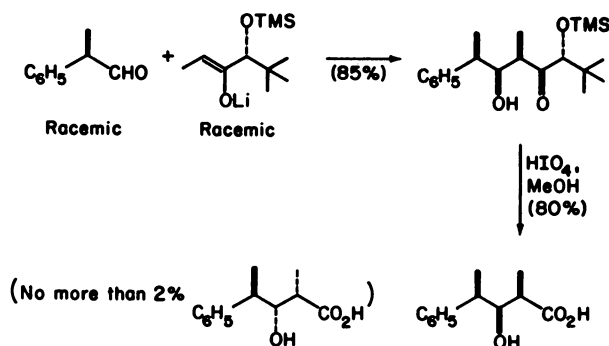
involved in the reaction, we refer to the phenomenon as <u>mutual kin-</u>
<u>etic resolution</u>, so as to avoid confusion. We may understand the
origin of this kinetic resolution with the aid of the same multi-
plicative model that we used to understand double stereodifferen-
tiation. Thus, let us assume that the erythro:threo diastereo-
selectivity is 80:1, that the inherent diastereoface selectivity of
the aldehyde is 10:1, and that the inherent diastereoface selec-
tivity of the enolate is 20:1. For each of the sixteen possible
stereoisomers that can result from the reaction of one of the enan-
tiomers of the aldehyde with one of the enantiomers of the enolate,
we can compute the probability of formation by multiplying together
three numbers. By summing all of the products, and taking the
appropriate ratios, we can therefore estimate the relative product
distribution expected from the reaction. The results of this exer-
cise are summarized in Figure 2 (only one-half of the products are
shown -- the other eight are the enantiomeric set and will be pro-
duced in precisely the same ratio in this double racemic reaction).

One thing which is seen immediately upon examination of Figure
2 is that the <u>threo</u> products are not expected to be formed in any
significant amount, because of the high <u>erythro:threo</u> ratio we
assumed. We also see that, for the <u>R</u> + <u>R</u> combination (top row),
there is a productive and a nonproductive combination. That is,
the two <u>erythro</u>-aldols resulting from the reaction of <u>R</u> aldehyde
with <u>R</u> enolate are expected to be produced in a ratio of 200:1. On
the other hand, the <u>erythro</u>-aldols resulting from reaction of <u>R</u>
aldehyde with <u>S</u> enolate will be produced in a ratio of about 1:2,
since the two reactants are working at cross-purposes in this
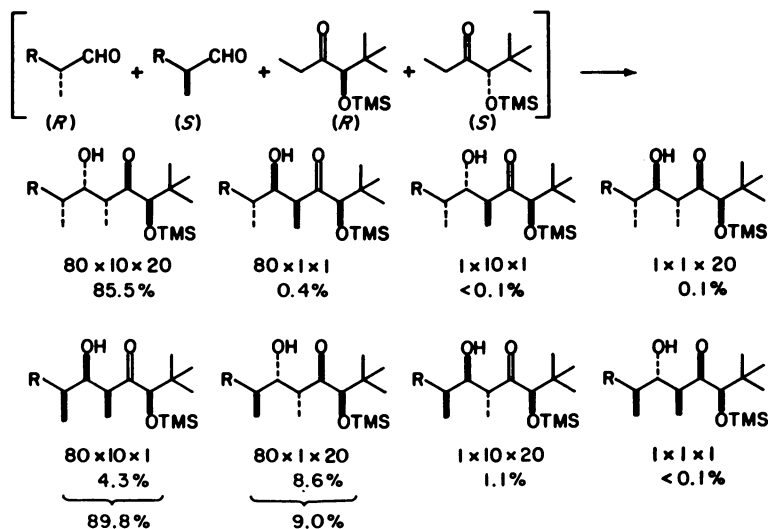
Figure 2.   One half of the stereoisomers possible from aldol condensation of racemic aldehyde with racemic ketone.

case.* Of course, cleavage of the aldol products to the respective β–hydroxy acids would still lead to a 10:1 ratio of the two erythro products corresponding to "Cram" and "anti–Cram" addition to the aldehyde -- the multiplicative approach does not change the net diastereoface selectivity of either reactant.

However, the use of this approach points up the origin of the observed mutual kinetic resolution. In part, at least, it is a consequence of the inherent diastereoface selectivity exhibited by the two reactants. Thus, if we ignore the threo isomers, the approximation used in Figure 2 leads to a prediction that the rate of the R + R reaction will be approximately seven times the rate of the R + S reaction.

The question remains of why our double racemic reaction shows net diastereoface selectivity of >49:1. It might be that we have been too conservative in selecting stereoselectivity factors. For example, there is a trend that the enolate used shows higher

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*Although the threo-aldols are produced in such small amount that they are not observed it is interesting to note that the situation is just reversed in this set of stereoisomers -- the R + S combination shows productive double stereodifferentiation and leads to a high ratio while the R + R combination shows nonproductive double stereodifferentiation.

inherent diastereoface selectivity as the R group attached to the aldehyde carbonyl with which it reacts becomes larger. In a similar manner, there is evidence that the diastereoface selectivity of α-phenylpropionaldehyde increases as the steric bulk of the nucleophile increases. It may also be that there is some independent factor which favors the R + R reaction over the R + S reaction. Thus, if there is some other reason favoring kinetic resolution, the net diastereoface selectivity of the aldehyde will benefit dramatically since this combination results in a very disparate ratio of the two erythro products. In any event, the reaction just discussed is but one example of this phenomenon; we have observed a total of five other cases at this point.

I believe that the phenomenon of double stereodifferentiation with mutual kinetic resolution may have general ramifications beyond the specific aldol condensations being discussed here. We can generalize as shown below:

Principle of Mutual Kinetic Resolution

A^* + B ⟶ diastereomers C + D

inherent diastereoselectivity of $A^* = \dfrac{C}{D} = X$

E^* + F ⟶ diastereomers G + H

inherent diastereoselectivity of $E^* = \dfrac{G}{H} = Y$

(R)-A + (R)-E $\xrightarrow{k_1}$

(R)-A + (S)-E $\xrightarrow{k_2}$

(S)-A + (S)-E $\xrightarrow{k_1}$

(S)-A + (R)-E $\xrightarrow{k_2}$
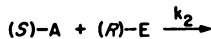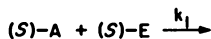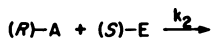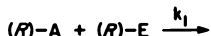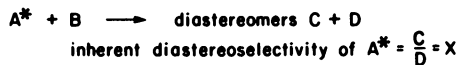
$$\text{mutual kinetic resolution} = \frac{k_1}{k_2} = \frac{XY+1}{X+Y}$$

That is, in order for the phenomenon to be observed, both reactants must show inherent diastereoface selectivity in their reactions with achiral partners. If one of the reactants shows no inherent diastereoface selectivity in its reactions with achiral reactants, then mutual kinetic resolution will not be observed regardless of the stereoselectivity of the other reactant. For an example, consider the case of an enzyme which mediates some reaction, say reduction of the carbonyl group. We can let the enzyme be A^* and assume that, because of its uniquely-evolved molecular structure, it shows very high inherent diastereoface selectivity (thus, it will reduce prochiral carbonyl compounds to chiral alcohols with very high enantiomeric excess). For B^*, let us take a chiral aldehyde that shows no inherent diastereoface selectivity in its

reaction with achiral reducing agents -- for example, 4-methylhexanal. The principle being expounded here predicts that the enzyme will not discriminate between R- and S-4-methylhexanal. On the other hand, consider an aldehyde which does show inherent diastereoface selectivity, such as α-phenylpropionaldehyde. In this case, double stereodifferentiation will result and the enzymatic reduction of one enantiomer of the aldehyde will be faster than for the other enantiomer; kinetic resolution will result.

I would now like to briefly discuss some experiments we have recently carried out that have a bearing on the role of the solvent and the other nucleophilic ligands on these enolate reactions. The experiment shown below clearly indicates that the species present in solution immediately following the aldol condensation (Y) is different from the species produced by treatment of the isolated aldol with LDA in the same solvent.
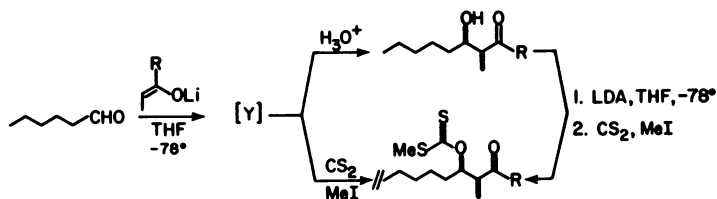
A similar dichotomy is seen in the following reaction, except that in this case it is the species produced from deprotonation of the
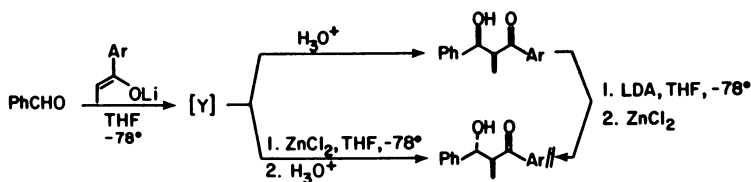
aldol which is unreactive. At this point we do not have definite proof as to the nature of the two species. However, our working hypothesis is that the aldol condensation leads directly to an aldolate that has the lithium cation chelated between the two oxygens. Since the lithium is no doubt tetra-coordinate, the other two ligands are probably a THF molecule and the molecule of diisoproylamine originally bonded to the lithium in the form of LDA. We believe that this species reacts slowly to form the xanthate and rapidly undergoes the $ZnCl_2$-catalyzed isomerization

to the threo- aldolate. We further believe that the product pro-
duced by deprotonation of the aldol is not chelated. In this case
the lithium is presumably bonded to the aldolate oxygen, the
diisopropylamine, and two solvent molecules. This species must
react rapidly to give the xanthate and be unreactive with respect
to erythro:threo equilibration.
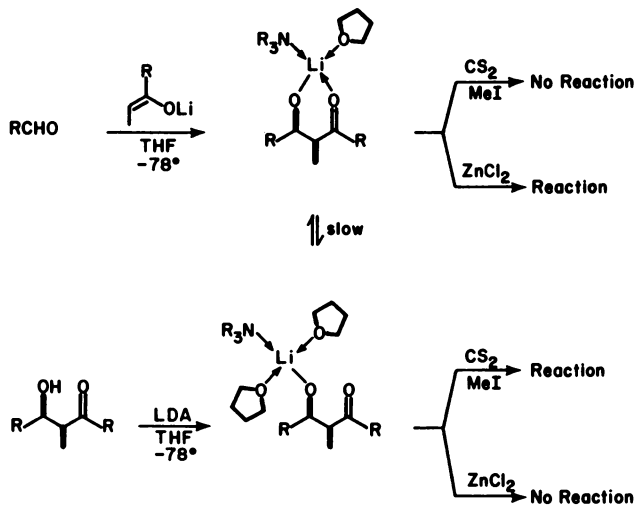
The foregoing hypothesis requires that ligand exchange on the
lithium cation be slow under the conditions of the experiments
described. In fact, there is little information available in the
literature on this point. Just recently, however, there has been a
convincing demonstration that lithium exchange on a lithium cation
can be very slow. Dr. Patricia Watson, of the Central Research
Department at the Dupont company, prepared an organometallic com-
plex by addition of bis(pentamethylcyclopentadienyl)methylytterbium
to a THF solution of methyllithium. (13) The product is a crystal-
line 1:1 adduct, which was recrystallized from diethyl ether and
subjected to single crystal x-ray analysis. The structure of the
recrystallized material is as follows:
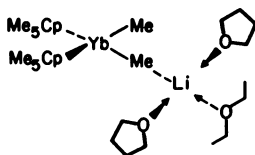
Thus, even though the material has been recrystallized from ether, two of the original THF ligands still remain bonded to the lithium. Upon repeated recrystallization from ether, or upon being boiled in ether, the remaining THF ligands are exchanged and eventually one may obtain a complex having three ether molecules.

This is an important result, which causes us to reexamine our view of the nature of many of these compounds. If oxygen ligands can exchange so slowly on the lithium cation, what about nitrogen ligands? It may be true that the lithium never becomes unbonded from the nitrogen when LDA is used to form a lithium enolate. Thus, the real structure of a monomeric lithium enolate might be:
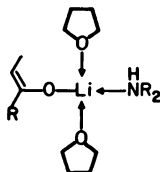
With this new view of lithium amides and lithium alkoxides in mind, we have begun to look more carefully at the effect of the ligands upon the stereochemistry of the aldol condensation. For example, instead of using LDA as the base to form an enolate, we have used the lithium amide derived from O-methylprolinol. Condensation of the derived enolate with benzaldehyde gives the (S,S)-aldol with 8% enantiomeric excess. This is slightly higher than the asymmetric induction we had previously seen with 1,2,3,4-tetramethoxybutane, even though the latter material was used as solvent (11). Similar results have been obtained with the lithium amides derived from O-methylephedrine and O-methylpseudoephedrine. At this point, the asymmetric induction observed with these chiral amides is only marginal. However, we think that with some careful design we can find chiral bases which will allow us to realize useful asymmetric induction in condensations of achiral enolates with achiral aldehydes.

One further insight into the coordination chemistry of these lithium enolates is obtained from the stereoselectivity observed in the reactions of chiral α-alkoxyketone enolates. For example, the

Rationally-Designed Chiral Auxillaries
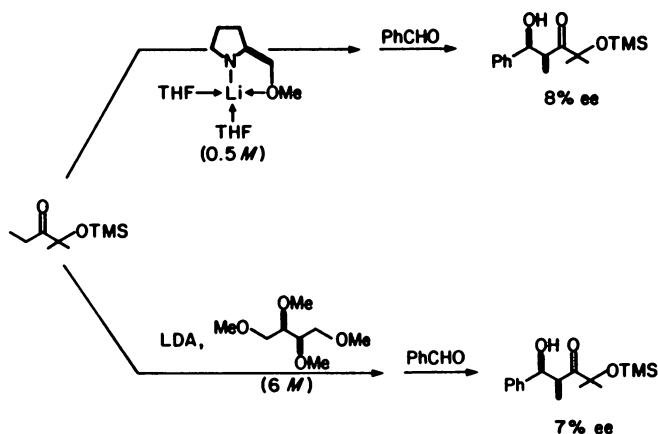
lithium enolate of the compound discussed earlier in this article
shows selectivity in the following sense:
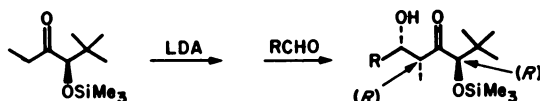
However, Masamune has examined the reactions of the boron enolates
of this type of compound and observes exactly the opposite sense of
diastereoface selectivity: (14)
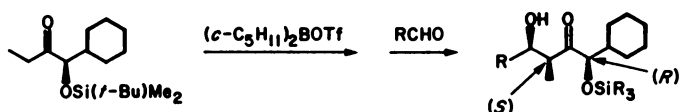
These apparently divergent results can be readily understood in
terms of the coordination chemistry of the two enolates. With
lithium, coordination can occur to the aldehyde and both sites in
the enolate. This imposes a structure on the enolate such that the
Re face of the (R)-enolate is shielded by the t-butyl group. Thus,
reaction occurs on the Si face. However, with the enolbronoate,
two of the boron ligands are alkyl groups. If the boron is to be
ligated to the enolate oxygen and the aldehyde carbonyl its tetra-
valency is saturated. Thus, it cannot also bond to the oxygen of
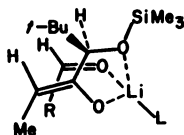
the α-alkoxy group.   In this case, it seems that the enolate
prefers to react from a conformation having the α C–O bond syn-
coplanar with the C=C. Thus, the cyclohexyl group shields the Si
face of the (R)–enolate, and reaction occurs on the Re face.
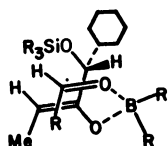
I believe that these observations presage a period during
which we, and others, will look more and more closely at the
details of important enolate reactions such as the aldol condensa-
tion and take account not only of the reactants themselves, but
also of the solvent and other potential ligands which are present
in the reaction medium.

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Asymmetric Carbon–Carbon Bond Forming Reactions via Chiral Chelated Intermediates

Diastereoselective Asymmetric Synthesis of 1,2-Disubstituted Cycloalkanecarboxaldehydes

KENJI KOGA

University of Tokyo, Faculty of Pharmaceutical Sciences, Hongo, Bunkyo-ku, Tokyo, Japan 113

1,4-Addition of Grignard reagents to Schiff bases of α,β-unsaturated aldehydes with optically active tert-leucine tert-butyl ester, followed by hydrolysis gives chiral β-substituted carboxaldehydes in 82-98% e.e. Similar reaction of α,β-unsaturated cycloalkanecarboxaldehydes followed by alkylation of either the corresponding magnesioenamine or the free aldehyde with alkyl halides leads to 1,2-disubstituted cycloalkanecarboxaldehydes of high diastereomeric as well as enantiomeric purity. The predominant diastereomer has the two alkyl groups trans to each other when the free aldehyde is alkylated but cis to each other when alkylation is performed on the Z-isomer of the magnesioenamine formed initially in the Grignard addition. Conversion of the Z-magnesioenamine to its E-isomer by heating followed by alkylation places the two alkyl groups trans to each other. Mechanistic explanations for this divergent behavior are provided.

The design of highly efficient asymmetric syntheses has been one of the most challenging and exciting fields in synthetic organic chemistry.[1] As part of our research program directed toward the development of new stereoselective reactions, we have reported an efficient method for asymmetric alkylations based on a strategy of fixing the intermediate conformation by chelation.[2] It appears that the conformation of the chiral moiety of Schiff bases (3), prepared from carbonyl compounds (1) and optically

$$
\begin{array}{ccc}
\overset{\displaystyle \diagdown C \diagup}{\underset{O}{\|}}\ \ \underset{\tilde{}}{1} &
\overset{\displaystyle \diagdown C \diagup}{\underset{\substack{N \\ | \\ R\text{-}CH\text{-}COOBu^t \\ *}}{\|}} &
\overset{\displaystyle \diagdown C \diagup}{\underset{\substack{\| \\ N}}{}}
\end{array}
$$

+

$$
\underset{\substack{NH_2 \\ | \\ R\text{-}CH\text{-}COOBu^t \\ *}}{} \qquad \underset{\tilde{}}{3}
$$

R'-M

R'-M coordinating to N and O=C(OBu^t), with C bearing * and R, H substituents

$$\underset{\tilde{}}{2} \qquad\qquad \underset{\tilde{}}{4}$$
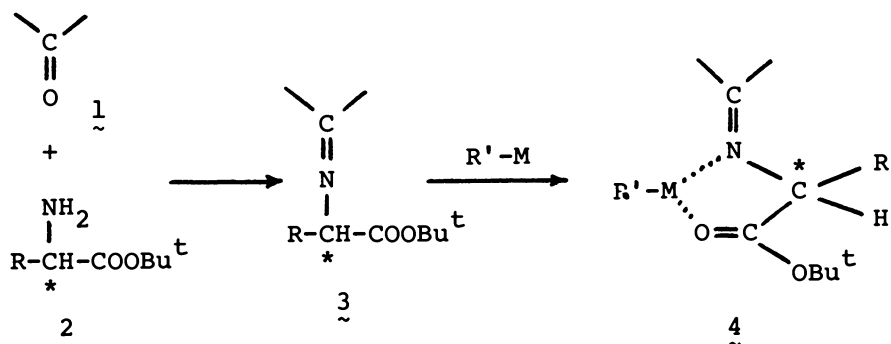
Chart 1.

active α-amino acid esters (2), can be effectively fixed as 4 in which both the imine nitrogen and ester oxygen coordinate to the metal (Chart 1). Optically active <u>tert</u>-leucine <u>tert</u>-butyl ester (2, R=Bu^t) was found to be an excellent chiral auxiliary reagent acting as a bidentate ligand. It was recovered without any racemization after the reaction. Some representative examples of its use in asymmetric synthesis are shown in Chart 2.

As an extension of this reaction, a diastereoselective asymmetric synthesis of 1,2-disubstituted cycloalkanecarboxaldehydes (19) was attempted[3] as shown in Chart 3. These compounds are useful chiral synthons having asymmetric tertiary and quaternary carbon atoms in vicinal positions. Three synthetic approaches were examined starting from cycloalkenecarboxaldehydes (8). In method A, optically active aldehydes (10), prepared by the above method via Grignard 1,4-addition to chiral α,β-unsaturated cyclic aldimines (9) followed by hydrolysis of the resulting magnesio-enamines (18), were metalated and alkylated as usual. In method B, the reaction was performed by a one-pot procedure via Grignard 1,4-addition to 9 followed by alkylation of the resulting 18 with alkyl halides in the presence of HMPA. In method C, the reaction was performed as in method B, except that the reaction mixture was heated to reflux for several hours before alkylation. The
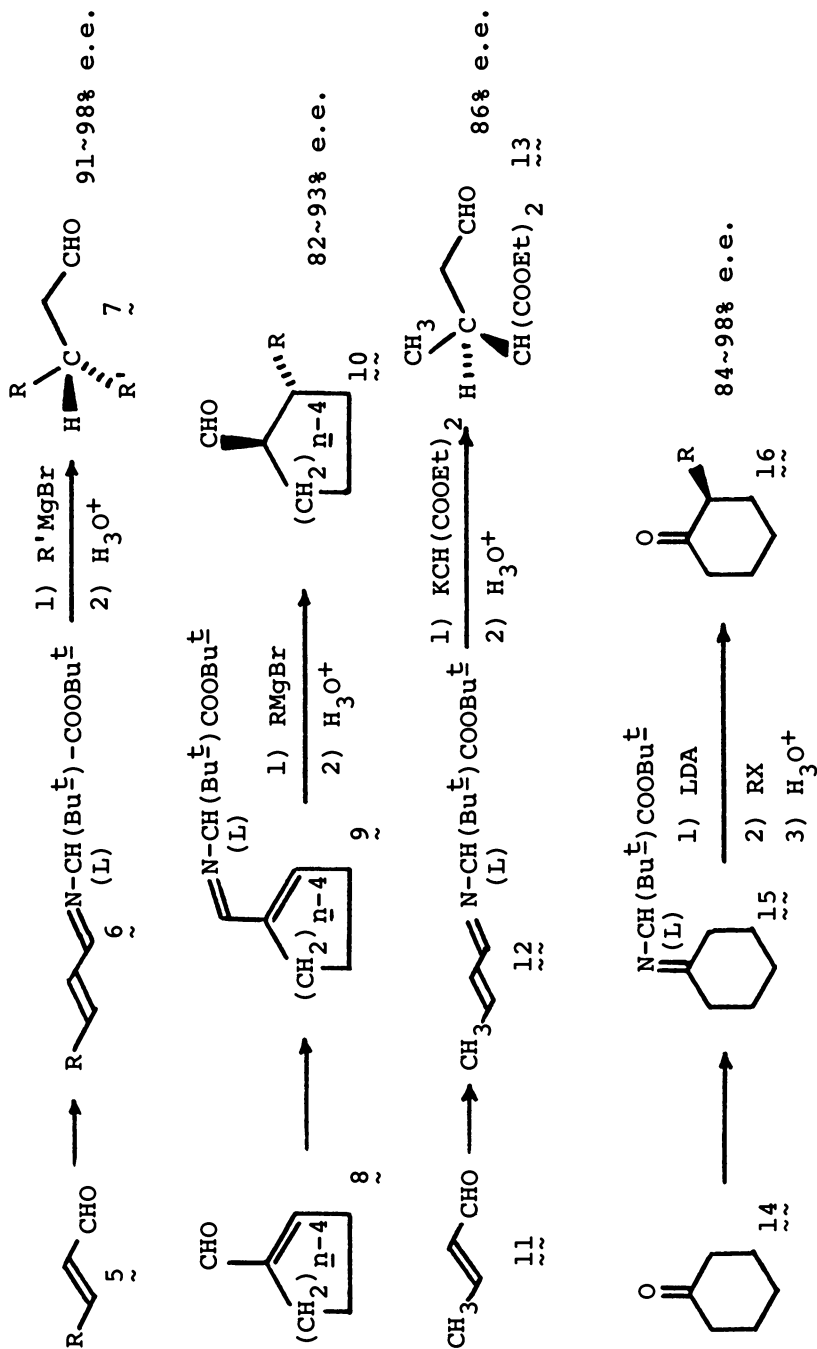
Chart 2.
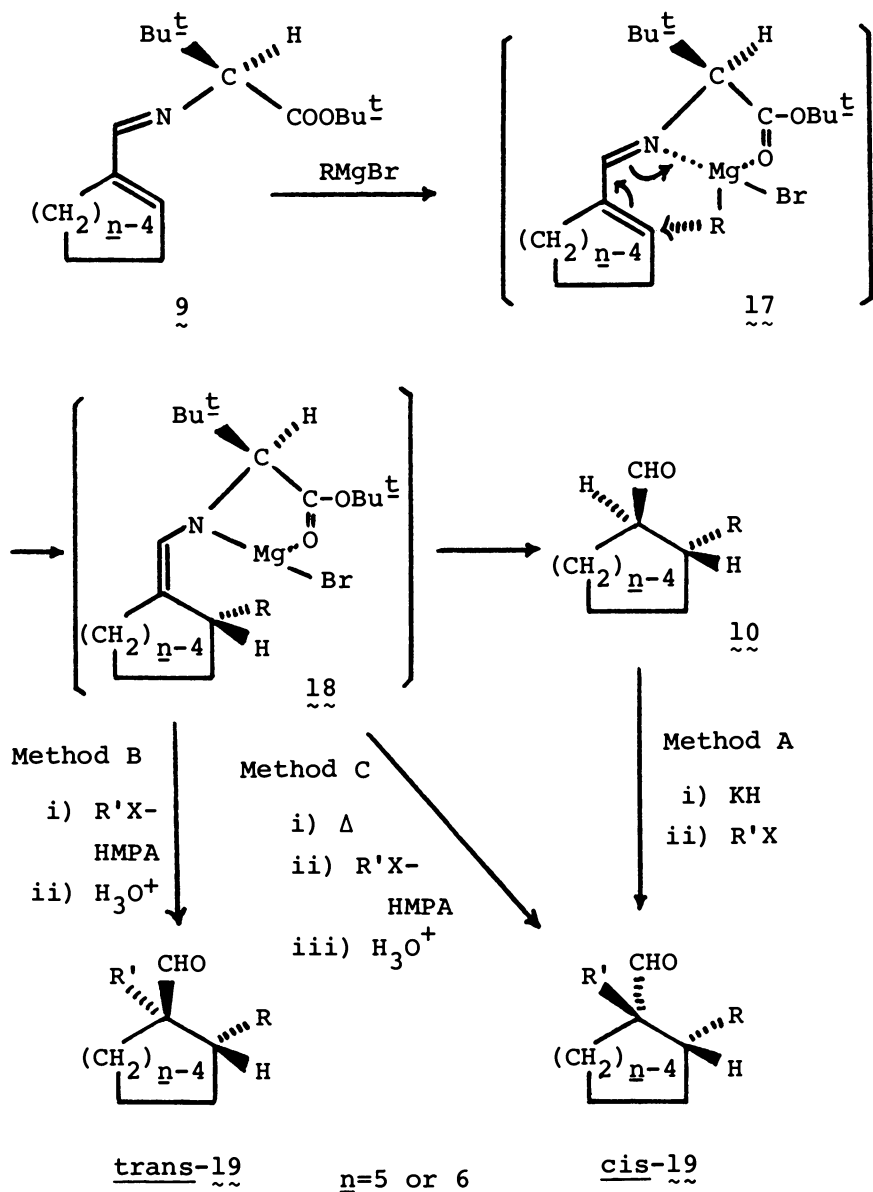
Chart 3.

results are summarized in Table 1. It should be noted that the
first step (conjugate addition) determines the enantioselectivity,
while the second step (alkylation) determines the diastereoselec-
tivity of the reaction.

The stereochemical course of the first conjugate addition
step by Grignard reagents, common to methods A, B, and C, is
already known to proceed via the s-cis conformation as shown in
17.[2a,d,g] The observed alkylation of the anion of 10 by method
A to give preferentially cis-19 is quite reasonable, based on the
premise that the reaction occurs from the side opposite to the R
group. Therefore, it is striking to find that, except in run 5,
the stereochemical course of the second alkylation step by method
B is reversed to give trans-19, not readily accessible by the
usual alkylation methods.

From mechanistic considerations of the first conjugate addi-
tion step proposed earlier,[2a,d,g] the double bond of the inter-
mediate magnesioenamine should be in the Z-configuration as shown
in 18. Therefore, a possible cause for the reversal of the ste-
reochemical course of the second alkylation step in method B is
considered to be the steric effect of the original chiral center
in the Z-configuration of the enamine moiety. The following
experiments were undertaken to examine this point.

As shown in Table 2, the reaction of α,β-unsaturated
aldimines (20), prepared from the corresponding cycloalkenecarbox-
aldehydes (8) and 2-methoxyethylamine, with Grignard reagents
followed by treatment with methyl iodide using method B was found
to give preferentially the corresponding cis-19. This means that
the second methylation occurred from the side opposite to the
initially introduced R group, as in the reaction of 10 by method
A. The 2-methoxyethylamine moiety of 20 is expected to function
as a bidentate ligand, similar to the α-amino acid ester moiety,
during the Grignard 1,4-addition step. Thus, it is highly prob-
able that magnesioenamine (21) with a structure similar to 18, but

Table 1   Asymmetric Synthesis of 1,2-Disubstituted Cycloalkanecarboxaldehydes (19)

Run	Method	n	RMgBr	R'X	Isolated yield[a] trans-19	cis-19	% e.e.[b]
1	A	5	C_6H_5MgBr	CH_3I	0	65	82
2	A	5	$CH_2=CHMgBr$	CH_3I	0	61	92
3	A	6	C_6H_5MgBr	CH_3I	1	62	91
4	A	6	$CH_2=CHMgBr$	CH_3I	11	61	93
5	B	5	C_6H_5MgBr	CH_3I	15	62	82
6	B	5	$CH_2=CHMgBr$	CH_3I	62	0	92
7	B	6	C_6H_5MgBr	CH_3I	55	0	91
8	B	6	$CH_2=CHMgBr$	CH_3I	67	0	93
9	B	6	$CH_2=CHMgBr$	CH_3I	67	0	93
10	B	6	$CH_2=CHMgBr$	$C_6H_5CH_2I$	63	0	93
11	B	6	$CH_2=CHMgBr$	$CH_2=CH-CH_2Br$	65	0	93
12	B	6	$CH_2=CHMgBr$	C_2H_5I	52	0	93
13	C	5	C_6H_5MgBr	CH_3OCH_2Cl	2	44	82
14	C	6	C_6H_5MgBr	CH_3I	0	49	91

a) After column chromatography.   b) Corrected value for the optical purity of 2 (R=Bu^t) used.

Table 2   The Reaction of α,β-Unsaturated Aldimine (20) by Method B
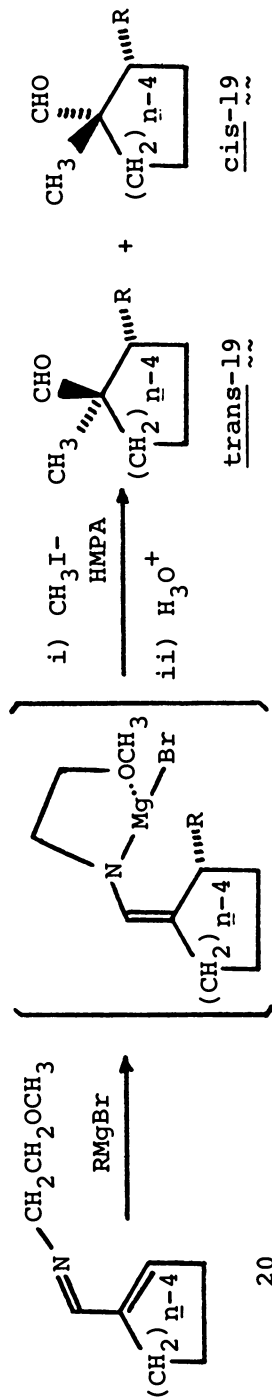
Run	n	RMgBr	Isolated Yield[a]	
			trans-19	cis-19
1	5	C_6H_5MgBr	0	17
2	5	$CH_2=CHMgBr$	8	25
3	6	C_6H_5MgBr	0	52
4	6	$CH_2=CHMgBr$	0	45

a) After column chromatography.

without a chiral center in the chelated ring, is produced. The
fact that the reaction of methyl iodide by method B gave prefer-
entially cis-19 from 21, but preferentially (except in run 5 in
Table 1) trans-19 from 18 clearly suggests that the original
chiral center in the chelated ring of 18 exerts a strong steric
influence on the second alkylation step.

The importance of the Z-configuration for 18 to give trans-
19 by method B was also demonstrated. It is known that E-Z iso-
mers of metalloenamines do not equilibrate under conditions simi-
lar to those employed in method B, but do equilibrate in THF under
reflux.[4] It is thus probable that equilibration prior to alkyla-
tion will affect the diastereoselectivity of the reaction.
Although the chemical yields were lower, probably due to the
instability of magnesioenamines at higher temperatures, methyla-
tion of magnesioenamines after heating (method C) was found to
give preferentially cis-19 as shown in Table 1. Additional sup-
port for the occurrence of E-Z isomerization of magnesioenamines
on heating was observed by ^{13}C NMR studies using an earlier re-
ported method.[4] Thus, starting from cyclohexenecarboxaldehyde
(8, n=6) enriched with ^{13}C at the aldehyde carbon, magnesioenamine
(18, n=6, R=C_6H_5) was prepared with phenylmagnesium bromide in
THF-d_8 at -23°C. The ^{13}C NMR spectrum of this magnesioenamine
showed a single peak (146.0 ppm) of enriched carbon before
heating, but a new peak (147.5 ppm) appeared after heating at
70°C. The intensity of the new peak relative to the initial peak
increased gradually, and the signals became complex after 3 hr at
70°C, probably due to partial decomposition.

These data clearly show that the formation of magnesioenamine
(18) having the Z-configuration and attack of alkyl halides under
the steric influence of the original chiral center of the tert-
leucine tert-butyl ester moiety are responsible for the predomi-
nant formation of trans-19 by method B. However, the substituent
R introduced is also expected to show a steric effect at the
second alkylation stage. Therefore, assuming that the configu-

ration of the magnesioenamine is retained in Z-stereochemistry
throughout the reaction, the stereochemical course of the second
alkylation step by method B is considered to be subject to the
two opposing steric effects of the original chiral center and the
newly created chiral center, of which the former apparently
predominates in many cases, while the latter is predominant when
a bulky R group is attached to the five-membered ring.

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Asymmetric Carbon–Carbon Bond Forming Reactions via Chiral Oxazolines

ALBERT I. MEYERS

Colorado State University, Department of Chemistry, Fort Collins, CO 80523

The use of chiral oxazolines as auxiliaries in C-C
bond forming reactions continues to provide chiral
compounds in high enantiomeric excess. Conjugate
addition-alkylation of α,β-unsaturated oxazolines
leads to 2,3-disubstituted alkanoic acids in high
ee's. Boron enolates of oxazolines, where the
chirality resides in the oxazoline or boron sub-
stituents, react with aldehydes to give β-hydroxy
esters in high erythro or threo selectivity with
good ee's. Aromatic chiral oxazolines containing
ọ-acyl groups react with organometallics furnish-
ing, after hydrolysis, phthalides in high ee's. A
further extension using aryl oxazolines leads to
chiral binaphthyls in 70-100% ee's.

2,3-Disubstituted Carboxylic Acids

      In our continuing program to utilize chiral oxazolines (1-7)
as auxiliary reagents in asymmetric synthesis, several novel
routes to chiral compounds have been developed. The previously
reported (3) conjugate addition (Fig. 1) to vinyl oxazolines 1
(pure E enantiomer) by organolithium reagents furnishing the
adduct 2 and subsequent hydrolysis gave 3,3-disubstituted car-
boxylic acids 3 in 95-99% ee. We have recently extended this
methodology to provide an additional chiral center in carboxylic
acids (Fig. 1). Thus, the intermediate lithio adduct 2 could be
treated with an alkyl halide to give the alkylated oxazoline 5,
which after hydrolysis affords the 2,3-disubstituted acids 6 in
77-82% diastereomeric purity. HPLC examination of the diastereo-
meric oxazolines 5 prior to hydrolysis indicates that the alkyla-
tion of 2 occurred with >99% stereoselectivity. Thus, virtually
no presence of diastereomeric impurities was observed. It may,
therefore, be concluded that the observed diastereomeric purity
for 6 was the result of partial racemization during the hydrolysis
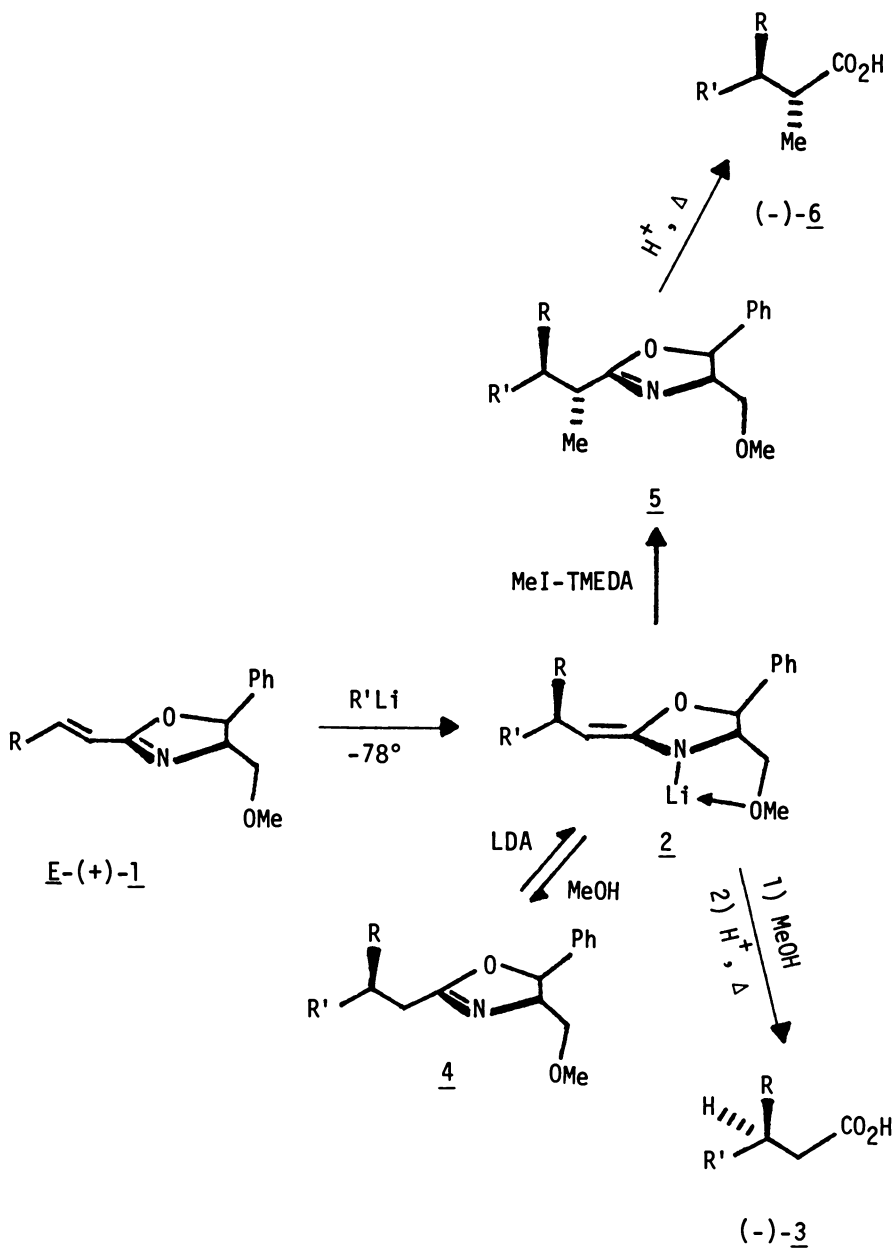
Figure 1. *Formation of 2,3-disubstituted alkanoic acids by conjugate addition and alkylation of α,β-unsaturated oxazolines.*

of 5. Several examples of this tandem dialkylation are given in
Table I. With regard to the absolute configuration of the acids
6, they are assigned on the basis of both known compounds and
previous predictions described in earlier work (1). It is inter-
esting to note that quenching adduct 2 to give the 2-alkyloxazo-
line 4 and then metalation back to 2 followed by alkylation gave
the 2,3-disubstituted acids 6 of the same configuration as that
obtained from 2 in the sequential dialkylation process. This
confirms that the same lithio azaenolate 2 is formed both by con-
jugate addition (1→2) and metalation (4→2). Since both processes
have been performed as separate methods, leading either to chiral
2-substituted carboxylic acids or 3-substituted chiral acids, the
absolute configuration of the 2,3-disubstituted acids 6 is consis-
tent with these earlier findings.

Table I. 2,3-Disubstituted Carboxylic Acids 6

R (in 1)	R'Li	Diastereo- meric Ratio 5	Yield 5	% Diastereomeric Ratio, 6	
				α–C	β–C
Me	Et	99	65	77 (R)	99 (R)
Me	n–Bu	99	80	82 (R)	99 (R)
t–Bu	n–Bu	99	82	80 (S)	99 (R)
n–Bu	t–Bu	99	75	79 (R)	99 (R)

Aldol Products via Boron Azaenolate

The use of chiral oxazolines as reagents for aldol type
products (Fig. 2) rich in erythro or threo β-hydroxy acids has
also been accomplished. In earlier work in our laboratory (8) we
described the formation of β-hydroxyesters 7 from lithio oxazo-
lines and various aldehydes in 20-25% ee. The absence of an α-
alkyl group was considered the major reason for the poor ee's of
the product which lacked stringent stereochemical requirements in
the transition state. The process was repeated with the 2-ethyl-
oxazoline and gave 8 in much higher selectivity mainly as the
threo-isomer and in 75% enantiomeric purity (7). We have now
investigated this aldol process using the boron "enolates" of
oxazolines 9 and 10 (Fig. 3) (9). It should be noted that boron
azaenolate 9 contains the chiral center on the organoborane,
whereas 10 contains the chiral center on the oxazoline.
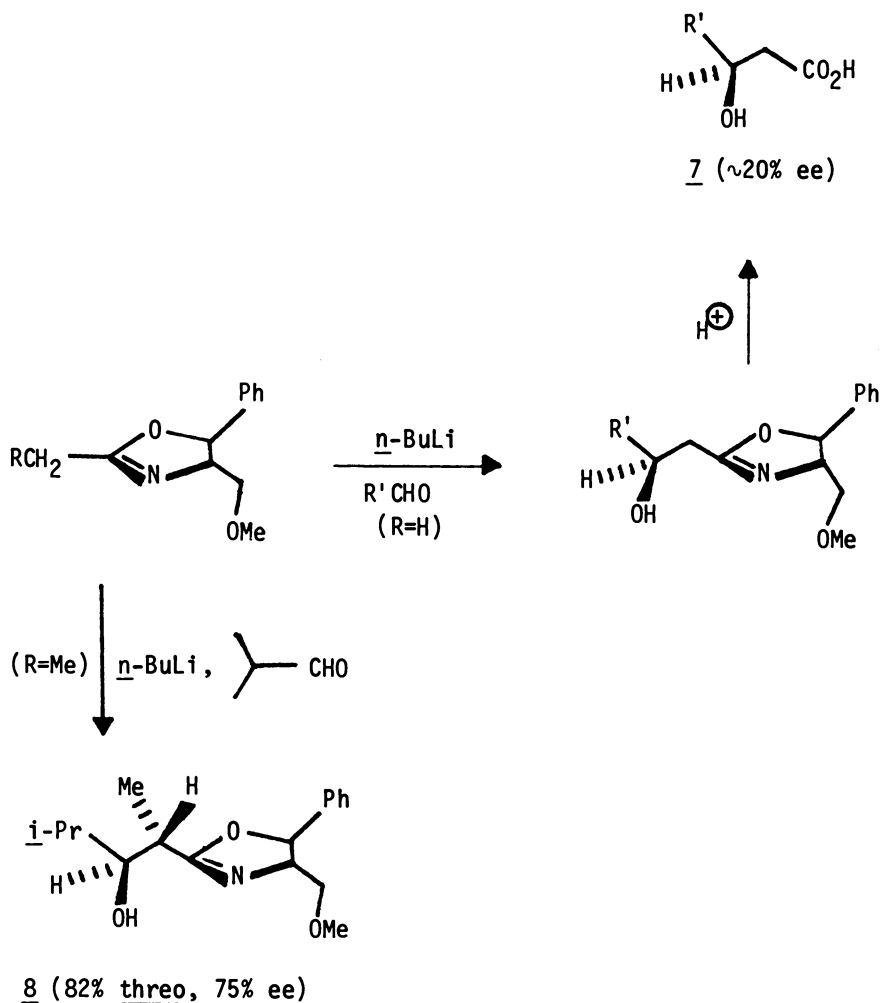
Figure 2. *Chiral oxazolines used as reagents for aldol-type products rich in* erythro *or* threo *β-hydroxy acids.*
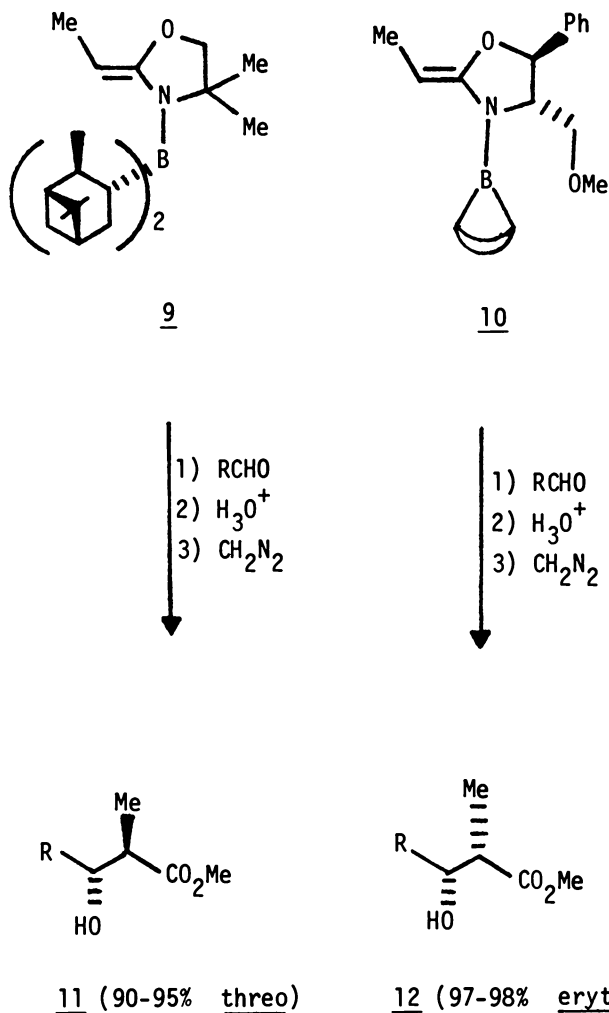
Figure 3. *Formation of β-hydroxyesters with an α-alkyl group by the aldol process using boron enolates of oxazolines 9 and 10.*

Treatment of 9 with various aldehydes gave the threo-β-hydroxy-ester 11 after hydrolysis and esterification, in 90-95% diastereo-selectivity with enantiomeric excess of 77-85% (Table II). On the other hand, the boron enolate 10, when treated similarly with aldehydes now gave the erythro β-hydroxy esters 12 in 97-98% diastereoselectivity though in somewhat poorer ee's (40-60%, Table III). ^{13}C NMR spectroscopy employing 9 and 10 with ^{13}C-enriched methyl groups confirmed that only a single enolate was formed at -78° under the conditions of kinetic control. Equili-bration of 9 or 10 took place by warming their ether solutions to -25° showing a steady increase in a second methyl signal until equilibrium was reached at 2:1. Unfortunately, which enolate is formed at -78° is not known at this time. When the condensation

Table II.   Chiral threo-hydroxyesters 11 from 9

RCHO	% threo-erythro	% ee	Conf'n. Major Isomer	$[\alpha]_D$ (CHCl$_3$)
EtCHO	92:8	77	2R,3R	-9.9
PrCHO	91:9	77	2R,3R	-2.5
n-PentCHO	90:10	77	2R,3R	-3.1
Me$_2$CHCHO	91:9	85	2R,3R	-12.5
CyclohexCHO	95:5	84	2R,3R	-8.1
t-BuCHO	94:6	79	2R,3S	-21.2

Table III.   Chiral erythro-hydroxyesters 12 from 10

RCHO	% erythro-threo	% ee	Conf'n. Major Isomer	$[\alpha]_D$ (CHCl$_3$)
EtCHO	98:2	40	2S,3R	1.4
Me$_2$CHCHO	98:2	41	2S,3R	-2.3
t-BuCHO	97:3	60	2S,3S	-6.6

with aldehydes was carried out with equilibrated 9 or 10, the diastereoselectivity in 11 and 12 decreased, as expected, to ∼80:20. Since the stereochemistry of the boron enolates 9 and 10 is not known, it is difficult to advance a reasonable mechanism except to postulate a chair-type six-membered transition state based on the Zimmerman model (10). This correctly predicts the stereochemistry of the product provided the Z boron enolates of 9 and 10 are employed (Fig. 4).

A variety of other oxazolines was investigated (Fig. 5) to probe the nature of structural parameters in determining the erythro threo ratios of β-hydroxy esters. Thus, reaction of boron enolates of 13-16 and 9-BBN also gave high erythro selectivity of 12 (R = i-Pr) when treated with isobutyraldehyde. It is interesting to note that 13 gave high threo selectivity (Table II) when diisopinocampheyl borane enolate 9 was employed while giving high erythro selectivity of 12 (R = i-Pr) using 9-BBN enolate. This implies a major effect on the product due to the nature of the boron substituents. Further work should help clarify this point.

Chiral Phthalides

Aromatic oxazolines have also been utilized (Fig. 6) as vehicles for asymmetric synthesis. Thus the chiral oxazoline 17, used as its lithio or magnesiohalide derivative 17b (from the bromo compound 17a) was treated with several carbonyl compounds to give the adducts 18, whose diastereomer ratios were assessed by ^{1}H-nmr or HPLC (Table IV). The extent of stereoselection was rather poor indicating a sterically undemanding transition state.

Table IV.

R_2CO	% Yield	Diast.[a] Ratio
PhCOMe	71	64:31
PhCHO	60	57:43
o-MeOPhCHO	63	59:41
n-BuCHO	64	51:49

a) Assessed on 18

min'm. 1,3-int'n.

threo-acids   erythro-acids

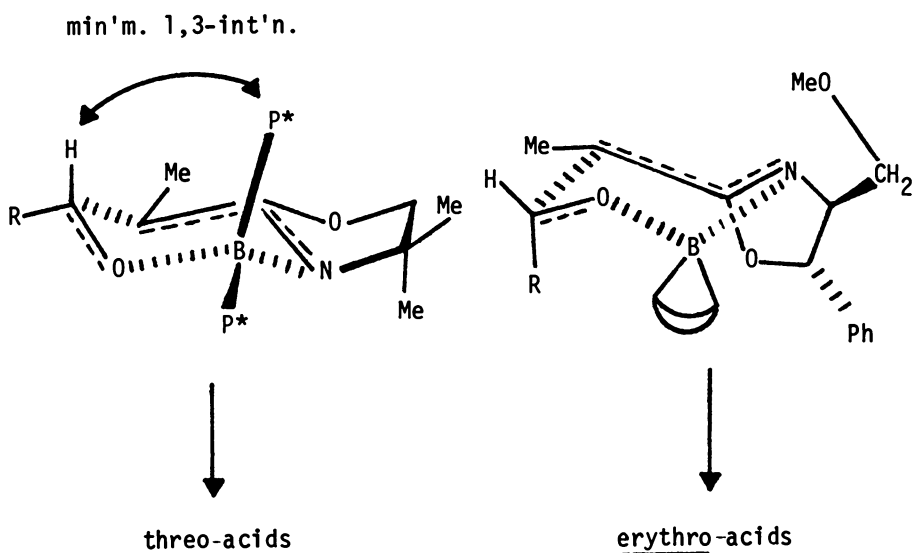Figure 4.   Prediction of stereochemistry of boron enolates 9 and 10 using chair-
type six-membered transition state based on the Zimmerman model.

13   14   15   (-)-16

(E/T for 12)

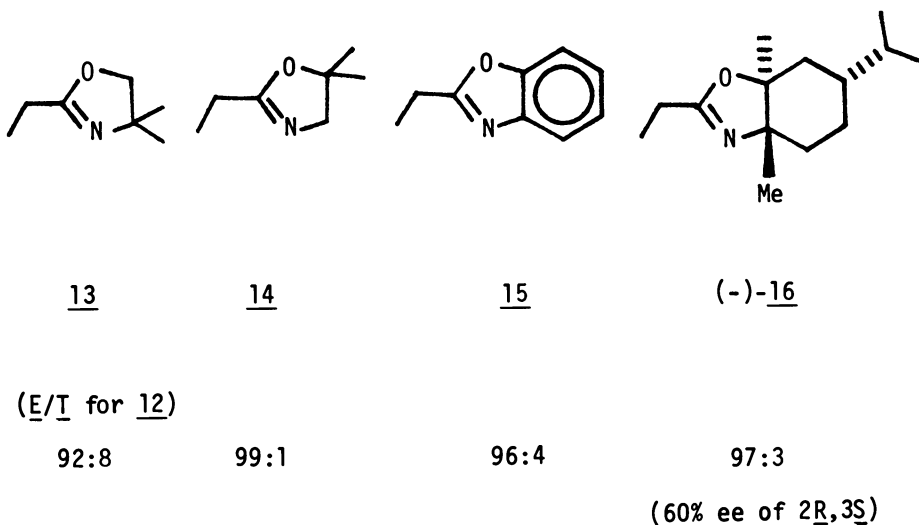92:8   99:1   96:4   97:3

(60% ee of 2R,3S)

Figure 5.   A variety of oxazolines used to determine erythro–threo ratios of
β-hydroxy esters.

These findings are in strong contrast to the highly successful
results (Fig. 7) of Mukaiyama (11) using the proline derivative
20. Hydrolysis of 18 in acidic medium gave the phthalide 19. In
order to assess the absolute configuration of the lactones, par-
ticularly those with a dialkyl substitution pattern, which are not
known in the literature, an x-ray study was performed using the
p-bromophenyl acetophenone, 19 (R = Me, R' = p-Bromophenyl, S
configuration). Pure enantiomers of 19 were obtained by MPLC-
assisted resolutions of 18 followed by hydrolysis with acid.

    We next turned to reversal of the nucleophile-electrophile
combination by preparing o-acylaryl oxazolines 21 and treating
them with organometallics (Fig. 8). Addition of organolithium or
Grignard reagent gave the adducts 22 which smoothly rearranged to
the iminolactones 23. HPLC analyses of 23 showed the ratio of
diastereomers to be rather low again suggesting that addition of
organolithium reagents to 21 was perhaps too fast with a low $\Delta\Delta G^{\ddagger}$.
However, when methylmagnesium chloride was treated with the o-
benzoyloxazoline 24, the reaction proceeded more slowly and, after
hydrolysis, the phthalide 25 was recovered almost enantiomerically
pure (Fig. 9) (12).

    Future efforts will now be directed to Grignard additions to
ketooxazolines in the hope that the above reaction possesses some
generality. The complexities of this system and factors affect-
ing the transition state will have to be more carefully addressed
before a general synthetic approach to chiral phthalides can be
achieved.

Chiral Binaphthyls

    An asymmetric synthesis of chiral binaphthyls has been accom-
plished utilizing naphthyloxazolines. The method is based on the
facile displacement of an o-methoxyl group in aryloxazolines by
various nucleophiles (13). The aromatic substitution process has
now also been found to proceed with o-methoxynaphthyloxazolines
(Fig. 10). A number of nucleophilic reagents smoothly displaced
the methoxyl group to 26 and after hydrolysis led to 1-substituted-
2-naphthoic acids 27. Utilization of this efficient coupling
reaction with chiral oxazolines was examined in an attempt to
reach chiral binaphthyls. Thus, 28 was treated with the Grignard
reagent of 1-bromo-2-methoxynaphthalene at room temperature in THF
to give the binaphthyl adduct 29 (Fig. 11). Nmr analysis showed
that the ratio of diastereomers in 29 was greater than 95:5 indi-
cating a high degree of stereoselection in the coupling reaction.
Hydrolysis of 29 followed by hydride reduction of the intermediate
ester gave the chiral binaphthyl 30 in ∿100% ee (confirmed by
LISR-nmr techniques). Two additional naphthyl Grignard reagents
were examined (Fig. 12) which led to products whose ratios were
not as high as in the methoxy naphthyl system, but, nevertheless,
were still formed in 60-70% ee. The crystalline nature of 29

17a, X = Br

17b, X = Li, MgBr

18

19
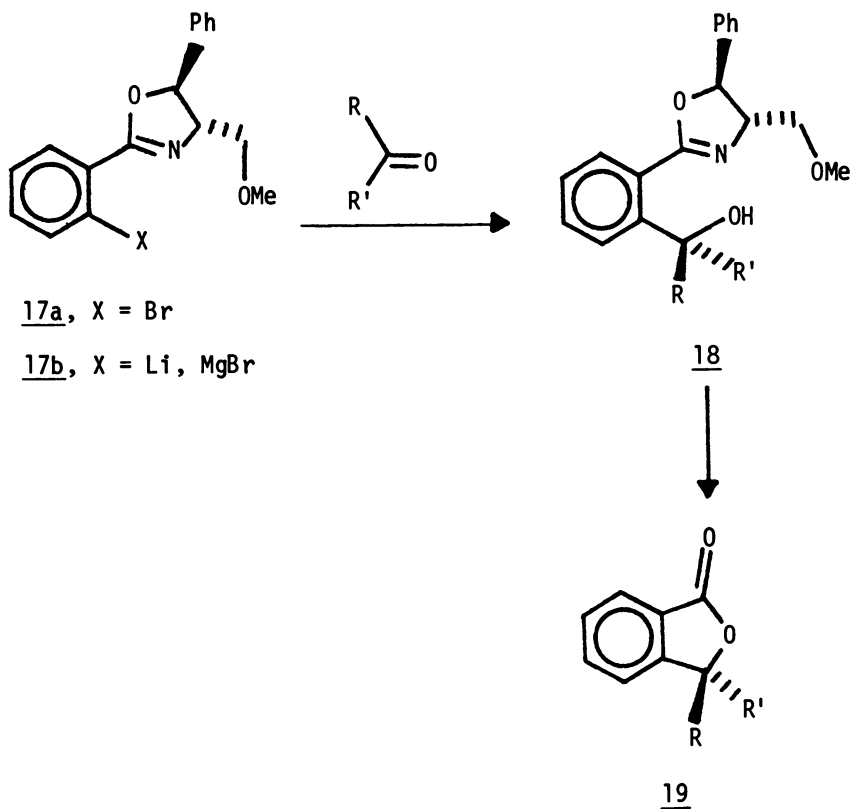
Figure 6. Aromatic oxazolines used as vehicles for asymmetric synthesis.

1) n-BuCHO

2) H₃O⁺, Ag₂O

20

88% ee
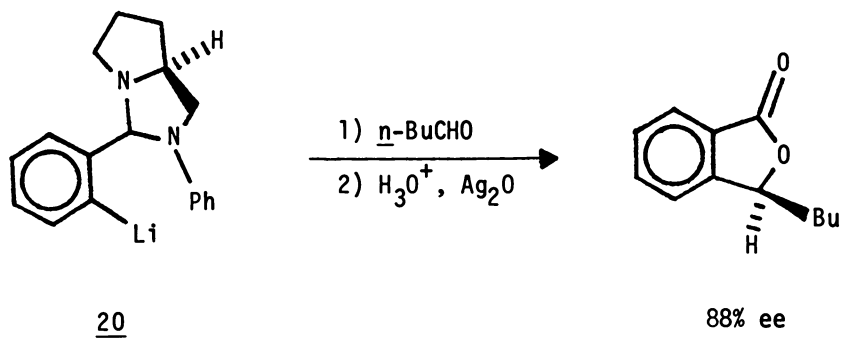
Figure 7. Asymmetric synthesis using proline derivative 20. (11)

Diastereomeric Ratios of <u>23</u>

<u>R</u>	<u>R'Li</u>	<u>% Yield</u>	<u>Ratio</u>
<u>t</u>-Bu	Ph	94	2:1
Ph	Me	85	2:1
Ph	<u>n</u>-Bu	86	1.2:1
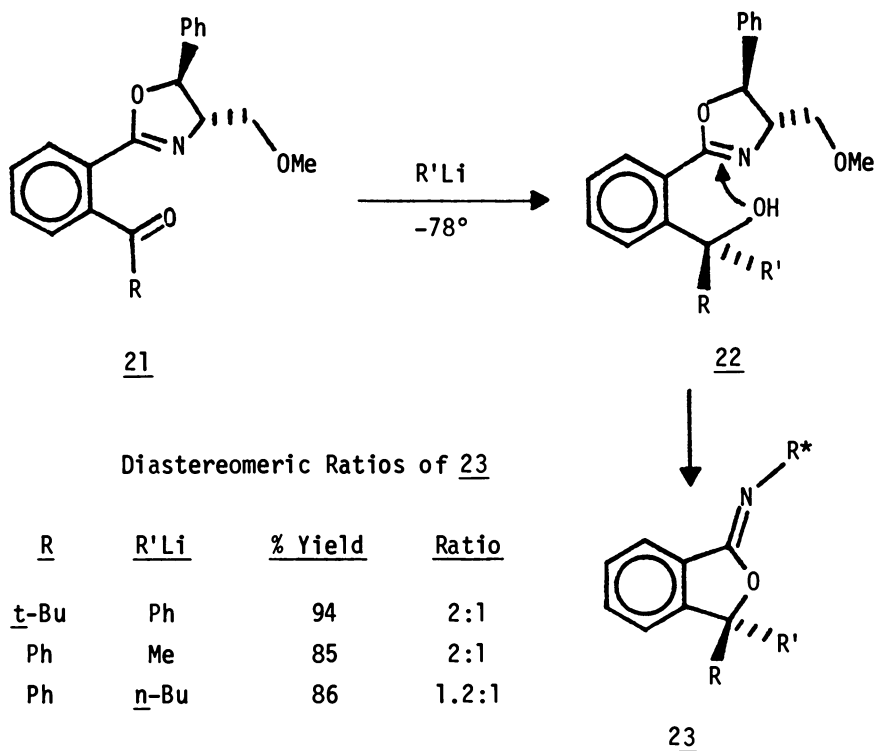
Figure 8. Synthesis of iminolactones, **23,** *by reaction of o–acylaryloxazolines with organolithium or Grignard reagent and rearrangement of product,* **22.**
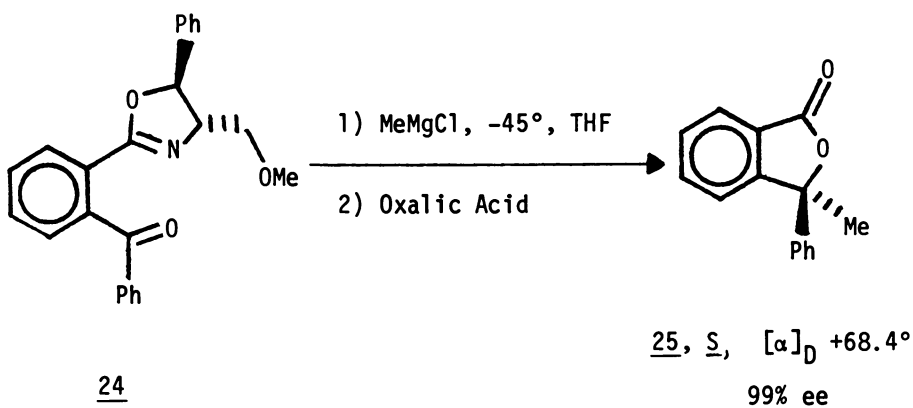
Figure 9. Preparation of phthalide, **25,** *by treatment of o-benzoyloxazoline,* **24,** *with Grignard reagent followed by hydrolysis.*

R	% 26	% 27
Me	84	88
n-Bu	90	67
Ph	84	67
PhCH₂	60	42
(naphthyl)	78	63 (ROH)
(p-tolyl oxazoline)	55	42
NEt₂	64	--
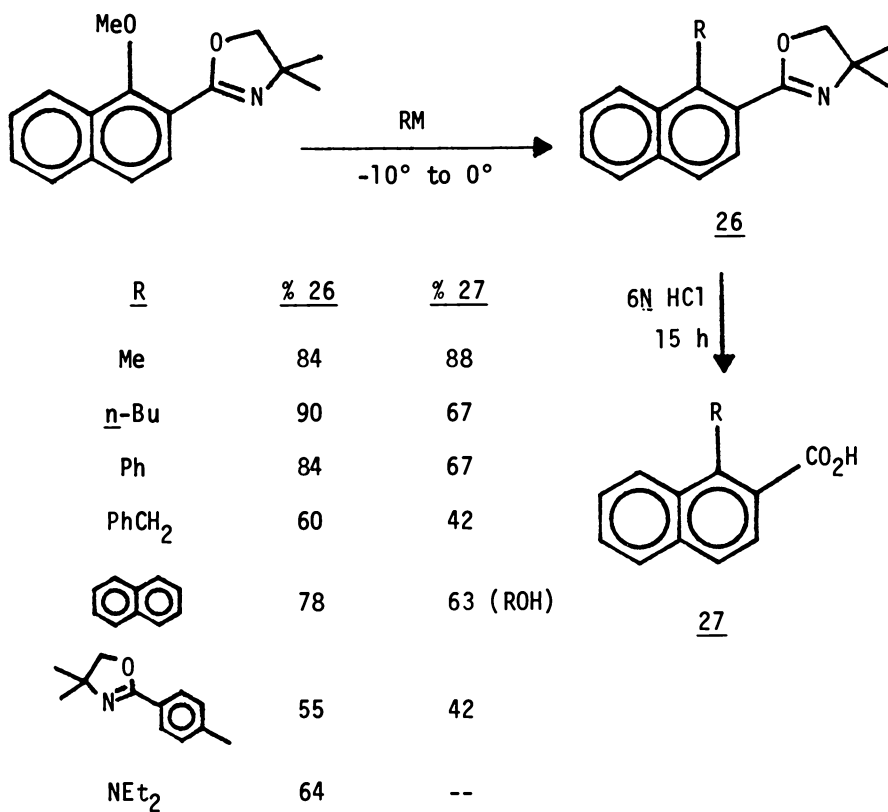
Figure 10. Synthesis of 1-substituted-2-naphthoic acids by aromatic substitution of o-methoxynaphthyloxazolines followed by hydrolysis.

28, $[\alpha]_D = +98.6°$

25°

95:5 by HPLC, NMR

29

1) H_3O^+
2) LAH

$\sim 100\%$ ee (by LISR)

30

$[\alpha]_D = -75.6°$ (solvent)
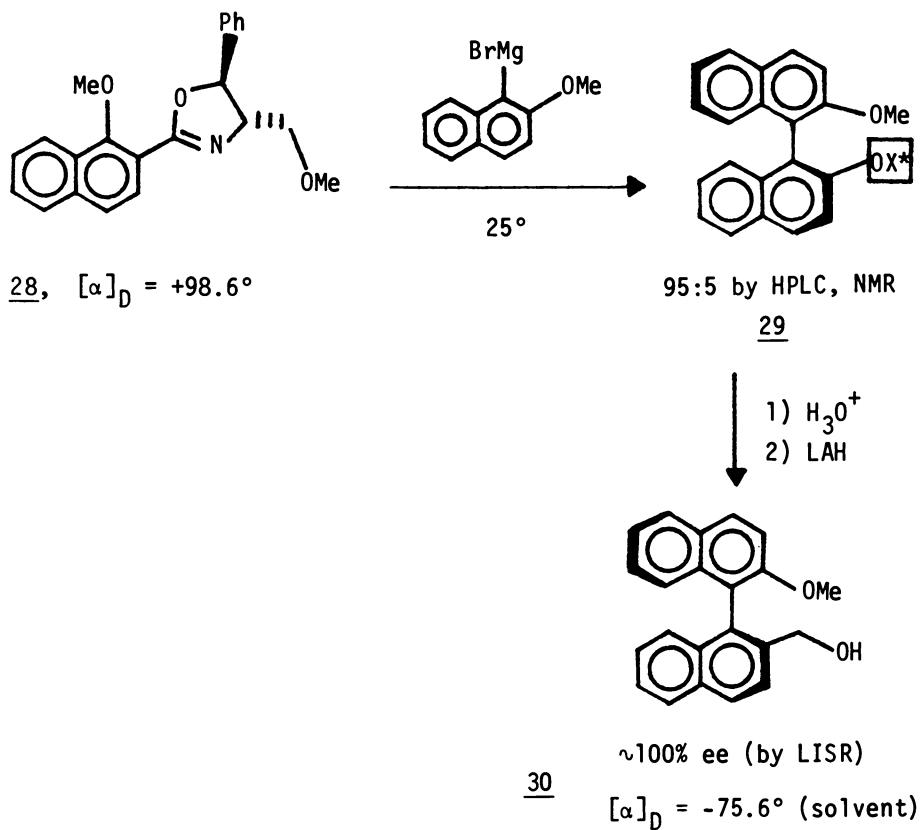
Figure 11. Asymmetric synthesis of chiral binaphthyls, 30, with high degree of stereoselectivity.

R	% Yield	Ratio Diastereomers
H	83.5	78:22 (HPLC)
		75:25 (PMR)
CH$_3$	68.0	75:25 (PMR)
OCH$_3$	71.0	>95:5 (PMR)
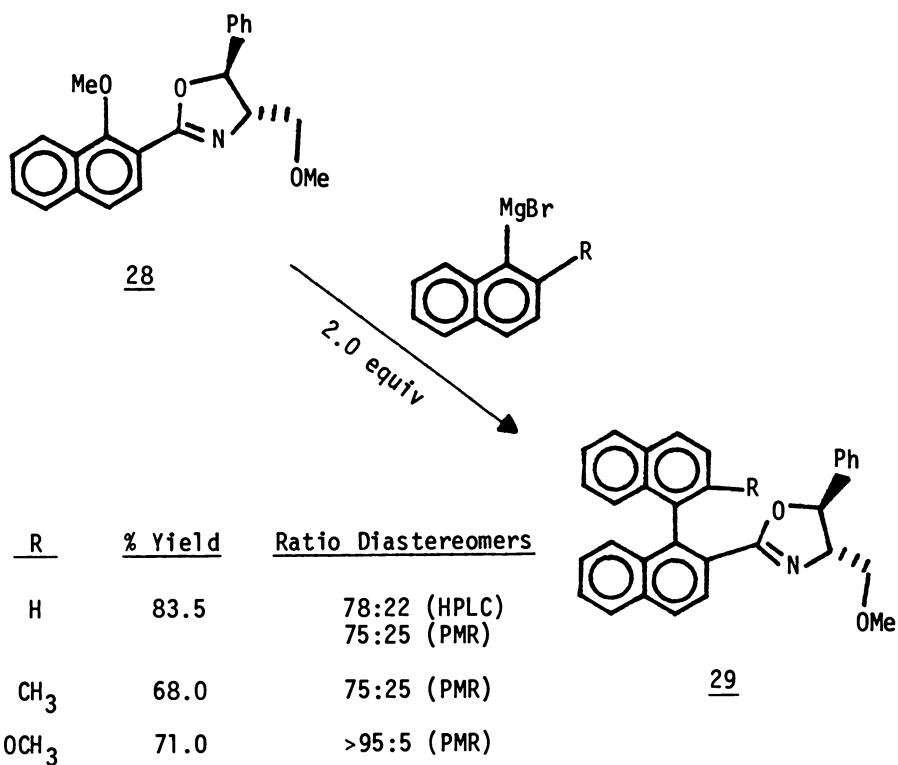
Figure 12. Asymmetric synthesis of chiral binaphthyls, 29, by reaction with naphthyl Grignard reagents. Ratios of diastereomers are given.

(R = H, Me, MeO) resulted in very easy purification to single
diastereomers by simple crystallization. However, since this was
not the current aim of the study, care was taken to avoid inadver-
tent resolution during the workup and purification of 29. The
most convenient method to reach chiral binaphthyls was to carry
out a tandem hydrolysis-reduction to the hydroxymethyl group (Fig.
13). Thus, the binaphthyloxazolines 29 were only partially hydro-
lyzed to the aminoesters 31 and then subjected to hydride reduc-
tion to the alcohol 30. The absolute configuration of the chiral
binaphthyls was determined by correlation methods to known deriva-
tives as well as CD spectral characteristics.

R	% Yield	$[\alpha]_D$	Conf'n.
H	56	+71.06	R
CH_3	43	+4.33	R
OMe	65	-75.6	R
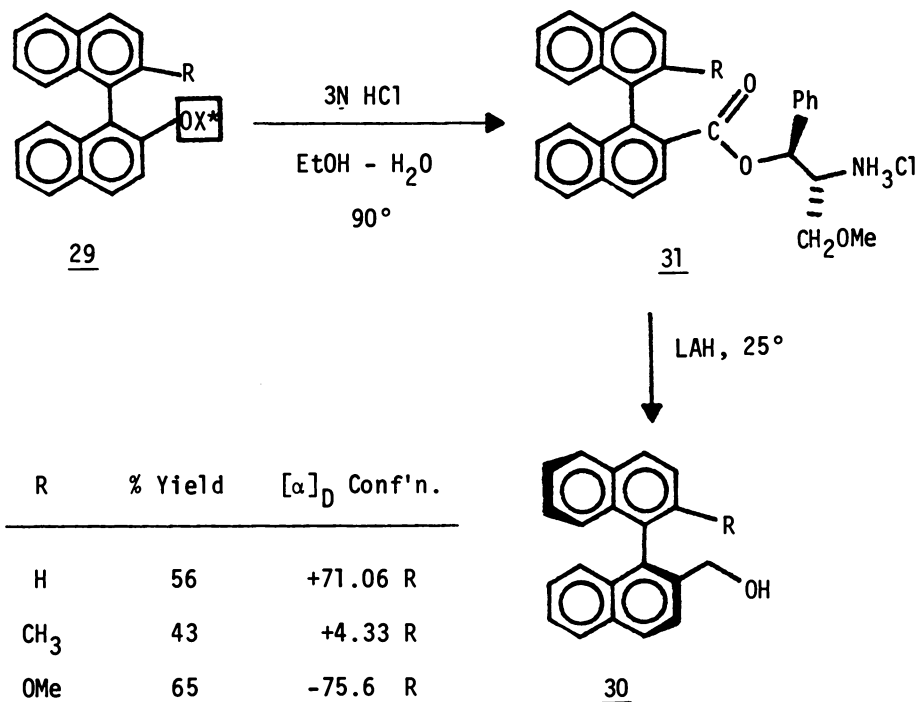
*Figure 13. Hydrolysis of binaphthyloxazolines, 29, to aminoesters, 31, and
reduction to alcohol producing chiral binaphthyls.*

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Highly Selective Synthesis with Novel Metallic Reagents

HITOSI NOZAKI, TAMEJIRO HIYAMA, KOICHIRO OSHIMA, and KAZUHIKO TAKAI

Kyoto University, Department of Industrial Chemistry, Kyoto, 606, Japan

Allylchromium reagents as produced from allylic bromides and Cr(II) salts in anhydrous THF or DMF react with carbonyl components to form homo-allylic alcohols. The aldehyde adducts, RCH(OH)-CHMeCH=CH$_2$, are oxidized with various recently described reagents to produce epoxy alcohols with different ways of steric control.--Alkylation of cyclopropane derivatives with R$_3$Al proceeds from preliminary heterolysis in one case, whereas the reaction introduces alkyl carbanions with S$_N$2-like inversion in other cases.--Catalysis with Pd(0) makes possible the substitution of an -OPO(OR)$_2$ group on an sp^2 carbon and finds a number of synthetic applications.--Finally, the aliphatic Claisen rearrangement is smoothly per-formed at room temperature by means of R$_2$AlX reagents (where X = R, H, or SPh etc.) involving "combined acid-base" attack.

This paper will deal with four topics: the first one is re-lated to allylchromium reagents, while the latter three refer to the behavior of trialkylaluminum or related species in different situations. The authors' main concern here is to describe new reactions useful for selective synthesis.

Allylchromium Reagents in Homoallyl Alcohol Synthesis

Organochromium compounds prepared from halides and Cr(II) species in anhydrous, aprotic, polar solvents provide means of selective synthesis as has been described previously (1,2). In particular, the Grignard type carbonyl addition of allylchromium reagents proceeds much more slowly and selectively than that of organomagnesium compounds.
　　　Scheme 1 indicates <u>threo</u> selectivity in the reaction of

Scheme 1

R	Solvent[a]	Yield (%)	threo (%)	erythro (%)
Ph	THF	96	100	0
Ph[b]	THF	87	100	0
Ph	DMF	92	75	25
n-Pr	THF	59	93	7
i-Pr	THF	55	95	5
i-Pr	DMF	78	66	34
n-Am	THF	70	97	3
n-Am	DMF	77	68	32
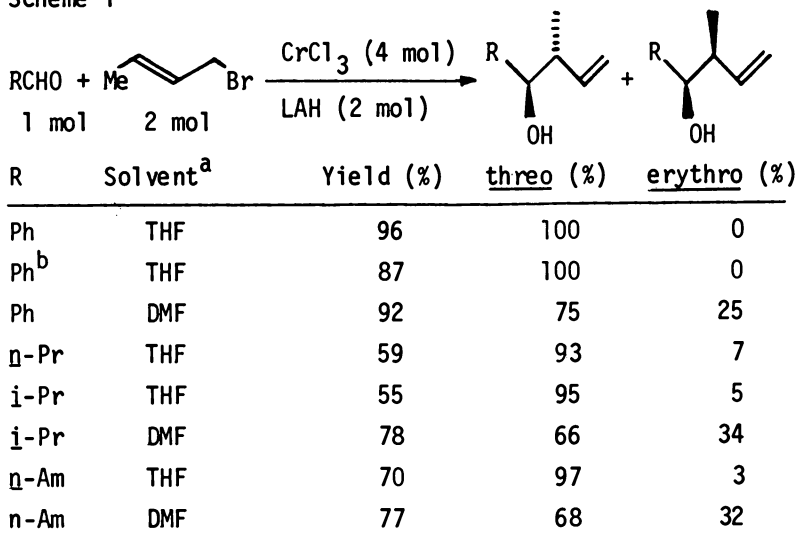
[a]The reaction was carried out at room temp for 2 h.
[b]The cis-isomer of crotyl bromide was used.

Scheme 2

Oxidant	Yield (%)	Isomer Ratio (%)
t-BuOOH/VO(acac)$_2$	52	76 : 24
t-BuOOH/Al(OBu-t)$_3$	51	18 : 82
mCPBA	69	55 : 45
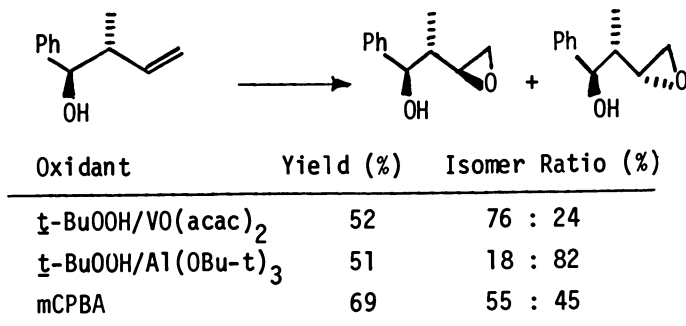
crotyl bromide (3) as reported also by Heathcock (4). Tetrahydro-
furan (THF) as solvent gives higher selectivities but somewhat
poorer yields than dimethylformamide (DMF). Epoxidation of the
resulting homoallylic alcohols has been investigated (Scheme 2).
The Sharpless and related epoxidation techniques (5,6) provide a
way to control the stereochemistry of three neighboring carbons.
The Cr(II) mediated reaction has been extended further to systems
involving aldehydes and 2,2-diiodopropane (with HI loss) as well
as vinyl iodides and bromides, all affording allylic alcohols (7).

## Alkylation of an sp^3 Carbon with Trialkylaluminum

The reaction of diethyl geranyl phosphate with R$_3$Al produces
quantitatively a mixture of geranyl-R and linalyl-R products in 9:1
ratio, while the corresponding neryl phosphate affords 4-RCMe$_2$-
substituted 1-methylcyclohexenes exclusively (8). Evidence for
the intermediacy of a carbocation species in the related reaction
shown in Scheme 3 is derived from the fact that the optical ac-
tivity of the starting acetate substrate is completely lost in the
ring cleavage reaction product (9,10). A possible explanation is
given in Scheme 4. Throughout these and subsequent reactions we
use no less than a 2:1 mol ratio of aluminum reagents which are
mostly dimeric. We postulate that the leaving acetate group is
substantially reduced in nucleophilicity by double complexation
with R$_3$Al, so that the cationic part is almost naked even in the
early ion-pair stage. The cyclopropylmethyl cation is isomerized
to the more stable benzylic one which is then slowly alkylated by
the complex anion part. It should be noted that the anionic com-
plex, but not the Lewis acid itself, participates in this key
step. Thus the R$_3$Al reagent may be called a "combined acid-base."
In sharp contrast, however, Scheme 5 gives an instance of a
methyl carbanion being introduced largely in an S$_N$2-type inversion
stereochemistry. Note that the substrate carries a cyclopropane
carbon doubly activated by 1,3-dicarbonyl groups. A possible ex-
planation is given in Scheme 6. The reaction can be utilized in
the selective synthesis of dl-neonepetalactone and its epimer.
The sequence involves (1) enolization (NaH) and phosphorylation
(ClPO(OEt)$_2$), (2) methylation (Me$_2$CuLi), (3) ozonolysis (MeOH,
-78°) and reduction, and (4) the final lactonization (PyH.OTs).

Alkylation of an sp^2 Carbon with the R$_3$Al-Pd(0) System

The methylation [step (2)] in the above sequence proceeds
smoothly due to the presence of an ethoxycarbonyl activating
group. A new technique (11) is based on the catalysis by a Pd(0)
complex and provides a methodology of alkyl substitution of an
enol phosphate moiety in the absence of such an activating group.
The results are given in Table 1. As the enolization of ketones
can be performed regioselectively, the technique furnishes an ap-
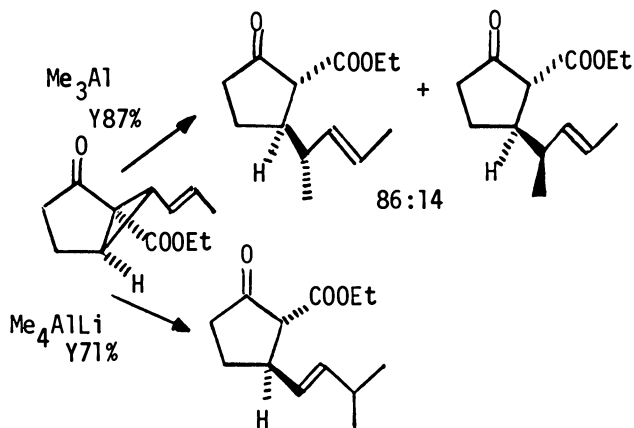proach to regioselective olefin formation from ketones.

Scheme 3

$$[\alpha] = 0°$$

Scheme 4

Scheme 5

86:14
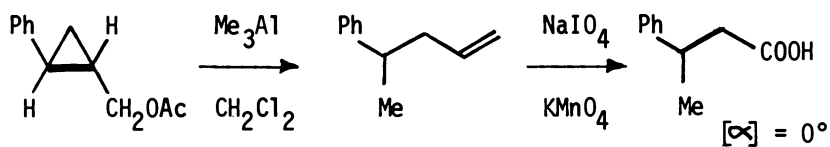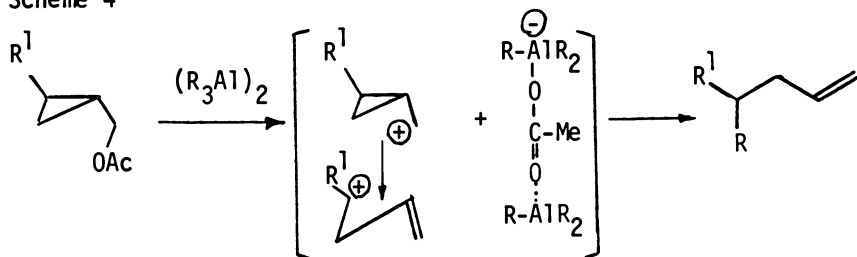
Scheme 6
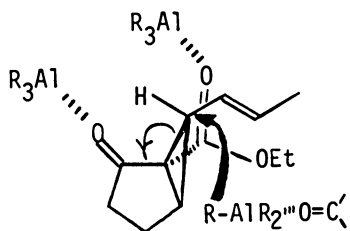
Table 1. Coupling on an sp^2 Carbon

Substrate	Reagent[a]	Time (h)	Product Y (%)
Me(CH$_2$)$_9$C(=CH$_2$)-OPO(OPh)$_2$	Me$_3$Al	2	91
	Et$_3$Al	3	71
	Me(CH$_2$)$_4$C≡CAlEt$_2$	3	47[b]
	PhC≡CAlEt$_2$	2	82[b]
	(E)-1-heptenylAlBu^i$_2$	4	66[c]
PhC(=CH$_2$)-OPO(OPh)$_2$	Me$_3$Al	2	94[d]
	Et$_3$Al	2	80
	PhC≡CAlEt$_2$	3	67[b]
4-t-Bu-1-cyclohexenyl-OPO(OPh)$_2$	Me$_3$Al	5	72
	PhC≡CAlEt$_2$	6	70[b]

[a]Pd(PPh$_3$)$_4$ 0.1/ClCH$_2$CH$_2$Cl at 25°.   [c](E)-Diene product only.

[b]Enyne product exclusively.   [d]G.l.p.c. yield.

In contrast to the analogous sp[2] carbon alkylation procedures (12,13), the present method does not affect coexisting vinyl sulfide groups as shown in Scheme 7 (14). This reaction provides access to ketones R'CH$_2$COR starting from R'CH$_2$COOH. Yields in parentheses indicate the formation of ethylated (R = Et) plus hydrogenated (R = H) products in the reaction of Et$_3$Al. In benzene solvent the ratio of these two products is roughly 2:1. In hexane the hydrogenated products are predominant.

Scheme 8 shows the synthesis of 1,3-dialkylated cyclohexenes from 2-cyclohexenones consisting of 1,4-addition of organocuprates, enol phosphorylation, and the final alkylation of the sp[2] carbon. Scheme 9 provides a novel addition to the technique of 1,2-transposition of a carbonyl moiety accompanied by alkylation in tandem (15). The desulfurization is best performed by Mukaiyama's TiCl$_4$ method (16).

Treatment of an enone, PhCOCH=CHMe, with RSLi (R = Ph, Et) and subsequent phosphorylation with ClPO(OPh)$_2$ give PhC[OPO(OPh)$_2$]=CH-CHSR-Me. The phosphate group is substituted by methyl by means of the present technique to produce PhCMe=CH-CHSR-Me, the transformation of which into PhCMe=CHCOMe is known (17). In effect the sequence furnishes a new route of 1,3-carbonyl transposition cum alkylation.

Aliphatic Claisen Rearrangement at Room Temperature

Sigmatropic rearrangement of allyl vinyl ether substrates usually requires heating at around 200°. Allyl phenyl ether rearranges at room temperature in the presence of Lewis acid reagents, which have, however, turned out to be ineffective with aliphatic ethers. The concept of "combined acid-base attack" previously mentioned (18,19) has motivated several successful experiments as shown in Schemes 10 through 12 (20).

A solution of Me$_3$Al in hexane (1 M, 4.0 mmol) was added to a solution of 1-butyl-2-propenyl vinyl ether (2.0 mmol, Scheme 10) in 1,2-dichloroethane (15 ml) at 25° under an Ar atmosphere and the mixture was stirred for 15 min. Workup and TLC (SiO$_2$) purification gave the olefinic alcohol (0.28 g, 91% yield), the E/Z ratio being almost 1:1.

As shown in Scheme 10 (b,c) an alkynyl or alkenyl group is introduced in preference to an alkyl group. Examples of reductive rearrangement are found in Scheme 11. With exception of a single instance producing a 2-phenylethenyl system, the resulting olefinic linkage has shown practically no stereoselectivity. The regular Claisen products, or γ,δ-unsaturated aldehydes, have been produced in the reaction with R$_2$AlSPh as summarized in Scheme 12. A combination of acid (Et$_2$AlCl) and base (PPh$_3$) has turned out to be effective. It is intriguing to note that the rearrangement of 3,4-dihydro-2-vinyl-2H-pyran affording 3-cyclohexenecarbaldehyde (60% yield) takes place in the presence of this couple at room temperature within one hour. The pyrolytic procedure without

Scheme 7

$$R'CH=C \overset{OPO(OPh)_2}{\underset{SPh}{}} \longrightarrow R'CH=C \overset{R}{\underset{SPh}{}}$$
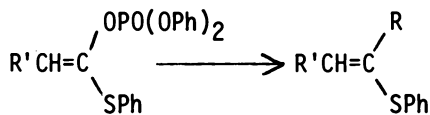
R'	R	Time (h)	Y (%)
Ph	Me	1	64
	Et	2	(55)[a]
n-Pr	Me	1	83
	Et	2	(82)[a]
	PhC≡C-	2	83

[a] A mixture of ethylation and hydrogenation product (see text).

Scheme 8

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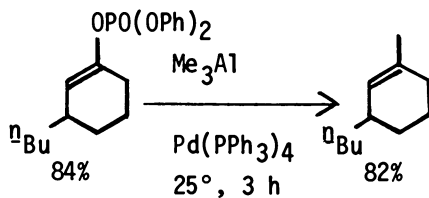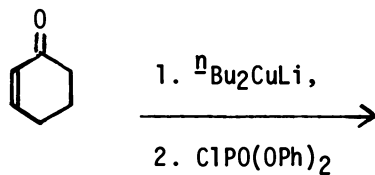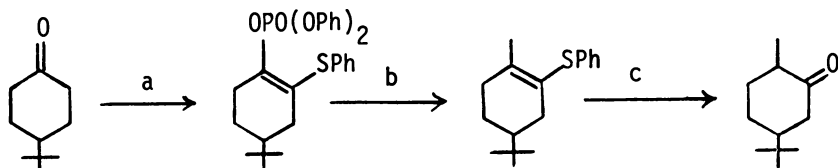
Scheme 9

a) 1. LDA/PhSSPh (Y78%), 2. NaH, ClPO(OPh)$_2$ (Y82%).

b) Me$_3$Al, Pd(PPh$_3$)$_4$ (Y80%). c) TiCl$_4$, aq, CH$_2$Cl$_2$ (Y78%).

Scheme 10

E/Z = 47/53
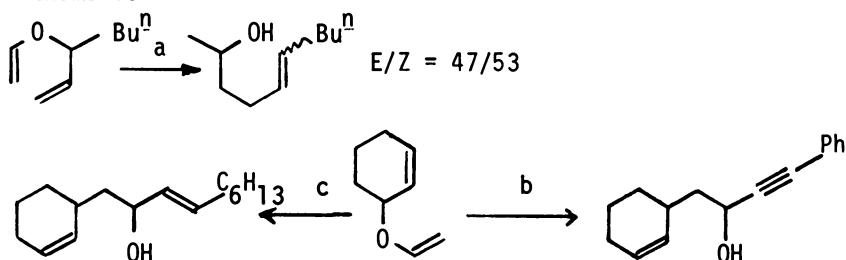
a) Me$_3$Al (Y91%). b) Et$_2$AlC≡CPh (Y82%). c) ^{i}Bu$_2$AlCH=CHC$_6$H$_{13}$-($\underline{E}$)

Scheme 11

R^1	R^2	Reagent	Y(%)	$\underline{E}$/$\underline{Z}$
^{n}Bu	H	A	82	38/62
^{n}Bu	H	B	80	40/60
^{n}Bu	Me	A	89	45/55
Ph	H	A	93	100/0
H	Ph	A	91	---
		A	90	---

A: ^{i}Bu$_3$Al (2.6).

B: ^{i}Bu$_2$AlH (2.5).

Scheme 12

R^1	R^2	Reagent	Y(%)	$\underline{E}$/$\underline{Z}$
^{n}Bu	H	A	84	39/61
^{n}Bu	H	B	81	43/57
^{n}Bu	Me	A	77	52/48
Ph	H	A	67	100/0
H	Ph	A	86	---
		A	78	---
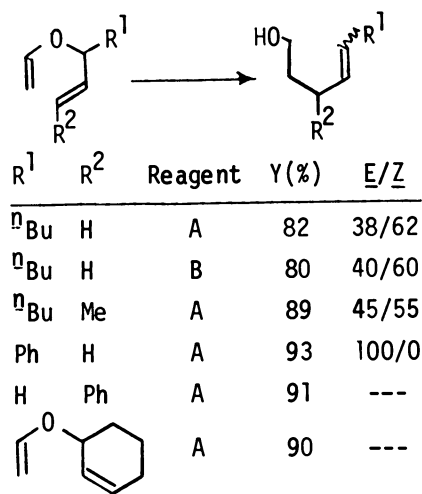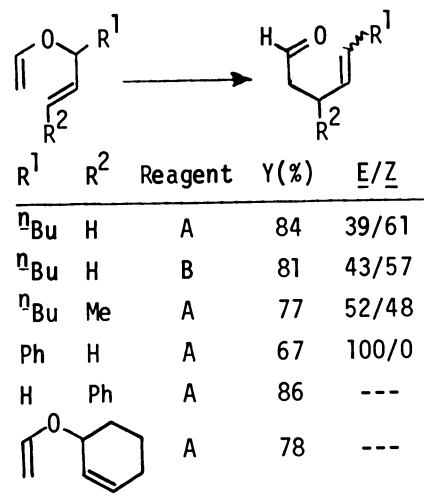
A: Et$_2$AlSPh (2.5).

B: Et$_2$AlCl (2) + PPh$_3$ (2.2).

such a reagent requires heating at 410°. The Et_2AlCl/PPh_3 system
can be compared with Mukaiyama's $R_2BOSO_2CF_3/NR'_3$ system (<u>21</u>) or
with Tsuji's R_2AlOR'/NR''_3 system (<u>22</u>). The possibility of an
$Et_2AlP^+Ph_3$ species being the active reagent in our reaction will
be investigated.

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Novel Approaches to the Asymmetric Synthesis of Peptides

IWAO OJIMA

Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan

A variety of dehydrodipeptides (N-protected free acids or methyl esters) have been hydrogenated with homogeneous rhodium catalysts bearing a variety of chiral diphosphine ligands. Diastereomer excess is frequently above 95%. The stereoselectivity of the reaction is, in a number of instances, quite different from that in hydrogenation of N-acyldehydro-amino acids. The synthesis of acylphenylalanyl-α,β-d_2-alanine methyl ester as a nearly pure diastereomer (and enantiomer) is described.

Dipeptides have also been synthesized by cyclo-addition of azidoketene (formed in situ from azido-acetyl chloride) to t-butyl esters of α-amino acids to give β-lactams which are then chromatographically resolved into diastereomers and cleaved by mild hydrogenolysis over palladium. By an extension of this method, tri-, tetra- and higher oligopeptides can be obtained. A salient feature is the high solubility of the β-lactam intermediates in common organic solvents which facilitates chromatographic purification. By an adaptation of this method, Leucine-Enkephalin (Tyr-Gly-Gly-Phe-Leu) t-butyl ester hydrochloride and its analog have been synthesized.

Peptide linkages are generally formed by the coupling of two optically active amino acid components through acyl chloride, acyl azide, mixed anhydride, carbodiimide, or enzymatic methods. These methods have been developed for the synthesis of naturally occurring polypeptides with minimum racemization. Recently, it has been shown that significant modifications of biological activities can be effected through inversion of configuration at one or more chiral centers, or through replacement of one or more "natural" amino acid residues by "unnatural" amino acid components in a bio-
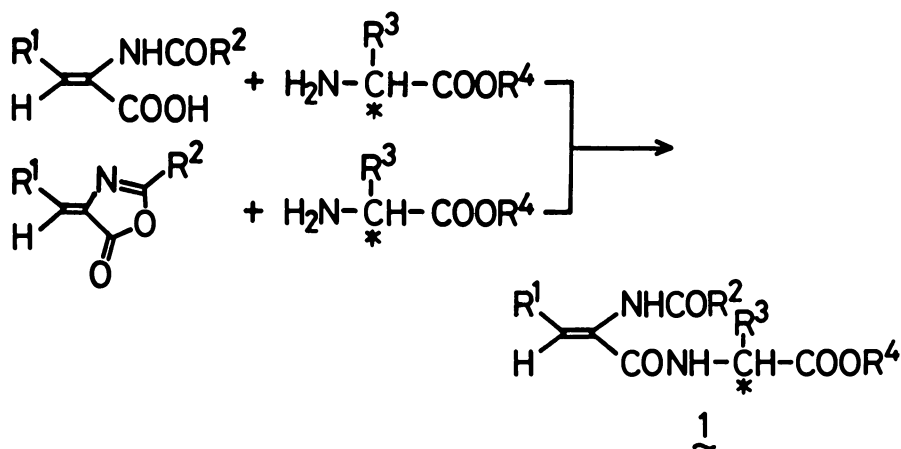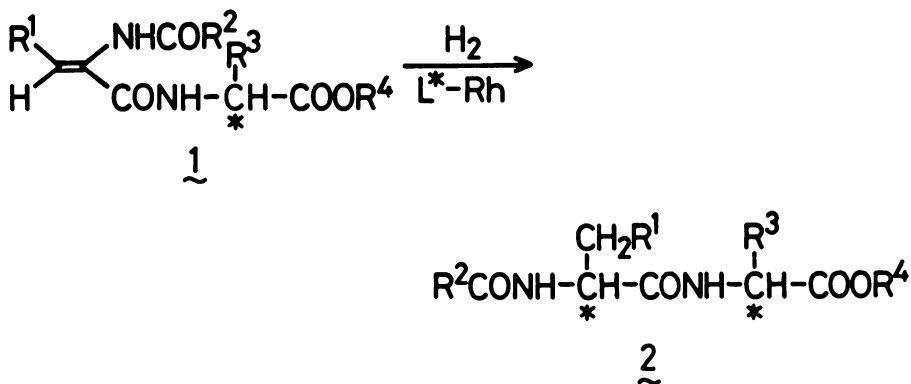
logically active polypeptide such as Enkephalin, Vasopressin, Angiotensin II, Gonadoliberin and other hormones (1). In order to obtain such synthetic polypeptides by the conventional methods mentioned above, it is indispensable to prepare chiral amino acids with "unnatural" configuration or "unnatural" substituents. As an approach to the synthesis of chiral oligo- and polypeptides with desired structures, we have been trying to develop facile approaches to obtaining chiral building blocks. We will describe here such approaches involving i) catalytic asymmetric hydrogenation, and ii) the use of β-lactams as synthetic intermediates.
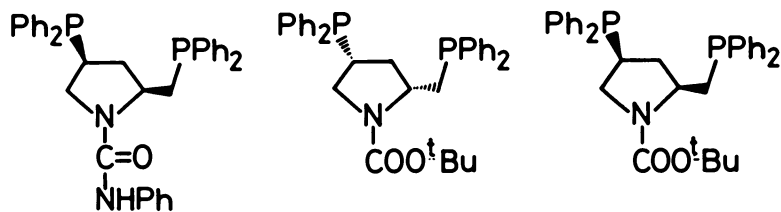
Synthesis of Chiral Dipeptides by Means of Asymmetric Hydrogenation of Dehydrodipeptides

As precursors of modified peptides, naturally occurring dehydropeptides may be interesting candidates since catalytic asymmetric hydrogenation can, in principle, convert the dehydroamino acid residue into an amino acid residue with either R or S configuration. Indeed, the homogeneous asymmetric hydrogenation of dehydro-α-amino acids catalyzed by rhodium complexes with chiral diphosphine ligands has turned out to be quite effective for the synthesis of chiral α-amino acids (2). An interesting point in this reaction is whether the chiral center of the dehydrodipeptide exerts a strong influence on the asymmetric induction, i.e., whether the optical purity of the newly formed chiral center is or is not affected by the already existing chiral center, and whether, in fact, we can synthesize dipeptides having the desired configurations.

N-acyldehydrodipeptides were readily prepared either by the condensation of N-acyldehydro-α-amino acids with α-amino acid esters or by the reaction of the azlactones of dehydro-α-amino acid with α-amino acid esters (eq. 1). Asymmetric hydrogenation of the N-acyldehydrodipeptides thus obtained (eq. 2) was carried out by using rhodium complexes with a variety of chiral diphosphines such as p-Br-Phenyl-CAPP (3), Ph-CAPP (3), (-)BPPM (4), (+)BPPM (4), (-)DIOP (5), (+)DIOP (5), diPAMP (6), Chiraphos (7), Prophos (8), BPPFA (9) and CBZ-Phe-PPM (Fig. 1)(10). The chiral catalysts were prepared in situ from chiral diphosphine ligand with [Rh(NBD)$_2$]$^+$-ClO$_4^-$ (NBD = norbornadiene). Typical results are summarized in Tables I-V.

As Table I shows, the efficiency of each chiral diphosphine ligand exhibited in the asymmetric hydrogenation of dehydrodipeptides is considerably different from that reported for the reaction of N-acyldehydroamino acids, especially in the case of Chiraphos and BPPFA, which are known to lead to much better enantioselectivity than DIOP in the dehydroamino acid case (2, 7, 9). When Ac-ΔPhe-(S)Phe-OH was employed as substrate, Chiraphos induced S configuration (Entry 17) and BPPFA led to R configuration (Entry 19) with low stereoselectivities; in both cases, the directions of asymmetric induction are opposite to those observed for α-acet-
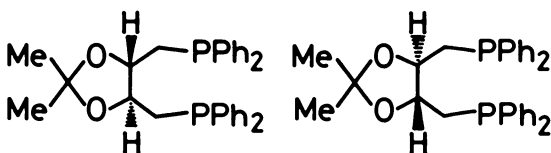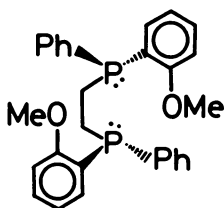
$$R^1 \diagup NHCOR^2 \diagdown COOH \quad + \quad H_2N-\overset{R^3}{\underset{*}{CH}}-COOR^4$$

$$R^1 \diagup \underset{O}{\overset{N}{\diagup}} R^2 \quad + \quad H_2N-\overset{R^3}{\underset{*}{CH}}-COOR^4$$

$$R^1 \diagup NHCOR^2 \diagdown CONH-\overset{R^3}{\underset{*}{CH}}-COOR^4$$

1

Equation 1.

$$R^1 \diagup NHCOR^2 \diagdown CONH-\overset{R^3}{\underset{*}{CH}}-COOR^4 \quad \xrightarrow[\text{L}^*-\text{Rh}]{\text{H}_2}$$

1

$$R^2CONH-\overset{CH_2R^1}{\underset{*}{CH}}-CONH-\overset{R^3}{\underset{*}{CH}}-COOR^4$$

2

Equation 2.

Ph-CAPP   **(+)BPPM**   **(−)BPPM**

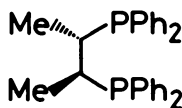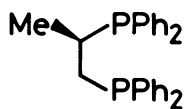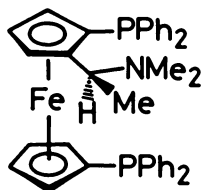**(+)DIOP**   **(−)DIOP**

diPAMP   **Chiraphos**

Prophos   **BPPFA**

Figure 1.   Typical chiral diphosphine ligands.

Table I. Efficiency of Chiral Diphosphine Ligands in the Asymmetric Hydrogenation of Typical Dehydrodipeptides[a]

Entry	Substrate	Ligand	Conditions (H_2 press., Temp., Time)			Conversion (%)[b]	Dipeptide (R,S)/(S,S)[b]
1	Bz–ΔPhe–(S)Phe–OMe	p-Br-phenyl-CAPP	1 atm,	40°C,	3h	100	99.2/0.8
2		(−)BPPM	1 atm,	40°C,	1h	100	98.7/1.3
3		(+)BPPM	1 atm,	40°C,	1h	100	0.9/99.1
4		(−)DIOP	5 atm,	25°C,	18h	100	84.1/15.9
5		(+)DIOP	5 atm,	25°C,	18h	100	15.0/85.0
6		diPAMP	10 atm,	50°C,	15h	100	2.2/97.8
7		Chiraphos	5 atm,	40°C,	10h	82	85.1/14.9
8		Prophos	5 atm,	40°C,	10h	99	4.1/95.9
9		BPPFA	5 atm,	40°C,	10h	51	18.7/81.3
10		dppb	1 atm,	40°C,	5h	85	37.8/62.2
11	Ac–ΔPhe–(S)Phe–OH	Ph–CAPP	5 atm,	40°C,	20h	100	98.0/2.0
12		(−)BPPM	10 atm,	50°C,	20h	100	96.2/3.8
13		(+)BPPM	10 atm,	50°C,	20h	97	0.6/99.4
14		(−)DIOP	5 atm,	40°C,	20h	100	81.8/18.2
15		(+)DIOP	5 atm,	40°C,	20h	89	5.9/94.1
16		diPAMP	5 atm,	50°C,	20h	86	1.4/98.6
17		Chiraphos	10 atm,	50°C,	20h	96	39.1/60.9
18		Prophos	10 atm,	50°C,	20h	95	18.8/81.2
19		BPPFA	50 atm,	50°C,	20h	23	61.2/38.8
20		dppb	10 atm,	50°C,	20h	99	34.1/65.9

a All reaction were run with 5.0×10^{-4} mol of the substrate and 5.0×10^{-6} mol of the catalyst.
b Determined by HPLC.

amidocinnamic acid.   Prophos induced high stereoselectivity
with Bz-ΔPhe-(S)Phe-OMe (Entry 8) whereas it was no longer a very
good chiral ligand for Ac-ΔPhe-(S)Phe-OH (Entry 18). Pyrrolidino-
diphosphines and diPAMP achieved extremely high stereoselectivi-
ties. There seems to be a trend that the chiral ligands which
form seven membered ring chelates with rhodium give rise to much
better results than those forming rigid five membered ring chelates
or quasi five membered ring chelates except diPAMP. The results
may imply that the seven membered ring chelate has flexibility for
"induced-fit" action like an enzyme, which is quite an important
factor for a chiral complex catalyst when the substrate is poly-
functional (11).
     As for the influence of the chiral center in the substrate on
asymmetric induction, considerable double asymmetric induction was
observed on using a dehydrodipeptide bearing a free acid terminus
such as Ac-ΔPhe-(S)Phe-OH (see Entry 12, 13, and 14, 15). To re-
alize the extent of double asymmetric induction in a quantitative
manner, one has to look not at the difference of the relative
amounts of diastereomers in percent but at the ratio of two diaste-
reomers, which is related to $\Delta\Delta G^{\ddagger}$: For BPPM, (R,S)/(S,S) = 25.3
(Entry 12, (-)BPPM), (S,S)/(R,S) = 165.7 (Entry 13, (+)BPPM); for
DIOP, (R,S)/(S,S) = 4.49 (Entry 14, (-)DIOP), (S,S)/(R,S) = 15.9
(Entry 15, (+)DIOP). Thus, the extent of double asymmetric induc-
tion turns out to be more pronounced for BPPM than for DIOP al-
though the apparent difference in optical purity is much smaller
for BPPM compared with that for DIOP. The results concerning the
double asymmetric induction indicate that the formation of the
(S,S)-isomer is preferred in these systems. An experiment using
an achiral diphosphine ligand, bis(diphenylphosphino)butane (dppb),
gave a consistent result (Entry 20), i.e. 31.8% asymmetric induc-
tion favoring the formation of the (S,S)-isomer of Ac-Phe-Phe-OH
was observed. On the other hand, when dehydrodipeptide methyl
esters were employed, only a slight effect of the existing chiral
center was observed as far as DIOPs were concerned, e.g., Bz-Phe-
Phe-OMe: (+)DIOP, (R,S)/(S,S) = 16.4/83.6, (-)DIOP, (R,S)/(S,S)
= 84.1/15.9; Ac-Phe-Phe-OMe: (+)DIOP, (R,S)/(S,S) = 19.4/80.6,
(-)DIOP, (R,S)/(S,S) = 81.6/18.4; Bz-Phe-Val-OMe: (+)DIOP, (R,S)/
(S,S) = 20.6/79.4, (-)DIOP, (R,S)/(S,S) = 83.0/17.0.
     The results could be interpreted by assuming exclusive coor-
dination of the N-acyldehydroamino acid moiety with the rhodium com-
plex in which the rest of the molecule, i.e. the α-amino ester moie-
ty, is located in the outer sphere of the chiral coordination site:
this may be the reason why virtually no double asymmetric induction
was observed. However, a simple asymmetric hydrogenation using
dppb as achiral ligand (Entry 10) disclosed preferential formation
of Bz-(S)Phe-(S)Phe-OMe with 24.4% asymmetric induction, which is
consistent with the result using Ac-ΔPhe-(S)Phe-OH as substrate
(Entry 20). Accordingly, it seems that the results of using DIOPs
are rather exceptional. In this context, we further looked at the
effect of the chiral center on the catalytic asymmetric induction

by using Ac-ΔPhe-(R)Phe-OMe and Ac-ΔPhe-(S)Phe-OMe as substrates, and CBZ-(S)Phe-PPM (3a), CBZ-(S)Val-PPM (3f) and CBZ-(S)Pro-PPM (3d) as chiral ligands for the cationic rhodium complex. The results are listed in Table II. As Table II shows, there is only a slight difference between the two substrates in percent asymmetric induction from a synthetic point of view, since the reactions achieve quite high stereoselectivities, yet there is a significant difference in $\Delta\Delta G^{\ddagger}$ since it is observed that the (R,R)/(S,R) ratio is three to four times larger than the (R,S)/(S,S) ratio in every case examined. Moreover, similar results were obtained in the asymmetric hydrogenation of Ac-ΔPhe-(R)Phe-OMe by using (−)BPPM and (+)BPPM as shown in Table III. Thus, the reaction using (−)-BPPM led to 99.6% production of Ac-(R)Phe-(R)Phe-OMe while that using (+)BPPM produced 98.5% of the (S,R)-isomer: (R,R)/(S,R) = 249 for (−)BPPM: (S,R)/(R,R) = 65.7 for (+)BPPM. Consequently, it may be said that there is a significant extent of double asymmetric induction for the reaction of dehydrodipeptide methyl esters, too, and the case of DIOP is rather exceptional.

Table III summarizes typical results for the asymmetric hydrogenation of a variety of N-acyldehydrodipeptides with pyrrolidinodiphosphines and diPAMP. As Table III shows, (R,S), (S,S), (S,R) or (R,R)-dipeptides in high optical purities can be readily synthesized by using these chiral ligands, and, in one recrystallization, easily lead to optically pure dipeptides.

Since catalytic asymmetric hydrogenation can generate either S or R configuration at the position of the dehydroamino acid residue, this method could be potentially useful for the specific labeling of certain amino acid residues in a polypeptide. The regiospecific and stereoselective labeling of an amino acid residue is difficult to achieve with the conventional stepwise peptide synthesis. We carried out the dideuteration of Ac-ΔPhe-(S)Ala-OMe with the use of the cationic rhodium complexes with (−)BPPM and (+)BPPM (Scheme 1), which gave Ac-(R,R)Phe(d₂)-(S)Ala-OMe [(R,R,S)/(S,S,S) = 98.7/1.3] and Ac-(S,S)Phe(d₂)-(S)Ala-OMe [(R,R,S)/(S,S,S) =0.5/99.5], respectively, without any scrambling of deuterium.

As it has been shown that the introduction of deuterium at the chiral center of certain amino acids, e.g., 3-fluoro-2-deuterio-(R)-alanine, changes biological activity remarkably (12), this stereoselective dideuteration may provide a convenient device for this kind of modification of biological activity.

Since pyrrolidinodiphosphines, e.g., Ph-CAPP, p-Br-Phenyl-CAPP and BPPM, gave excellent stereoselectivities, we prepared a series of new chiral pyrrolidinodiphosphines, in which the nitrogen atom of PPM (4, 11) is linked up with a variety of α-aminoacyl groups. The rhodium complexes with these ligands may serve as good biomimetic models of reductase when they are anchored on polymers especially polyamides. α-Aminoacyl-PPMs (3) were prepared by the condensation of PPM with an N-CBZ-α-amino acid or an N-CBZ-dipeptide in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenztriazole (HOBT)(eq. 3).

Table II. Effect of Chiral Center in Dehydrodipeptides on Stereoselectivity[a]

Entry	Ligand	Substrate	Ac-Phe-Phe-OMe (R,S)/(S,S)[b]	or (R,R)/(S,R)[b]
1	CBZ-(S)Phe-PPM(3a)	Ac-ΔPhe-(S)Phe-OMe	98.0/2.0	
2	CBZ-(S)Phe-PPM(3a)	Ac-ΔPhe-(R)Phe-OMe		99.5/0.5
3	CBZ-(S)Pro-PPM(3d)	Ac-ΔPhe-(S)Phe-OMe	98.1/1.9	
4	CBZ-(S)Pro-PPM(3d)	Ac-ΔPhe-(R)Phe-OMe		99.5/0.5
5	CBZ-(S)Val-PPM(3f)	Ac-ΔPhe-(S)Phe-OMe	98.9/1.1	
6	CBZ-(S)Val-PPM(3f)	Ac-ΔPhe-(R)Phe-OMe		96.2/3.8

[a] All reactions were run with 5.0×10^{-4} mol the substrate and 5.0×10^{-6} mol of the catalyst at 40°C and 1 atm of hydrogen for 2h. Conversion was 100% for every case examined.
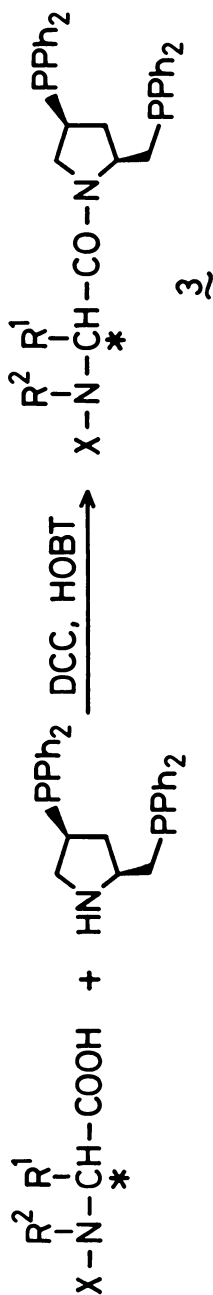
[b] Determined by HPLC.

Table III. Typical Results on the Asymmetric Hydrogenation of Dehydrodipeptides

Substrate	Ligand	Conditions (H$_2$ press., Temp., Time)	Conversion (%)	Dipeptide (R,S)/(S,S)[a] or (R,R)/(S,R)[b]
Bz-ΔPhe-(S)Phe-OMe	p-Br-phenyl-CAPP	1 atm, 40°C, 3h	100	99.2/0.8
	(+)BPPM	1 atm, 40°C, 1h	100	0.9/99.1
Bz-ΔPhe-(S)Val-OMe	p-Br-phenyl-CAPP	10 atm, 40°C, 20h	100	98.0/2.0
	diPAMP	10 atm, 40°C, 24h	100	1.0/99.0
Ac-ΔPhe-(S)Phe-OMe	Ph-CAPP	1 atm, 40°C, 46h	100	99.0/1.0
	(+)BPPM	1 atm, 40°C, 1h	100	0.6/99.4
Ac-ΔPhe-(S)Phe-OH	Ph-CAPP	5 atm, 40°C, 20h	100	98.0/2.0
	(+)BPPM	10 atm, 40°C, 20h	100	0.6/99.4
Ac-ΔPhe-(S)Val-OH	Ph-CAPP	10 atm, 50°C, 20h	100	96.3/3.7
	diPAMP	10 atm, 50°C, 20h	100	3.0/97.0
Bz-ΔLeu-(S)Phe-OMe	(-)BPPM	1 atm, 40°C, 24h	100	95.3/4.7
	(+)BPPM	1 atm, 40°C, 16h	100	3.6/96.4
Ac-ΔPhe-(R)Phe-OMe	(-)BPPM	1 atm, 40°C, 2h	100	99.6/0.4[b]
	(+)BPPM	1 atm, 40°C, 2h	100	1.5/98.5[b]
Ac-ΔPhe-(R)Phy-OMe	(-)BPPM	5 atm, 40°C, 24h	100	95.7/4.3[b]
	diPAMP	10 atm, 40°C, 24h	100	2.6/97.4[b]
Bz-ΔPhe-(R)Phe-OMe	CBZ-(S)Phe-PPM	1 atm, 40°C, 1h	100	99.5/0.5[b]
Ac-Δ(Ac)Tyr-(R)Ala-OMe[c]	Ph-CAPP	5 atm, 40°C, 24h	100	99.8/0.2[b]
Ac-Δ(AcO)(MeO)Phe-(R)Ala-OMe[d]	Ph-CAPP	5 atm, 40°C, 24h	100	99.4/0.6[b]
Ac-Δ(F)Phe-(S)Leu-OMe[e]	(+)BPPM	5 atm, 40°C, 64h	100	0.9/99.1

a Determined by HPLC. (R,S)/(S,S) unless otherwise noted. b (R,R)/(S,R). c (Ac)Tyr = 4-acetoxy-tyrosyl. d (AcO)(MeO)Phe = 3-methoxy-4-acetoxyphenylalanyl. e (F)Phe = 4-fluorophenylalanyl.

Scheme 1.

$$X-N-CH-COOH \quad + \quad HN \xrightarrow[\text{DCC, HOBT}]{} \quad X-N-CH-CO-N$$

(with R^2, R^1 substituents; PPh$_2$-substituted pyrrolidine)

3

3a	$R^1 = PhCH_2$, $R^2 = H$, $X = CBZ$:	CBZ-(S)Phe-PPM
3b	$R^1 = Me$, $R^2 = H$, $X = CBZ$:	CBZ-(S)Ala-PPM
3c	$R^1 = Me$, $R^2 = H$, $X = CBZ$:	CBZ-(R)Ala-PPM
3d	$R^1, R^2 = (CH_2)_3$, $X = CBZ$:	CBZ-(S)Pro-PPM
3e	$R^1, R^2 = (CH_2)_3$, $X = CBZ$:	CBZ-(R)Pro-PPM
3f	$R^1 = ^iPr$, $R^2 = H$, $X = CBZ$:	CBZ-(S)Val-PPM
3g	$R^1 = R^2 = H$, $X = CBZ$:	CBZ-Gly-PPM
3h	$R^1 = ^iPr$, $R^2 = CBZ-(S)Phe$, $X = H$:	CBZ-(S)Phe-(S)Val-PPM
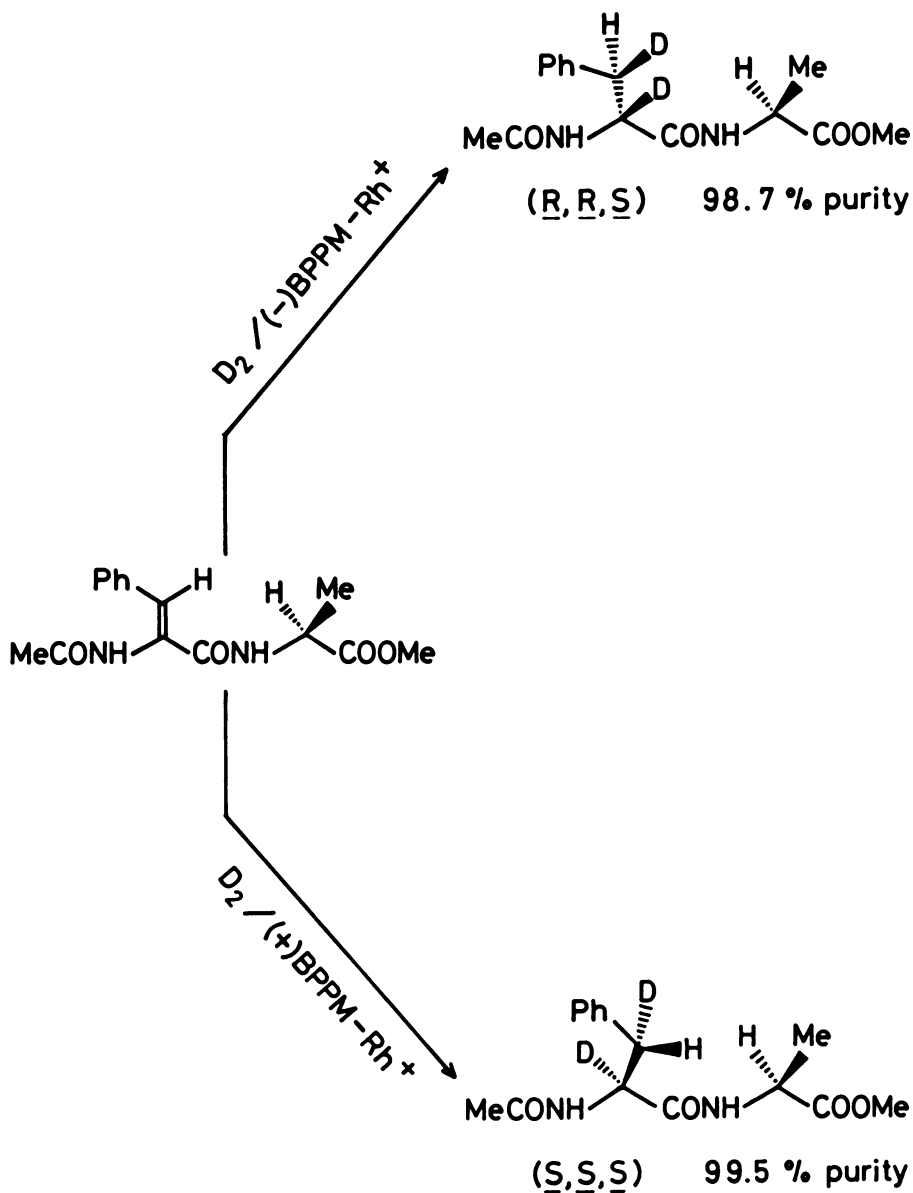
Equation 3.

Typical results on using Bz-ΔPhe-(S)Phe-OMe as substrate are listed in Table IV. Table V summarizes the results on using CBZ-(S)Phe-PPM (3a) as chiral ligand for the reaction of several de-hydrodipeptides. As Table IV shows, (i) the stereoselectivities attained by these α-aminoacyl-PPMs are as high as by other pyr-rolidinodiphosphines, and (ii) there is no significant difference in stereoselectivity by changing the amino acid residue except in the case of CBZ-(R)Pro-PPM (3e), which shows lower stereoselectiv-ity and a lower hydrogenation rate than CBZ-(S)Pro-PPM (3d) and other α-aminoacyl-PPMs. It should be noted that the reaction rate is considerably higher than that realized by other pyrrolidinodi-phosphines such as Ph-CAPP and BPPM. These results may indicate a promising activity of the corresponding polymer anchored catalyst.

Peptide Synthesis by the Use of β-Lactams as Building Blocks

Although synthesis of β-lactams has been extensively studied in connection with the naturally occurring antibiotics, little at-tention has been paid to the β-lactam ring as a synthetic inter-mediate. The cleavage of β-lactam rings usually takes place at the N–C(O) bond (type a), e.g., hydrolysis gives α-amino acids. How-ever, conceptually, other types of cleavage are possible, i.e., cleavage at N–C^4, C^3–C^4, C^2–C^3 or metathesis (Scheme 2).

Among these possibilities, we found that exclusive cleavage of the N–C^4 bond (type b) takes place in a palladium catalyzed hydrogenolysis when an aryl substituent was attached to C^4 (13). For instance, 1-(1-methoxycarbonyl-1-phenyl)methyl-3-benzyloxy-4-phenylazetidin-2-one (Scheme 3) has three benzylic positions capa-ble of being cleaved. It is well known that the cleavage of the benzyl-oxygen bond is by far faster than that of the benzyl-nitro-gen bond; in particular, the benzyl-nitrogen bond in N-benzylamides can hardly be cleaved under ordinary conditions. It is therefore reasonable to anticipate that cleavage of the benzyl-oxygen bond will be the only reaction observed. To our surprise, however, the cleavage of the β-lactam ring was much faster than that of the benzyl-oxygen bond; the other benzyl-nitrogen bond remains intact as expected (14). The result clearly indicates that the ring strain of the β-lactam greatly accelerates the N–C^4 cleavage.

Metallic palladium was found to be an effective catalyst for the selective hydrogenolysis of the N–C^4 bond, whereas Rh-C, Pt-C, Ru-C, PdCl$_2$, PdCl$_2$(PhCN)$_2$, and Pd(PPh$_3$)$_4$ were inactive. Raney-Ni showed some activity, but its activity and selectivity were by far lower than those found for palladium.

As 3-substituted-4-arylazetidin-2-ones can easily be synthe-sized by cycloaddition of a Schiff base to a ketene which is gen-erated in situ from an acyl chloride and triethylamine (15), the type b cleavage can serve as a new synthetic route to functiona-lized amides, α-amino acids and α-hydroxy acids (Scheme 4).

We carried out the asymmetric synthesis of an α-amino-carboxamide using (3,4-dimethoxyphenyl)methylidene-(R)-1-phenyl-

Table IV. Asymmetric Hydrogenation of Bz-ΔPhe-(S)Phe-OMe by Using α-Aminoacyl-PPMs (3) as Chiral Ligand[a]

| Entry	Ligand	Conditions (H$_2$ press., Temp., Time)	Conversion[b] (%)	Bz-Phe-Phe-OMe (R,S)/(S,S)[b]
1	CBZ-(S)Phe-PPM (3a)	1 atm, 40°C, 1h	100	98.0/2.0
2	CBZ-(S)Ala-PPM (3b)	1 atm, 40°C, 1h	100	97.7/2.3
3	CBZ-(R)Ala-PPM (3c)	1 atm, 40°C, 1h	100	97.6/2.4
4	CBZ-(S)Pro-PPM (3d)	1 atm, 40°C, 1h	100	98.1/1.9
5	CBZ-(R)Pro-PPM (3e)	1 atm, 40°C, 18h	100	83.0/17.0
6	CBZ-(S)Val-PPM (3f)	1 atm, 40°C, 1h	100	96.2/3.8
7	CBZ-Gly-PPM (3g)	1 atm, 40°C, 4h	100	97.8/2.2
8	CBZ-(S)Phe-(S)Val-PPM (3h)	1 atm, 40°C, 2h	100	96.4/3.6

a All reactions were run with 5.0 × 10^{-4} mol of the substrate and 5.0 × 10^{-6} mol of the catalyst in 15 mL of ethanol.

b Determined by HPLC.

Table V. Asymmetric Hydrogenation of Dehydrodipeptides by Using CBZ–(S)Phe–PPM (3a) as Chiral Ligand[a]

Entry	Substrate	Conditions (H$_2$ press., Temp., Time)			Conversion[b] (%)	Dipeptide (R,S)/(S,S)[b]
1	Ac–ΔPhe–(S)Phe–OMe	1 atm,	40°C,	2h	100	97.9/2.1
2	Bz–ΔPhe–(S)Val–OMe	1 atm,	40°C,	3h	100	98.2/1.8
3	Ac–ΔPhe–(S)Ala–OMe	1 atm,	40°C,	1h	99	98.3/1.7
4	Ac–ΔPhe–(S)Phe–OH	1 atm,	40°C,	3h	99	97.6/2.4
5	Ac–ΔPhe–(S)Val–OH	1 atm,	40°C,	24h	97	96.0/4.0

a All reactions were run with 5.0×10^{-4} mol of the substrate and 5.0×10^{-6} mol of the catalyst in 15 mL of ethanol.
b Determined by HPLC.
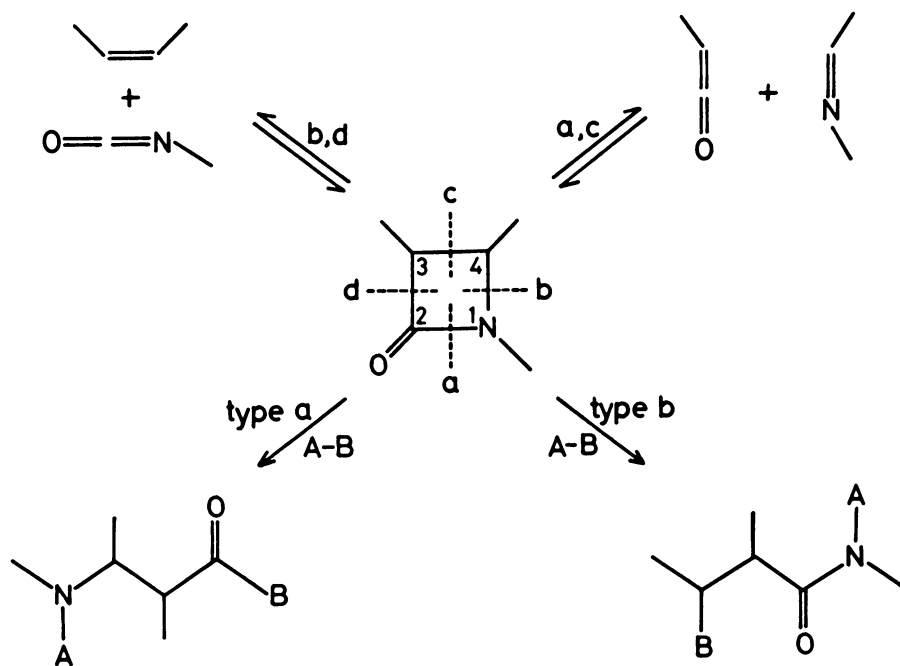
Scheme 2.
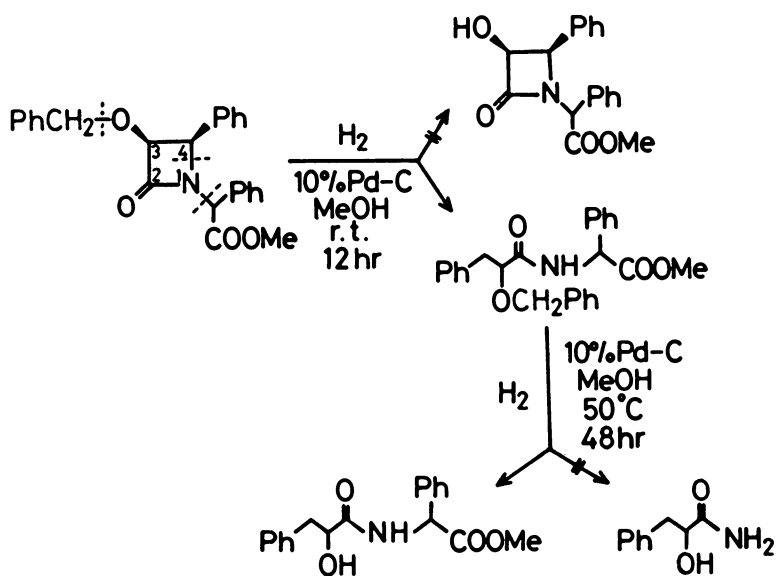
Scheme 3.
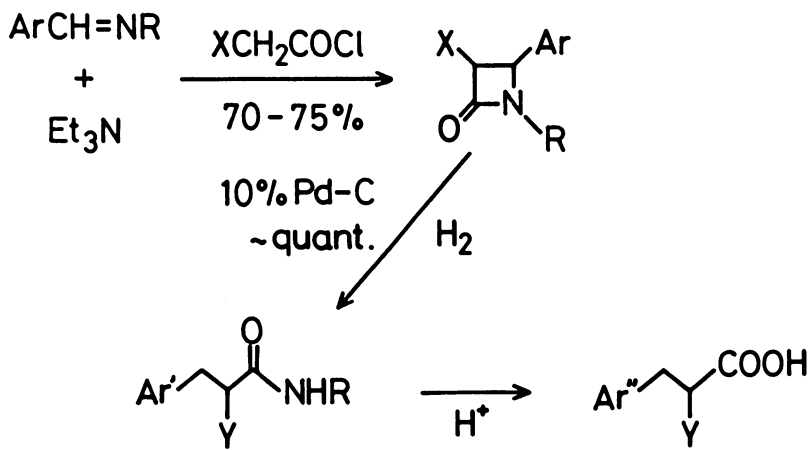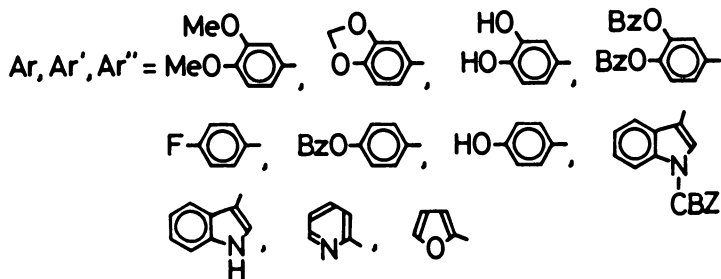
Scheme 4.

ethylamine as the Schiff base (13). The extent of chirality trans-
fer was 40%, the (3R,4R,1'R)-isomer being predominantly produced.
Hydrogenolysis of the resulting β-lactam afforded N-[(R)-1-phenyl-
ethyl]-2-amino-3-(3,4-dimethoxyphenyl)propionamide in 94% yield:
(2S,1'R)/(2R,1'R) = 70/30. The two diastereomers were readily
separated by column chromatography on silica gel. The (2S,1'R)-
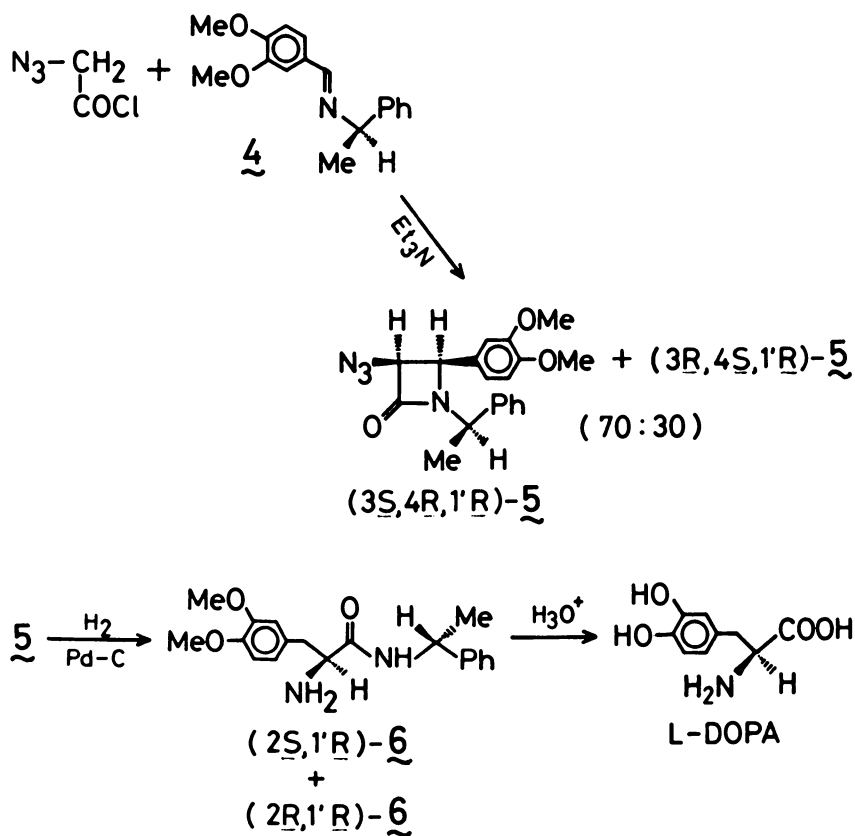isomer was easily hydrolyzed to give L-DOPA (Scheme 5).

In a similar manner, we synthesized dipeptides (Scheme 6) and
their hydroxy analogs (depsipeptide unit) (Scheme 7) starting from
the Schiff bases of α-amino acid esters (14). Optically pure di-
peptides were synthesized via separation of the two diastereomers
of the azido-β-lactam by HPLC as typified in Scheme 8. It turned
out that no racemization at all took place during the ring opening
(14).

Since a β-lactam derived from the Schiff base of an α-amino
acid ester was thus proved to be the synthetic equivalent of di-
peptide, we prepared tripeptide and tetrapeptide "synthons" in-
volving one or two β-lactams, which were further submitted to hy-
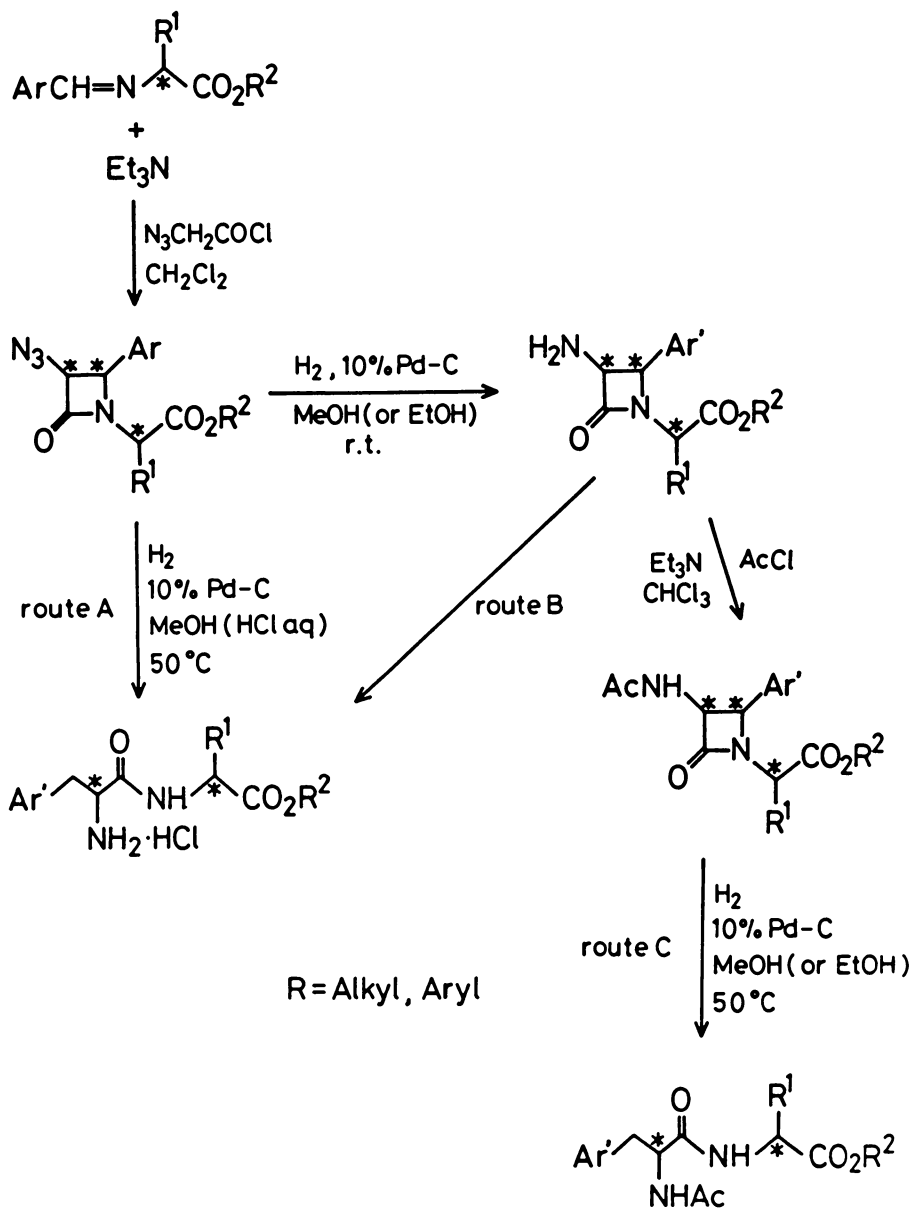drogenolysis to give the corresponding tri- and tetrapeptides
(Scheme 9)(16).

The tripeptide synthon (B) was prepared by the coupling of an
N-protected α-amino acid with an amino-β-lactam such as 8. The
tetrapeptide synthon (C) was obtained by the coupling of a β-lactam
carboxylic acid (9a) with an amino-β-lactam (8a) as typified in
Scheme 10. The tripeptide synthon (D) was prepared by azidoketene
cycloaddition to a β-lactam Schiff base such as 26 (Scheme 14).
The tandem style bis-β-lactam (C) was further transformed to a
tetra-β-lactam, which gave an octapeptide upon hydrogenolysis
(Scheme 11).

A striking feature of these di-, tri-, or tetrapeptide syn-
thons is that they are highly soluble in regular organic solvents
such as ether, ethyl acetate, chloroform etc., and even the octa-
peptide synthon is readily soluble in chloroform. Thus, these
compounds can be chromatographed on an ordinary silica gel column
in conventional fashion unlike other known peptide precursors.
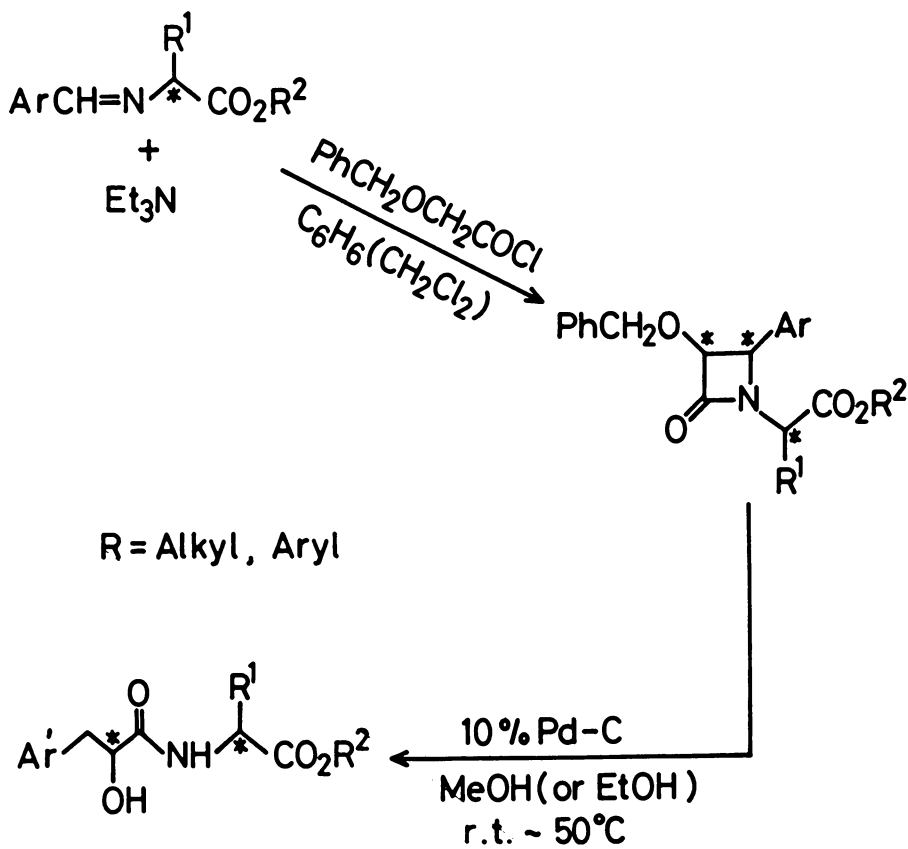This characteristic should provide an important advantage in pep-
tide synthesis.

The above-described "β-lactam method" has been applied to the
synthesis of Leucine-Enkephalin (Tyr-Gly-Gly-Phe-Leu) (17). We
prepared the Tyr-Gly synthon (15) and the Gly-Phe-Leu synthon (17)
following the procedure mentioned above, and coupled them by using
DCC, HOBT to give bis-β-lactam 18 (98%) (Scheme 12) in which two
β-lactams were connected with a Gly-Gly chain. This β-lactam
displayed a high solubility in common organic solvents, and was
purified by column chromatography on silica gel. The hydro-
genolysis of the bis-β-lactam on Pd-C in the presence of hydro-
chloric acid gave Leucine-Enkephalin t-butyl ester hydrochloride
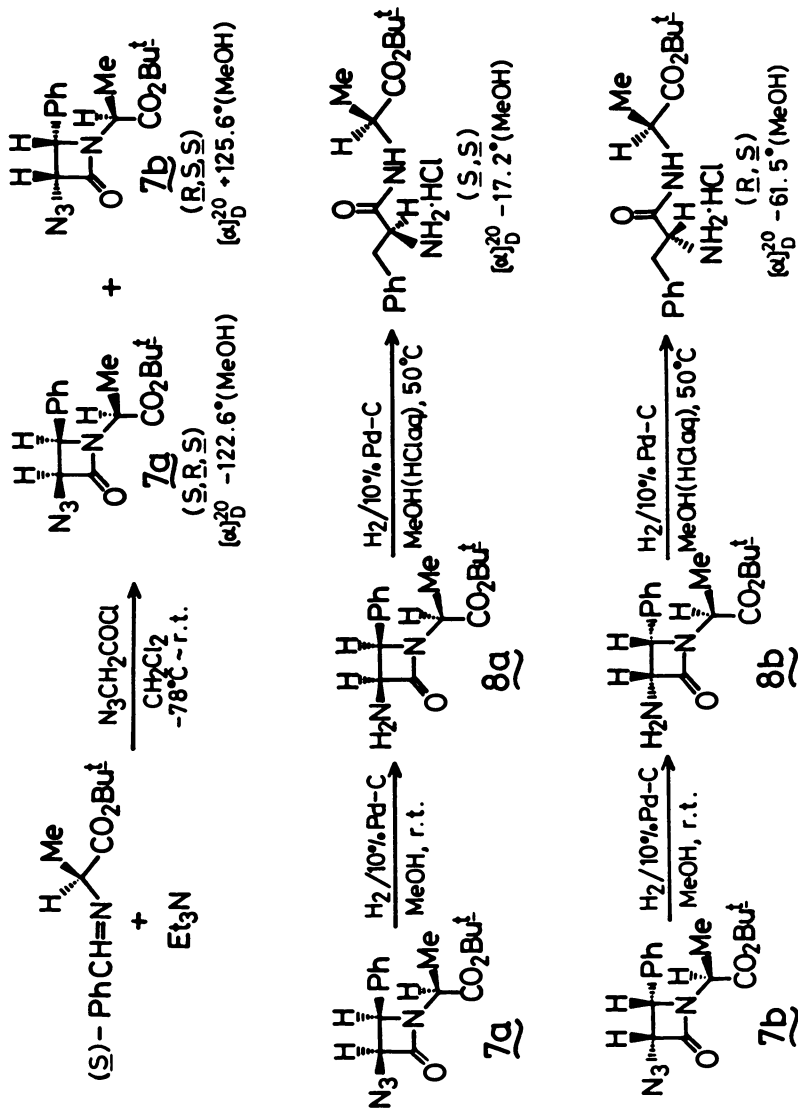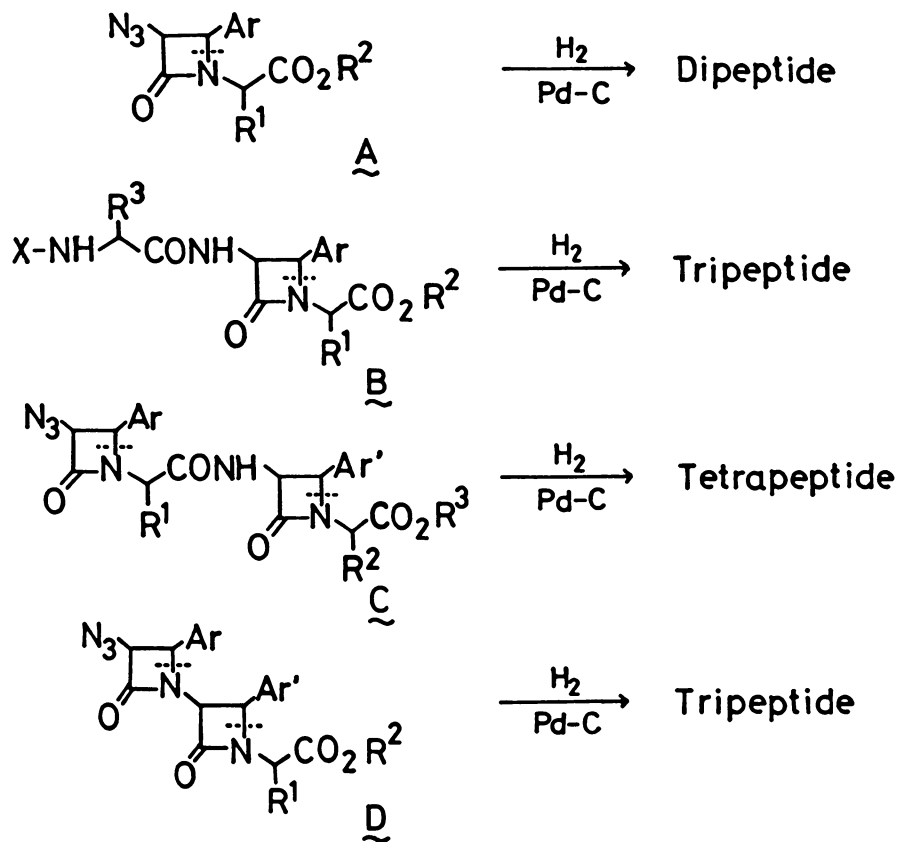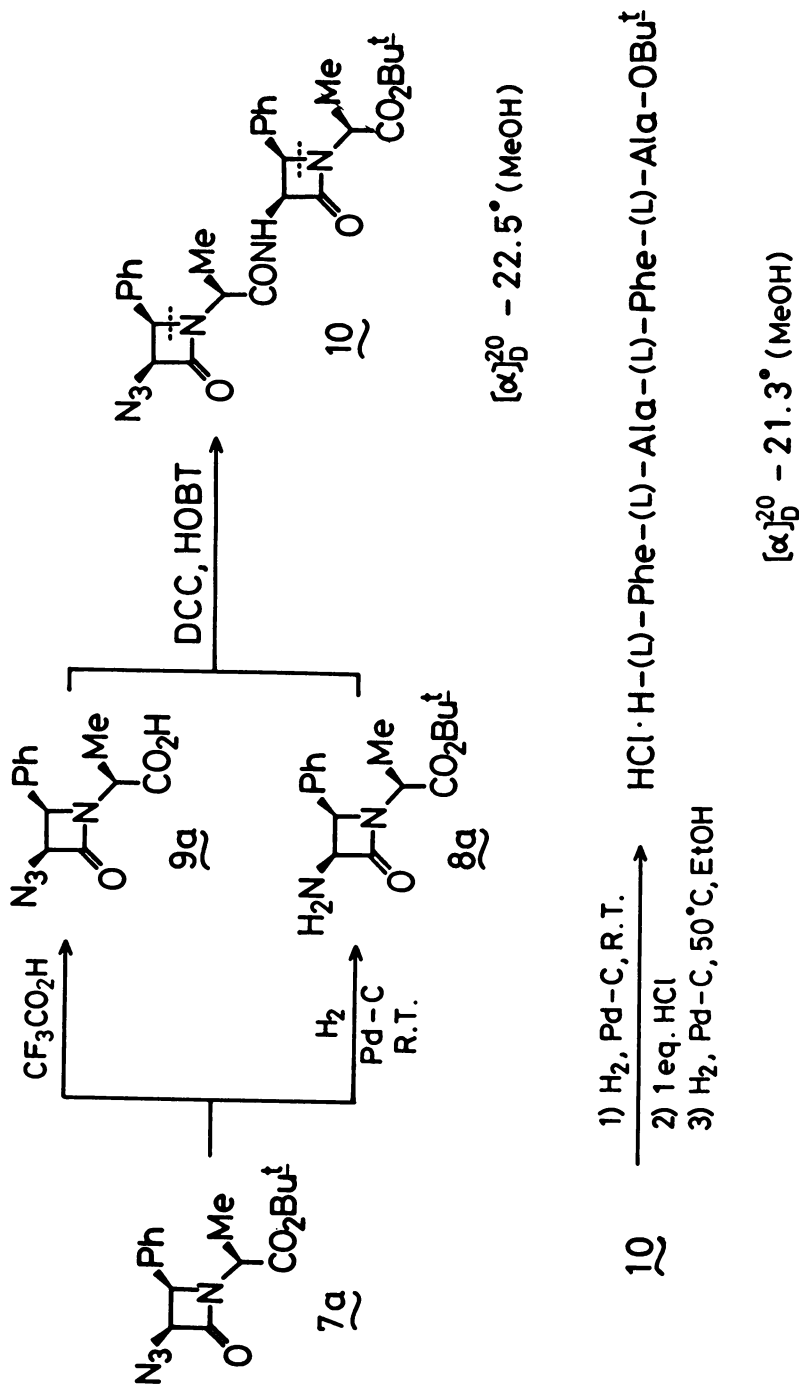(84%). In a similar manner, a Leucine-Enkephalin analog, (L)Tyr-

Scheme 5.

Scheme 6.

ArCH=N⁎CO₂R² with R¹

$$ArCH=N\overset{*}{}CO_2R^2$$

+

Et₃N

PhCH₂OCH₂COCl
C₆H₆(CH₂Cl₂)

PhCH₂O ⁎ ⁎ Ar
CO₂R²
R¹
(β-lactam with O and N)

R = Alkyl, Aryl

10% Pd–C
MeOH (or EtOH)
r.t. ~ 50°C

Ar′ ⁎ NH⁎ CO₂R²
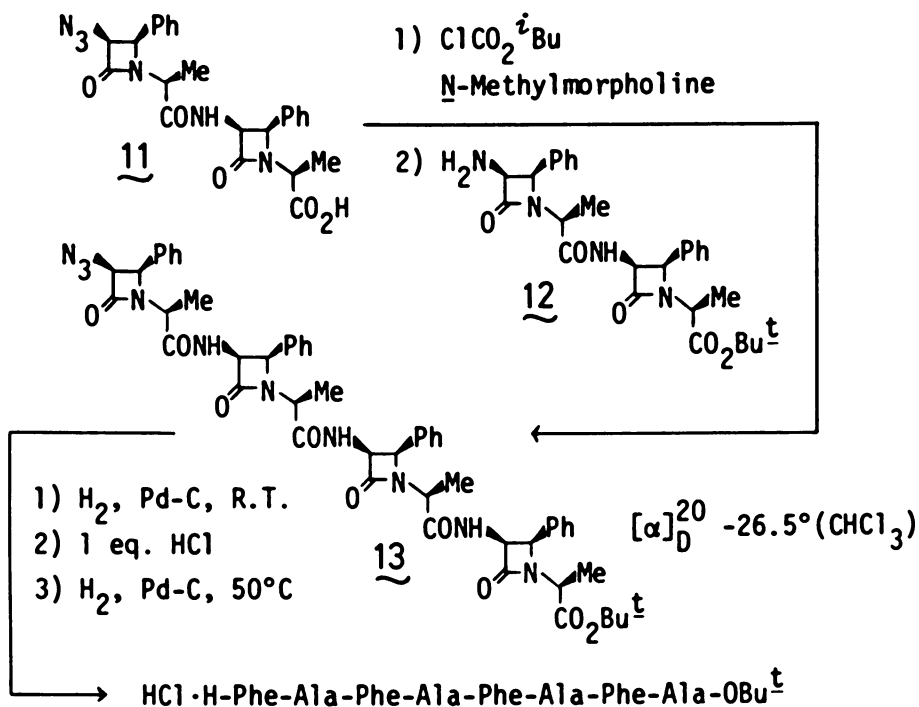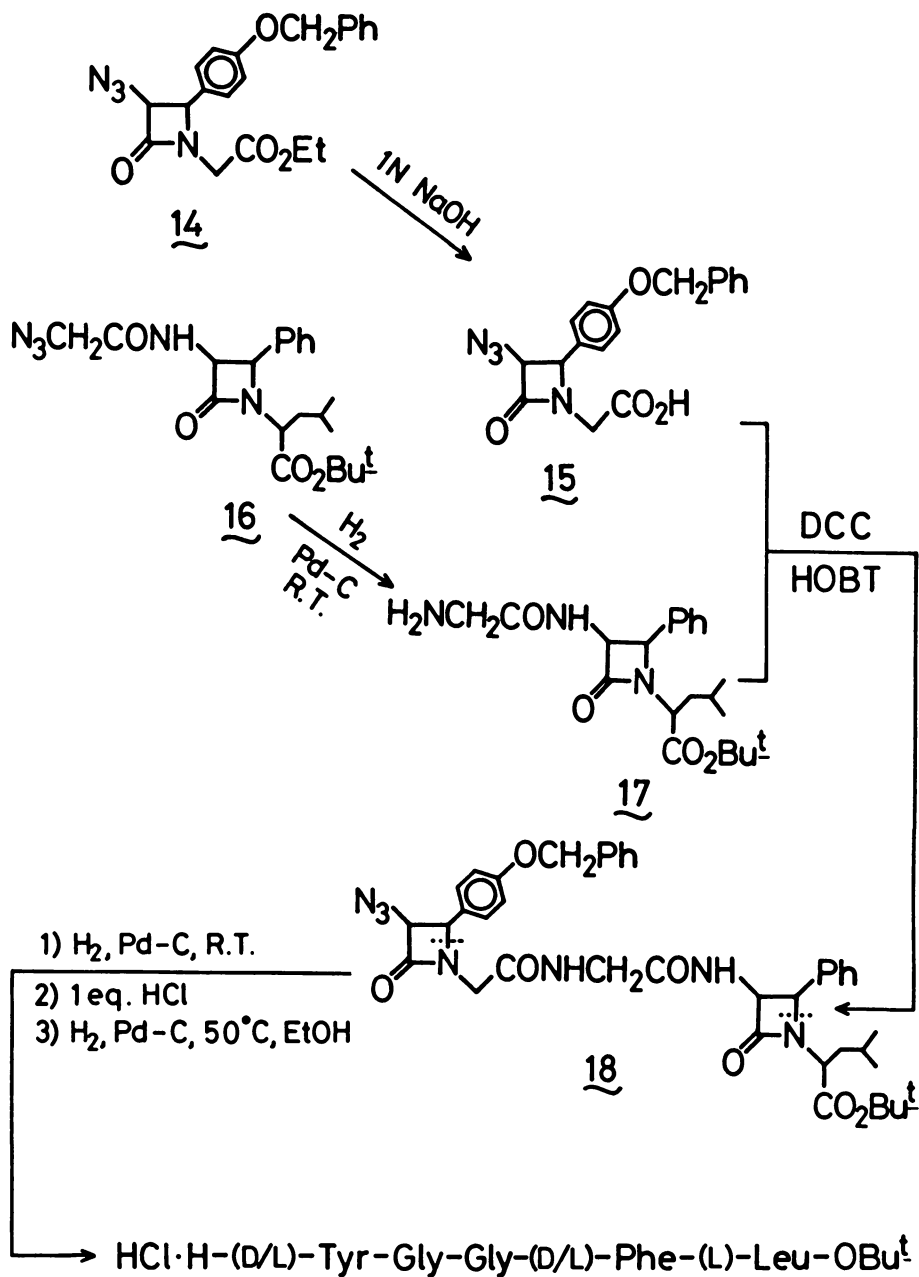OH R¹
(with O)

Scheme 7.

Scheme 8.

Scheme 9.
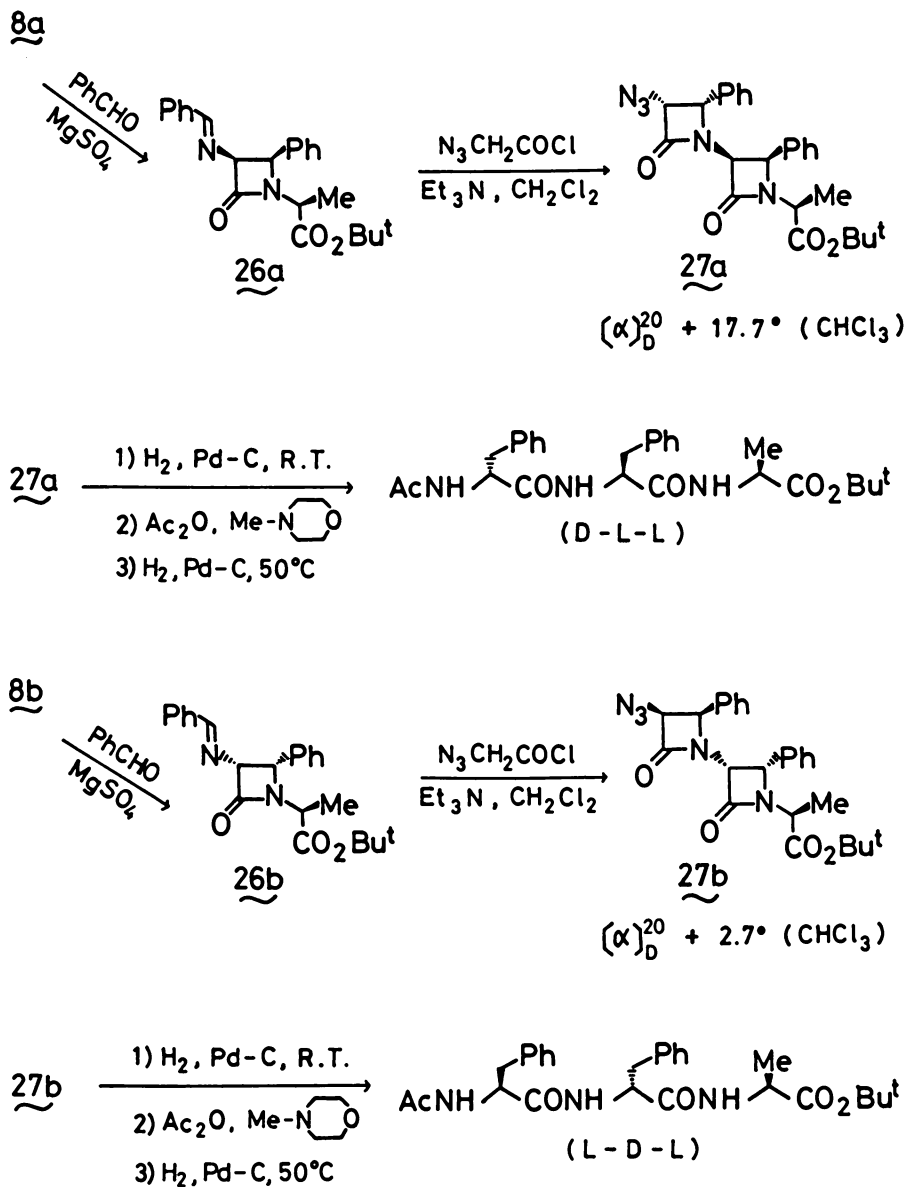
Scheme 10.

Scheme 11.

Scheme 12.

(D)Ala–Gly-(L)Phe-(L)Leu–ol which has been shown to have stronger opioid activity than the parent Enkephalin, was synthesized in good yield (Scheme 13).

For the synthesis of bis-β-lactam (ῼ) (Scheme 14), the synthetic equivalent of a tripeptide, a quite effective asymmetric reaction in the formation of β-lactam was found: The azidoketene cycloaddition to a diastereomerically pure 3-benzylideneamino-β-lactam (26a or 26b) proceeds in a completely stereoselective manner to give only one of the possible two isomers of (ῼ) (18). The stereochemistry of the cycloaddition was readily established by submitting the resulting bis-β-lactam (27a or 27b) to hydrogenolysis. The tripeptides thus obtained were fully identified with authentic samples by HPLC analysis. It becomes clear, thus, that the stereochemistry of the newly added β-lactam is opposite to that of the parent β-lactam.

In conclusion, we have been developing two new methods for peptide synthesis and modification, viz., catalytic asymmetric hydrogenation of dehydrodipeptides and the use of β-lactams as building blocks. Of course, each method has advantages and limitations. We believe, however, that the combination of these two methods provides novel and effective approaches to chiral peptides having a variety of biological activities.

Scheme 13.

8a

26a

27a

$[\alpha]_D^{20}$ + 17.7° (CHCl$_3$)

27a
1) H$_2$, Pd-C, R.T.
2) Ac$_2$O, Me-N⟩O
3) H$_2$, Pd-C, 50°C

AcNH–CH(Ph)–CONH–CH(Ph)–CONH–CH(Me)–CO$_2$Bu^t

(D – L – L)

8b

26b

27b

$[\alpha]_D^{20}$ + 2.7° (CHCl$_3$)

27b
1) H$_2$, Pd-C, R.T.
2) Ac$_2$O, Me-N⟩O
3) H$_2$, Pd-C, 50°C

AcNH–CH(Ph)–CONH–CH(Ph)–CONH–CH(Me)–CO$_2$Bu^t

(L – D – L)

Scheme 14.

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Asymmetric Carbon–Carbon Bond Formation Using Enantiomerically Pure Vinylic Sulfoxides

GARY H. POSNER, JOHN P. MALLAMO, KYO MIURA, and MARTIN HULCE

Johns Hopkins University, Department of Chemistry, Baltimore, MD 21218

A new, general method is developed for preparation of various 3-substituted carbonyl compounds of high enantiomeric purity. Application of this method is made to asymmetric synthesis of either enantiomer of 3-methylalkanoic acids, of enantiomerically pure 3-methylcyclopentanone, 3-methylcyclohexanone, 3-naphthylcyclopentanone 16 and 3-vinylcyclopentanone 18. 9,11-Seco steroid 16 and steroid intermediate 18 are precursors of enantiomerically pure steroids equilenin and estrone of natural absolute configuration. The basis for this asymmetric synthetic method rests on the transfer of chirality from the sulfoxide sulfur atom to the β-carbon carbon atom during organometallic β-addition to enantiomerically pure α-carbonyl α,β-ethylenic sulfoxides, and the amount of asymmetric induction is highest (i.e., > 98%) with cyclopentenone sulfoxide (S)-(+)-10.

Stimulated by the optical activity of most naturally-occurring compounds and by the complete asymmetric induction in most chemical reactions occurring in biological systems, organic chemists have long sought ways to prepare optically active compounds directly without using resolution techniques and ways to mimic the absolute stereocontrol in enzymic reactions. In recent years, progress in this area of asymmetric synthesis has been extraordinary (1). Two industrially important processes exemplifying this type of recent advance include asymmetric catalytic hydrogenation using chiral rhodium complexes (2) and asymmetric steroid synthesis using natural amino acids as chiral directors (3). Many literature reports within the past 5 years document the phenomenal success of the organic chemist in achieving often very high asymmetric inductions during formation of carbon-carbon bonds via nucleophilic addition to electrophilic olefins (1c,d,4).

During the past three years, we have had excellent success in
achieving some asymmetric syntheses (5). We have focused atten-
tion specifically on faithful transfer of chirality from the sul-
fur atom of some α-carbonyl α,β-ethylenic sulfoxides to the β-
carbon atom during organometallic β-addition reactions. This type
of high asymmetric induction in forming carbon-carbon bonds has
led to successful preparation of several classes of optically
active synthetic intermediates such as 3-methylalkanoic acids and
3-methylcycloalkanones. In addition, this asymmetric methodology
has been applied successfully to preparation of more complex,
enantiomerically pure molecules such as steroids and steroid in-
termediates.

The first literature report of asymmetric β-addition to an
enantiomerically pure α,β-ethylenic sulfoxide appeared in 1971
and involved β-addition of piperidine to propenyl sulfoxide 1
(eq. 1) (6). The absolute stereochemistry of this reaction was
rationalized by Stirling in terms of transition state 1a in which
the nucleophile approached the β-carbon atom on that side of the
double bond remote from the bulky tolyl group in the conformation
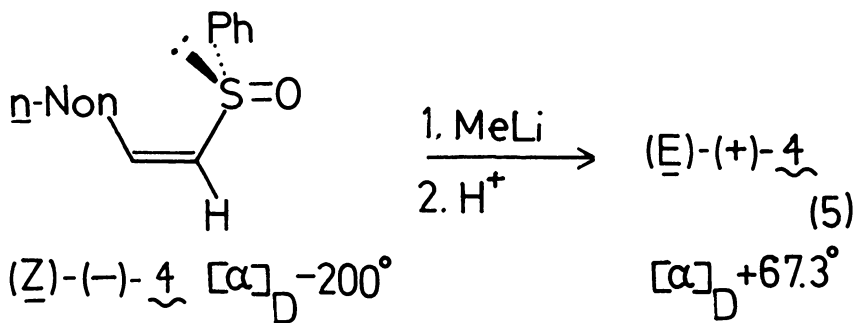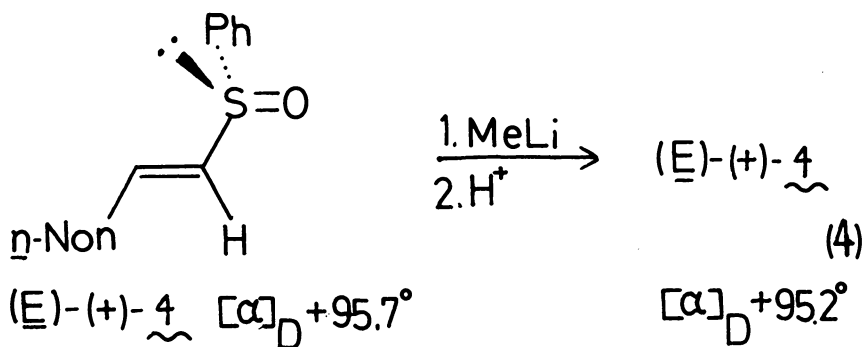shown in model 1a (6).
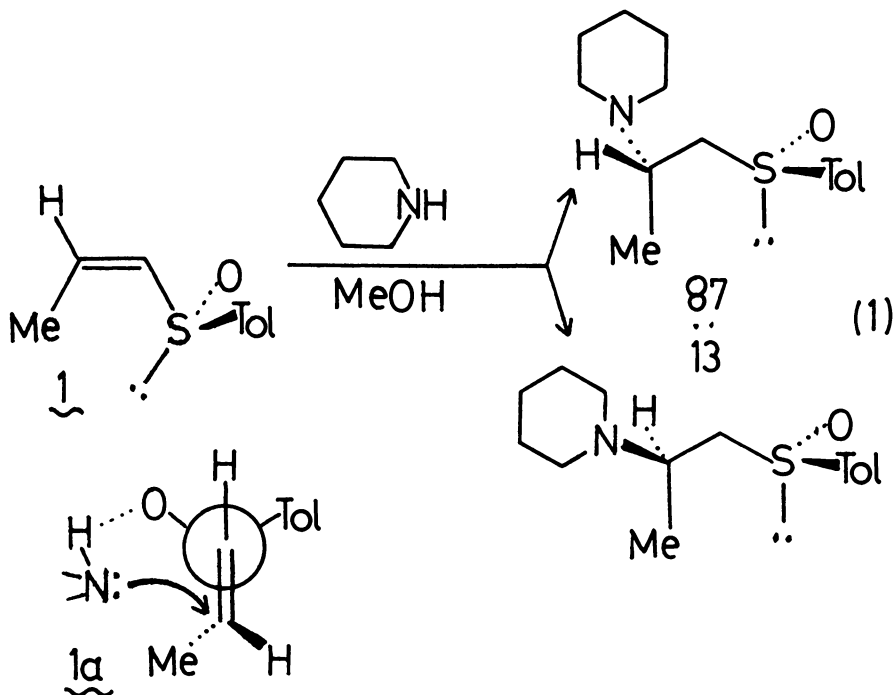
In 1973 Tsuchihashi reported asymmetric induction during carbon-carbon bond formation between nucleophilic malonate and electrophilic enantiomerically pure styryl sulfoxide 2, producing intermediate diastereomeric carbanions 3a and 3b (eq 2) (7). Selective formation of diastereomer 3a in this irreversible, kinetically controlled addition was rationalized in terms of the preference for an α-sulfinyl carbanion to have the carbon lone-pair orbital <u>trans</u> to the sulfinyl oxygen orbital in a polar solvent.
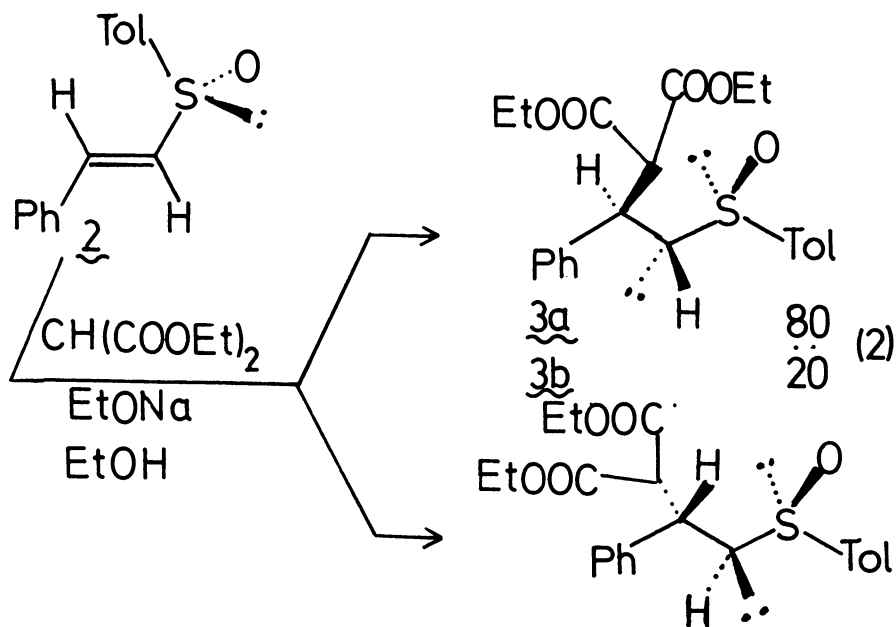

Pursuing these two reports as well as our own interest in organometallic additions to unsaturated sulfur compounds, (8) we examined the behavior of some 1-alkenyl aryl sulfoxides toward relatively non-basic organocopper reagents with the aim of attaching a <u>hydrocarbon</u> group β to the sulfur atom in a stereo-controlled fashion. To our surprise, rather than <u>addition</u> to the carbon-carbon double bond, metalation occurred regiospecifically at the 1-position generating a vinylmetallic species; likewise, methyllithium and several lithium amides produced such vinyl-metallic species which reacted successfully with a variety of electrophiles to give various 1-substituted 1-alkenyl sulfoxides (e.g., eq 3) (9).

$$\text{(3)} \qquad 90\%$$
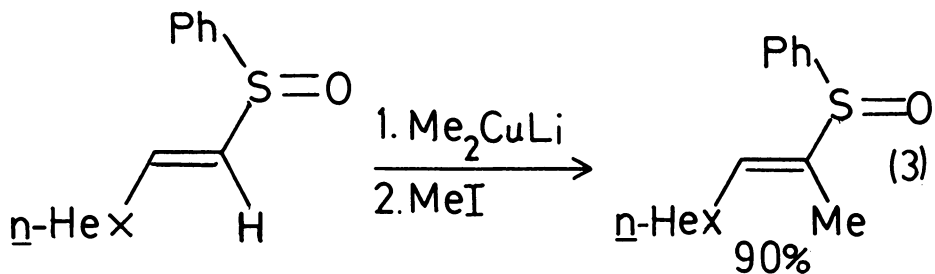
Using enantiomerically pure 1-alkenyl aryl sulfoxides (E)-(+)-4 and (Z)-(-)-4, we found that 1-deprotonation and then repro-tonation of the (E)-(+)-4 isomer produced no double bond isomeri-zation and no racemization, whereas similar treatment of the (Z)-(-)-4 isomer produced double bond isomerization and some racemiza-tion (eqs. 4,5) (5a).


$$(E)-(+)-4 \qquad [\alpha]_D +95.7°$$
$$(E)-(+)-4 \qquad [\alpha]_D +95.2° \qquad \text{(4)}$$

$$(Z)-(-)-4 \qquad [\alpha]_D -200°$$
$$(E)-(+)-4 \qquad [\alpha]_D +67.3° \qquad \text{(5)}$$

   Carboxylation of such a 1-lithio 1-alkenyl sulfoxide led to
a diastereomerically and enantiomerically pure α-carboxyl α,β-
ethylenic sulfoxide such as 5a after protonation of the intermedi-
ate lithium carboxylate and to the corresponding methyl ester 5b
after methylation with methyl iodide-hexamethylphosphoramide
(HMPA) (eq. 6) (5a).

$$(S)-(+)-5a, R=H, >95\%$$

$$(6)$$

$$(S)-(+)-5b, R=Me. 80\%$$
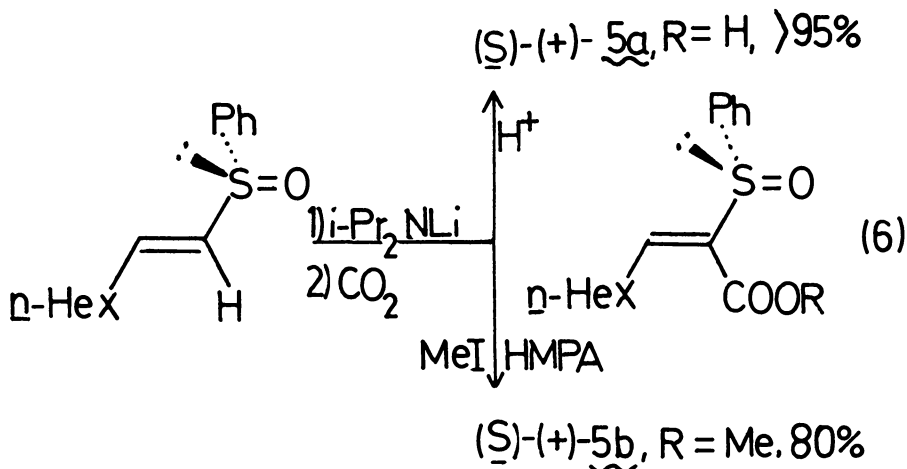
   We reasoned that metal ion complexation with α-carboxyl α,β-
ethylenic sulfoxides such as 5a and 5b should produce a chelate
such as 6, locking the sulfoxide group into the conformation
shown. Approach of a nucleophilic methylmetallic species toward
the β-carbon atom should now occur from the unshielded side of
the carbon-carbon double bond and should lead therefore to (R)-3-
methylalkanoates with high asymmetric induction. Working model 6
further suggested that aromatic groups bulkier than phenyl and
metal ions that form strong complexes might possibly lead to com-
plete asymmetric induction.

$$6$$
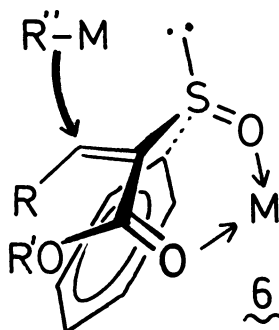
α–Carboxyl α,β–ethylenic sulfoxide 5a reacted with dimethyl-coppermagnesium iodide in a conjugate manner; sodium amalgam reductive cleavage of the intermediate α–sulfinyl carboxylic acid produced (R)-(+)-3-methylnonanoic acid in 61% enantiomeric excess (eq. 7). Likewise, α–methoxycarbonyl α,β–ethylenic sulfoxide 5b reacted with dimethylcopperlithium followed by reductive sulfur-carbon bond cleavage and saponification to produce (R)-(+)-3-methylnonanoic acid in 65% enantiomeric purity (eq. 8, 53% overall yield). Reversing the order of introducing the larger and the smaller alkyl groups at the prochiral β–carbon atom afforded mainly that enantiomer having opposite absolute stereochemistry. Thus (E)-1-propenyl sulfoxide (+)-7 reacted with di-n-butylcopperlithium and then underwent reductive carbon–sulfur bond cleavage and saponification to form (S)-(-)-3-methylheptanoic acid (8) in 59% enantiomeric purity (eq. 9) (5a). Higher asymmetric inductions, however, have been achieved recently by Meyers, by Mukaiyama and by Koga in synthesis of 3-methylalkanoic acids (4).
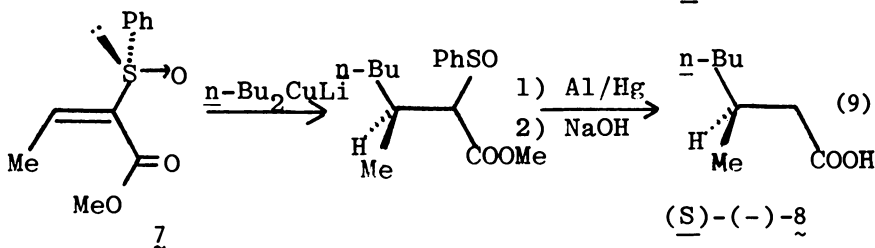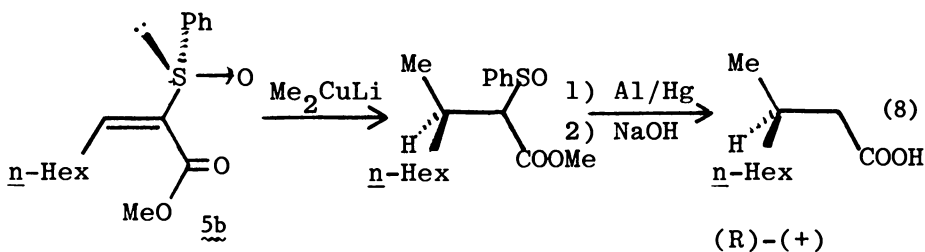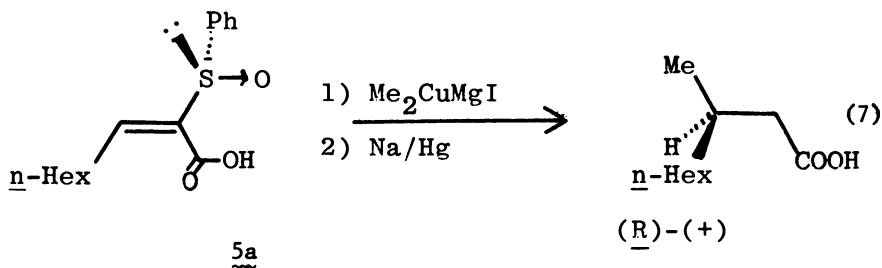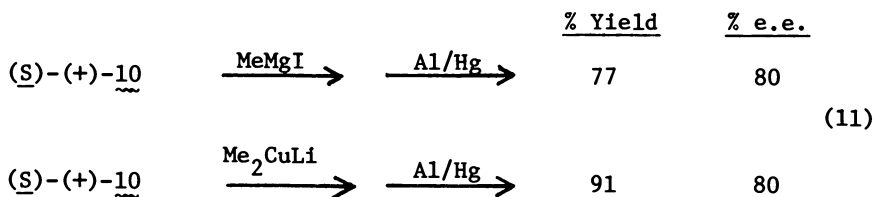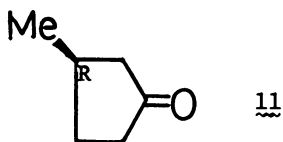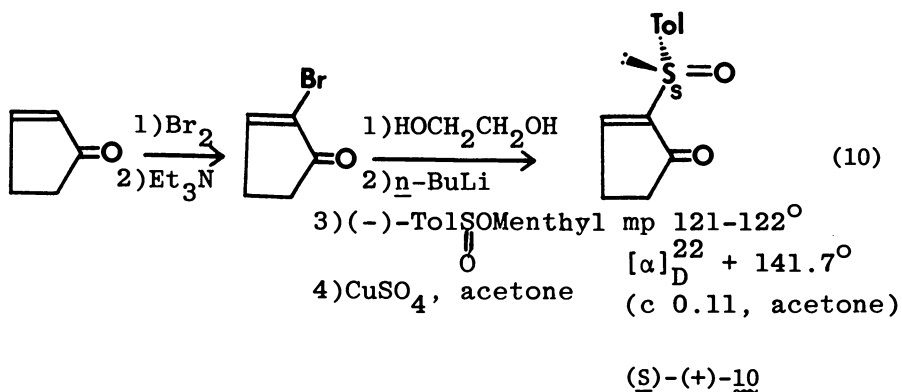
In sharp contrast to these highly successful methods for enantioselective synthesis of some <u>acyclic</u> systems, virtually no general method has been reported for enantio-controlled preparation of <u>cyclic</u> compounds. Because so many optically pure carbocycles are found in nature and are important synthetic intermediates, the need for effective and highly asymmetric syntheses of such compounds is obvious. More specifically, although many enantiomerically pure naturally-occurring 3-alkylcarbocycles with small 3-alkyl groups are known, asymmetric synthesis of these compounds via attachment of the small alkyl group is usually an extremely difficult process. Despite attempts at asymmetric induction during organometallic conjugate addition to 2-cycloalkenones using optically active solvents (<u>10</u>) or optically active ligands, (<u>11</u>) only poor enantioselectivity has been achieved.

We reasoned that some <u>cyclic</u> enone sulfoxides should form an even more rigid chelate than that formed from the corresponding <u>acyclic</u> alkenyl sulfoxides when complexed with metal ions; model <u>9</u> exemplifies the case for a cyclopentenone sulfoxide and suggests a high degree of stereocontrol during the nucleophilic addition reaction.
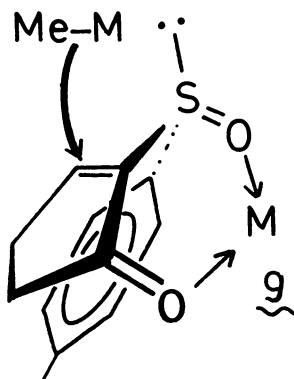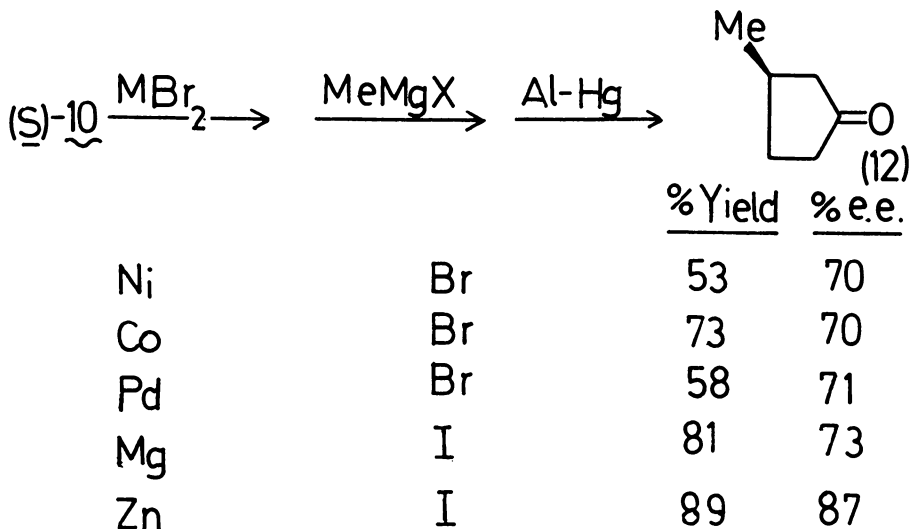

Cyclopentenone sulfoxide (<u>S</u>)-(+)-<u>10</u> was prepared via eq. 10 in good yield on a few mg as well as on a 10-gm scale (<u>5a</u>). This enone sulfoxide, which is crystalline and stable at least for several months, reacted with methylmagnesium iodide [in the absence of copper (I)] in a conjugate manner; aluminum amalgam carbon-sulfur bond reductive cleavage produced (<u>R</u>)-(+)-3-methylcyclopentanone (<u>11</u>) in 71% chemical yield and in 80% enantiomeric purity (eq. 11). The absolute stereochemistry of this asymmetric induction is consistent with working model <u>9</u> and approach of the methyl nucleophile from the <u>pro</u>-(<u>R</u>) direction. Likewise, dimethylcopperlithium reacted with cyclopentenone sulfoxide (<u>S</u>)-(+)-<u>10</u> to give, after reductive sulfur-carbon bond cleavage, (<u>R</u>)-(+)-
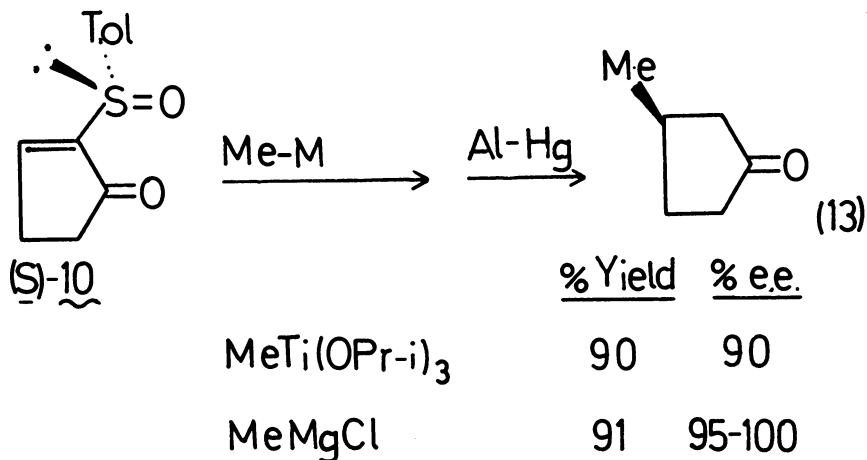
3-methylcyclopentanone ($\underline{11}$) in 91% chemical yield and 80% enantio-meric purity.

$$\text{(10)}$$

1)HOCH$_2$CH$_2$OH
2)$\underline{n}$-BuLi
3)(-)-TolSOMenthyl
4)CuSO$_4$, acetone

mp 121-122°
$[\alpha]_D^{22}$ + 141.7°
(c 0.11, acetone)

($\underline{S}$)-(+)-$\underline{10}$

$\underline{11}$

			% Yield	% e.e.
($\underline{S}$)-(+)-$\underline{10}$	MeMgI	Al/Hg	77	80
($\underline{S}$)-(+)-$\underline{10}$	Me$_2$CuLi	Al/Hg	91	80

$$\text{(11)}$$

       To preform a strong enone sulfoxide-metal ion complex and thus possibly to increase the amount of asymmetric induction, several metal dibromides were added to cyclopentenone sulfoxide ($\underline{S}$)-(+)-$\underline{10}$. As shown in eq. 12, only zinc dibromide was highly effective in raising the extent of asymmetric induction during methyl Grignard conjugate addition.

$$(S)\text{-}\underline{10} \xrightarrow{\text{MBr}_2} \xrightarrow{\text{MeMgX}} \xrightarrow{\text{Al-Hg}}$$

(12)

		% Yield	% e.e.
Ni	Br	53	70
Co	Br	73	70
Pd	Br	58	71
Mg	I	81	73
Zn	I	89	87

The best stereochemical results, however, were obtained with the new and bulky methylmetallic reagent, methyl triisopropoxy-titanium, (<u>12</u>) and with methylmagnesium <u>chloride</u> (eq. 13). Presumably, the more electrophilic <u>chloro</u>magnesium species formed a stronger complex with the bidentate enone sulfoxide than did the bromo or the iodomagnesium species (<u>13</u>) and thus forced the β-addition to proceed entirely through the chelated and therefore locked conformation shown in model <u>9</u>.

$$(S)\text{-}\underline{10} \xrightarrow{\text{Me-M}} \xrightarrow{\text{Al-Hg}}$$

(13)

|	% Yield	% e.e.
MeTi(OPr-i)$_3$	90	90
MeMgCl	91	95-100

We have also prepared (R)-(+)-3-methylcyclohexanone (13) via methylmetallic conjugate addition to enantiomerically pure cyclohexenone sulfoxide (S)-(+)-12 (eq. 14). Equations 13 and 14 represent highly successful asymmetric syntheses of 3-methylcyclopentanone and 3-methylcyclohexanone and illustrate a general new method for preparation of 3-alkylcarbocycles of high or virtually complete enantiomeric purity (14).
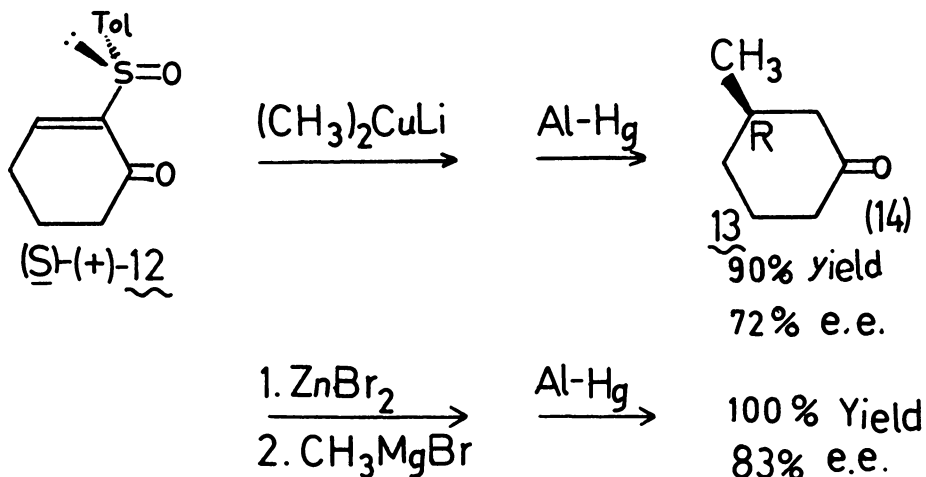

Besides conjugate addition of the small methyl group, cyclopentenone sulfoxide (S)-(+)-10 also underwent conjugate addition of a large naphthyl group. As shown in scheme I, we have applied this reaction which proceeds with complete asymmetric induction to efficient construction of 3-naphthylcyclopentanone 14 having the natural absolute steroid configuration at carbon 14 (steroid numbering). Reductive cleavage of the sulfinyl group using dimethylcopperlithium allowed regiospecific formation of enolate ion 15 which underwent carbon alkylation to give only 9,11-seco steroid 16 having the desired 13S-14S absolute stereochemistry! Synthetic seco steroid 16 was identical by HPLC, NMR, IR, mass spectrometry, melting point (116.5-118°C), mixed melting point and optical rotation [[α]$_{365}^{22}$ = +168° (c 0.36, CHCl$_3$)] to a sample of 16 prepared by degradation of natural estradiol (5a). Because we have previously converted racemic 16 into the racemic steroid equilenin 17, (15) preparation of enantiomerically pure 16 amounts to a formal total synthesis of enantiomerically pure equilenin 17.

3-Vinylcyclopentanone 18 and the corresponding enol silyl ether 19 have been used recently in some elegant, creative, and efficient constructions of estrones via intramolecular Diels-Alder cycloaddition reactions of intermediate 0-quinodimethanes (Scheme II) (16-18). Only one report, however, has appeared
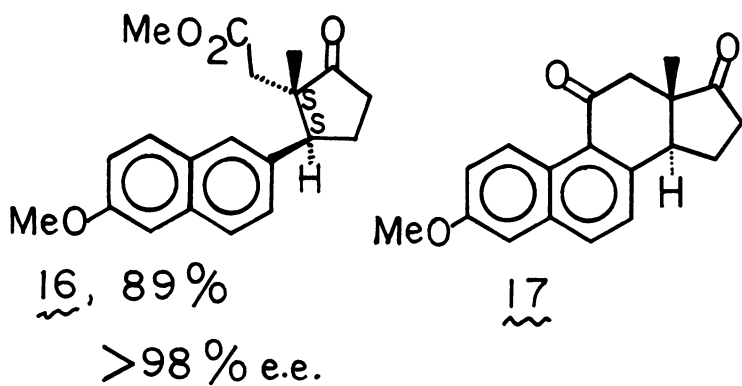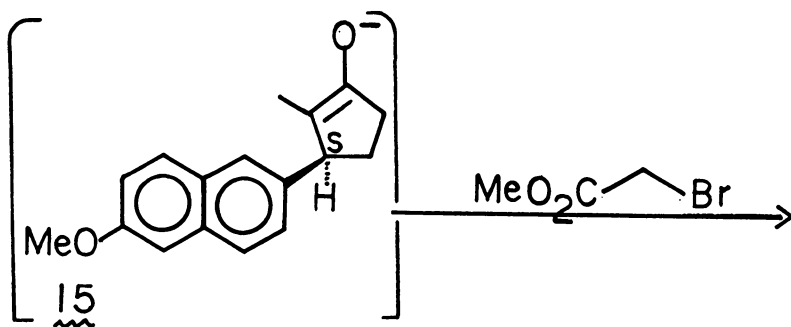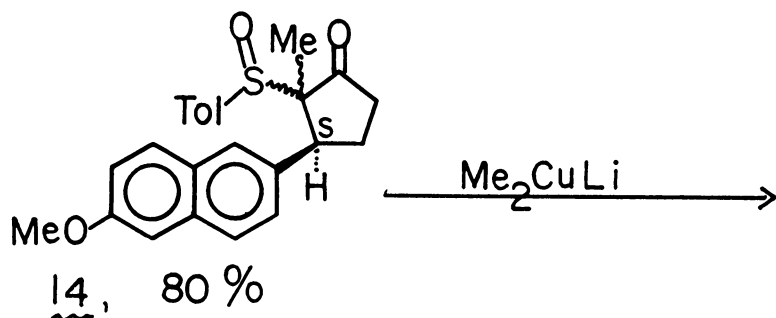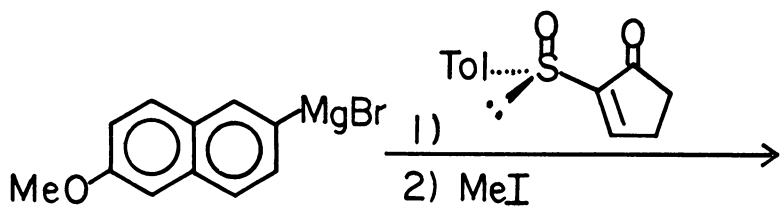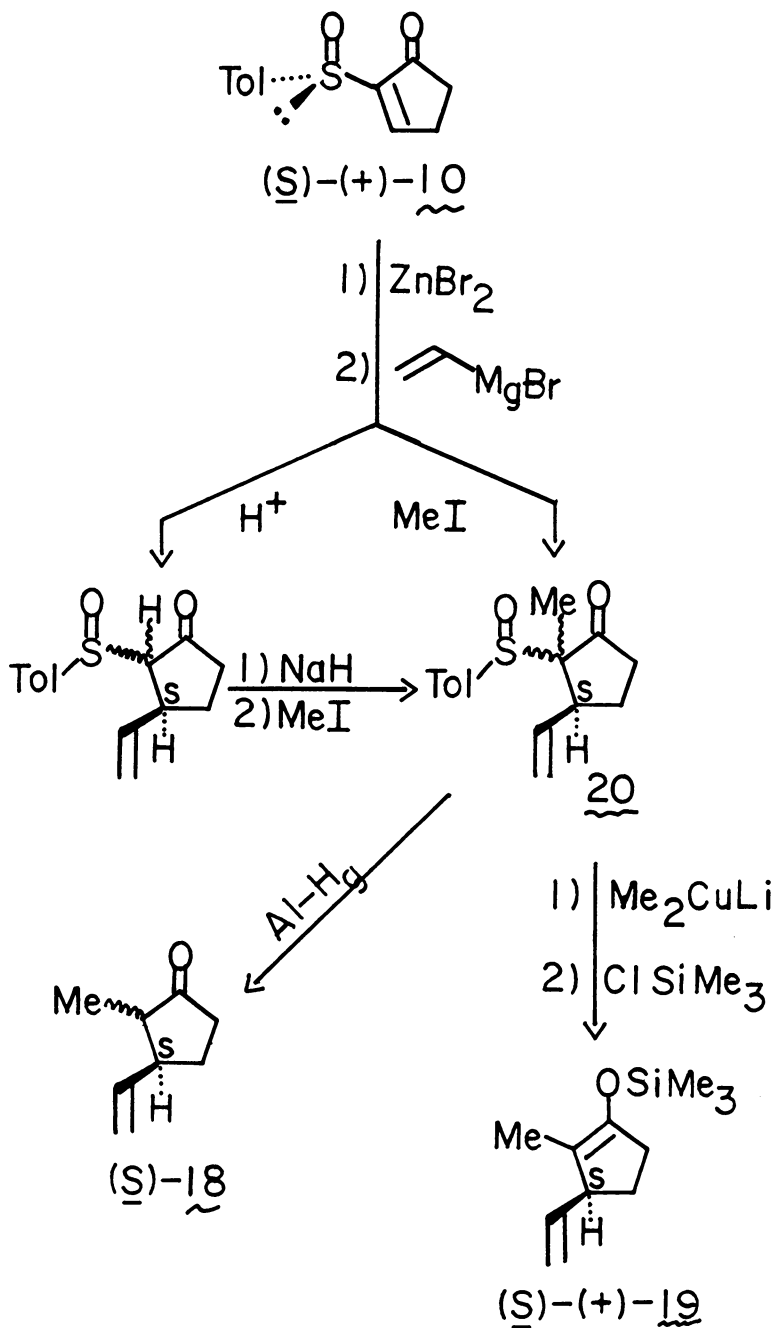
Scheme I.
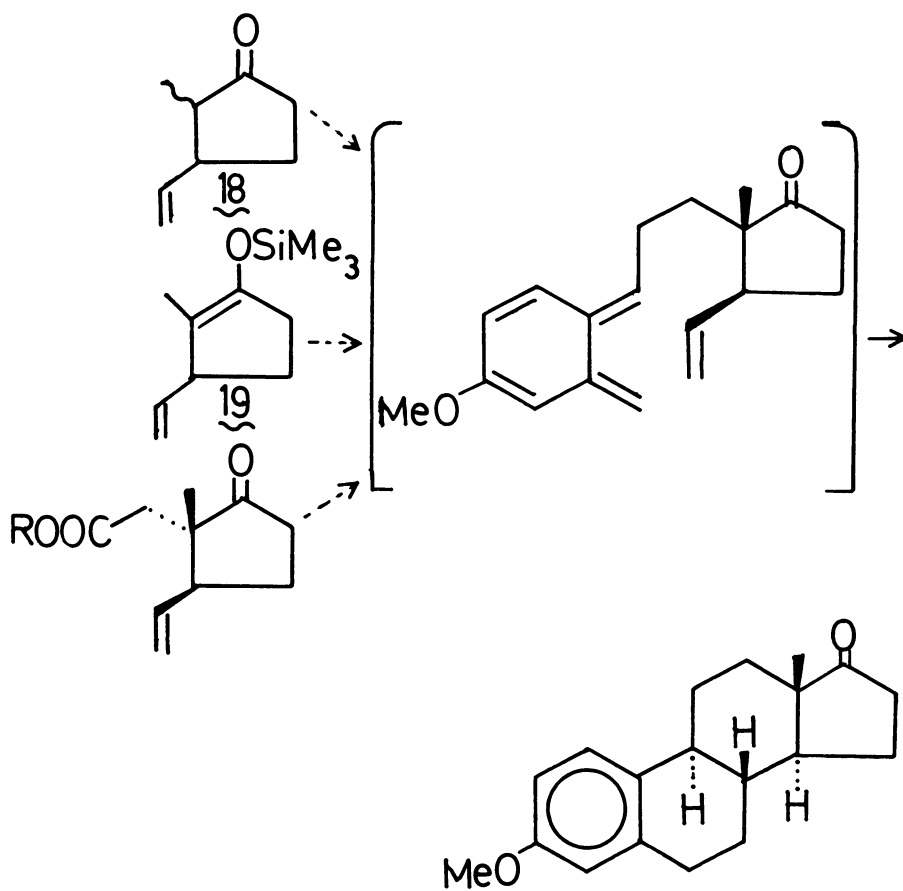
Scheme II.

involving asymmetric synthesis of optically active steroid inter-
mediate 18 used in preparation of optically active estrones <u>via</u>
generalized scheme II (<u>161</u>).

We found that enantiomerically pure cyclopentenone sulfoxide
(<u>S</u>)-(+)-10 reacted with vinylmagnesium bromide in the presence of
a catalytic amount of cuprous bromide and then with methyl iodide
to give 2,2,3-trisubstituted cyclopentanone 20 (Scheme III). Tri-
substituted cyclopentanone 20, however, could be formed in better
yield (∿75%) via the corresponding <u>sodio</u> enolate. Aluminum amal-
gam reductive cleavage produced 3-vinylcyclopentanone (<u>S</u>)-18 in
80% enantiomeric purity. The amount of asymmetric induction was
improved dramatically, however, by first complexing cyclopente-
none sulfoxide (<u>S</u>)-10 with zinc dibromide and then adding vinyl-
magnesium bromide. In this way, following scheme III, <u>3-vinyl-
cyclopentanone (S)-18 was formed in >98% enantiomeric purity and
in 55-60% overall yield</u>! Reductive cleavage of α-sulfinylcyclo-
pentanone 20 using dimethylcopperlithium followed by addition of
trimethylsilyl chloride gave enantiomerically pure enol silyl
ether (<u>S</u>)-(+)-19 in 54% overall yield (<u>5b</u>). This complete asym-
metric induction in synthesis of steroid intermediates (<u>S</u>)-18 and
and (<u>S</u>)-19 amounts to a formal total synthesis of enantiomerically
pure estrone!

It is clear from the results summarized here that some very
successful, general, and highly useful asymmetric syntheses of
carbon-carbon bonds can be performed using enantiomerically pure
1-carbonyl 1-alkenyl sulfoxides and various organometallic re-
agents. These results add significantly to the rapidly growing
number of new, rationally designed, and highly stereocontrolled
C-C bond-forming synthetic methods and should be especially use-
ful in asymmetric synthesis of enantiomerically pure 3-substituted
carbocycles.

Scheme III.

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Asymmetric Reactions: A Challenge to the Industrial Chemist

GABRIEL SAUCY and NOAL COHEN

Hoffmann–La Roche Incorporated, Chemical Research Department, Nutley, NJ 07110

A variety of established industrial processes for the manufacture of and new synthetic approaches to certain optically active compounds such as pharmaceuticals, vitamins, and fine chemicals are surveyed. Among the techniques for obtaining optically pure intermediates covered in this review are classical or modified optical resolutions, the utilization of starting materials from the chiral pool, as well as stoichiometric and catalytic asymmetric transformations.

The development of practical and economical processes for large scale industrial preparation of certain optically active compounds such as pharmaceuticals, fine chemicals, and vitamins has been and continues to be a major challenge. Historically, a number of efficient industrial processes have evolved which are based on classical resolution (e.g. D-biotin (1,2) and D-pantothenic acid (3)) or the use of optically active starting materials (e.g., vitamin C (4)). More recently, attractive processes utilizing asymmetric reactions have been designed (5). From an industrial point of view, the use of chiral catalysts to generate asymmetry is particularly advantageous. Unfortunately, our lack of understanding of the quantitative aspects which govern the degree of asymmetry created is a serious problem. The development of chiral catalysts useful to industry is presently very much dependent on the empirical approach. New insight and knowledge are needed to design rational approaches in asymmetric synthesis. This review is intended to show how industry has solved or, at least, confronted the problem of producing certain optically active target compounds in a practical and economical manner, using selected examples from the area of pharmaceuticals, vitamins, and fine chemicals.

L-Dopa

Prior to the pioneering development of the asymmetric
hydrogenation process for producing L-Dopa by Knowles and co-
workers at Monsanto (5), we had investigated an alternative
approach involving hydrogenation of the chiral substrate 1
using an achiral catalyst (6). This produced the mixture of
epimeric amides 2 and 3 which could be converted, in 89%
overall yield, to the desired isomer 3 via simultaneous base
catalyzed equilibration - crystallization. Unfortunately,
hydrolysis of 3 to L-Dopa gave unacceptably low yields, of
the order of only 50%.

19-Norsteroids

Very substantial asymmetric induction at C-13 was found
to take place upon condensation of the optically active hydroxy
vinyl ketone 4 (R=C2H5) with 2-methylcyclopentane-1,3-dione
(5) giving predominantly the dienol ether 6 (7). The exploita-
tion of this fortuitous result enabled us to design several
efficient routes to optically active 19-norsteroids and estrone
(8). The key chiral annulating agents 4 were secured by
various schemes relying on classical resolutions or microbio-
logical reduction of δ-keto acids giving optically active
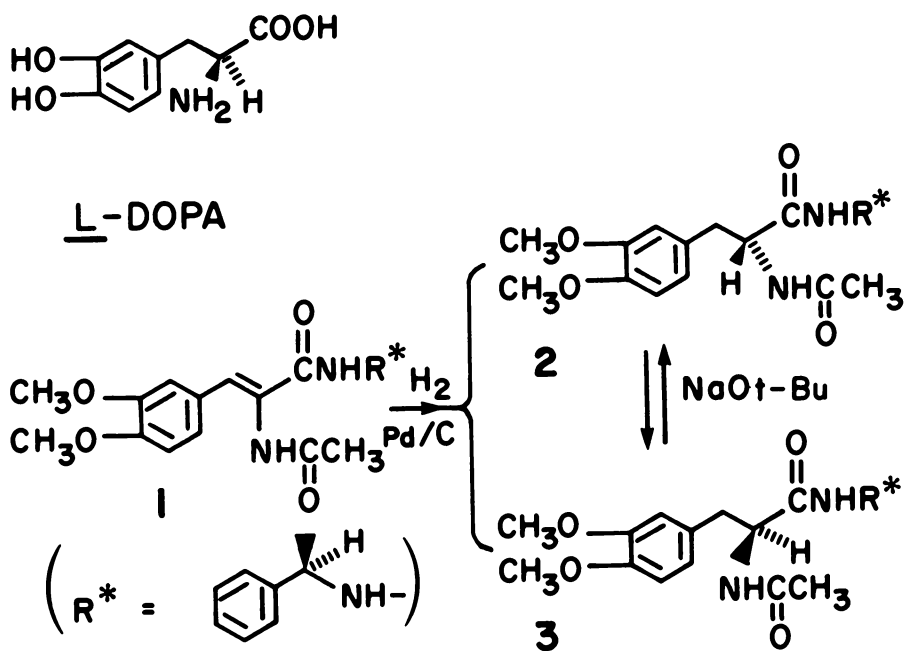δ-lactones .
Of particular interest is the regio- and enantiospecific
reduction of diketo acid 7 with Margarinomyces bubaki affording
the keto lactone 8. The latter serves as the chiral starting
point in an asymmetric total synthesis (+)-estr-4-ene-3,17-
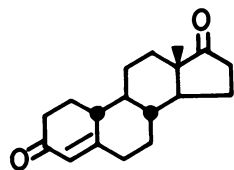dione via key intermediate 9 (9).
A most impressive example of catalytic asymmetric synthesis
forms the basis for still another and very efficient approach
to 19-norsteroids (10,11). The exact mechanism responsible
for the extremely high asymmetric induction noted in the
crucial conversion of prochiral 10 to ketol 11 and (S)-enedione
12 still needs to be clarified (12,13). Nonetheless, these
chiral aldol products serve very effectively as steroid CD-
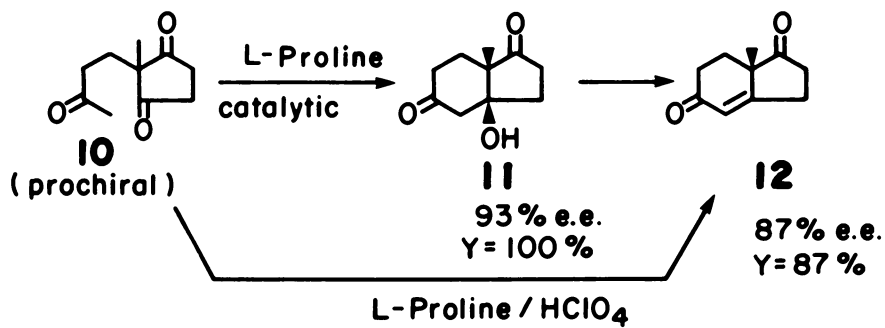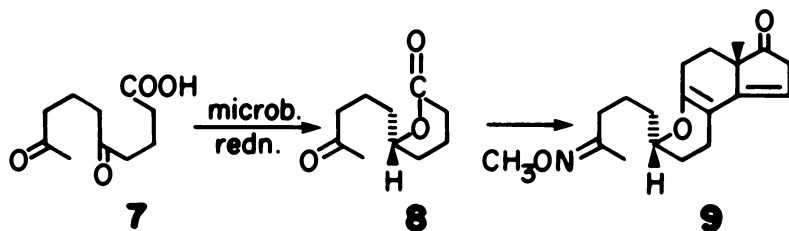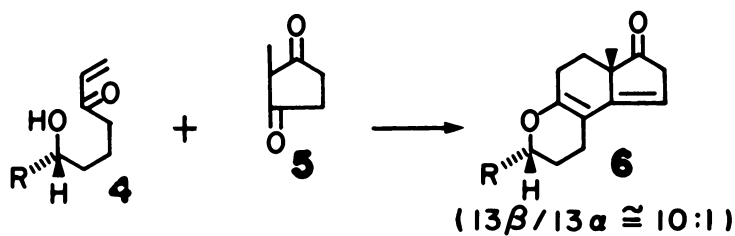ring synthons (8,14-21).

Zeaxanthin

Zeaxanthin, which occurs in corn and many other plants,
is an important carotenoid. Its synthesis in optically active
form can be achieved on the basis of the three approaches
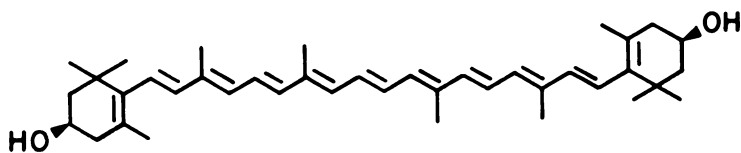depicted.
In the first case (22), optical activity is introduced by
asymmetric reduction of the enedione 13 with yeast, giving
dione 14. Stereo- and regioselective reduction then produced
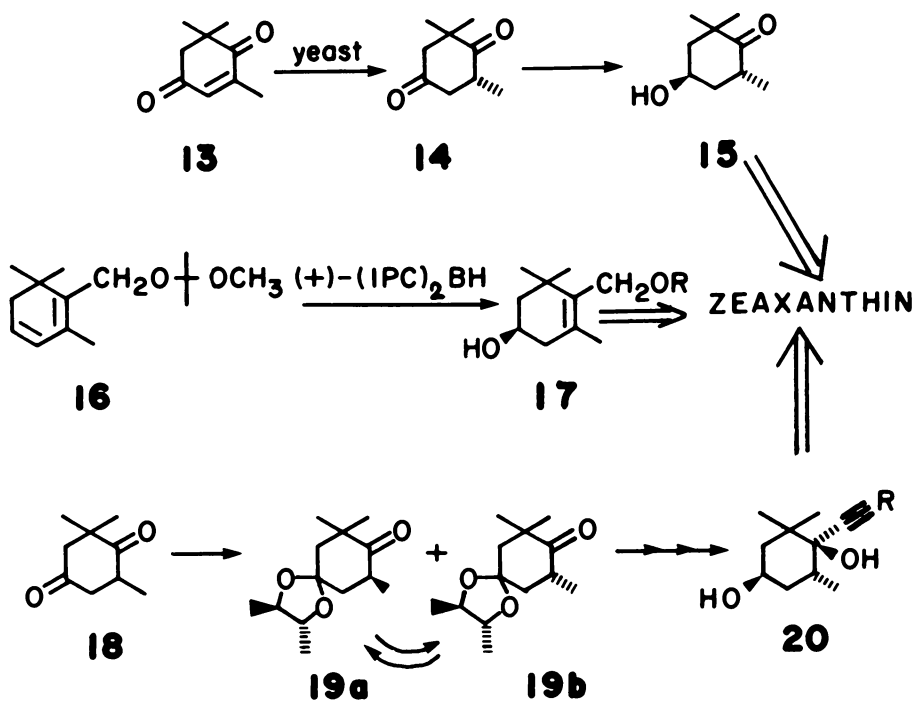the key ketol 15. In the second approach (23), the cyclohexa-

L-DOPA

19-NORANDROSTENEDIONE

$(13\beta / 13\alpha \cong 10:1)$

10
(prochiral)

L-Proline
catalytic

11
93% e.e.
Y = 100%

12
87% e.e.
Y = 87%

L-Proline / HClO$_4$

ZEAXANTHIN

diene 16, available from safranal, is subjected to an asymmetric
hydroboration with (+)-diisopinocampheylborane giving inter-
mediate 17. In this context, it should be noted that asym-
metric hydroboration of dienes has also been applied at Hoffmann-
La Roche in a synthesis of prostaglandin intermediates having
industrial potential (24).

The third approach to zeaxanthin (25) exploits the special
features of keto acetal 19b which is theoretically available
in quantitative yield starting from the diketone 18 and (2R,3R)-
2,3-butanediol. Fortunately, 19b is crystalline and less
soluble than its epimer 19a. Equilibration with sodium hydroxide
thus favors the desired epimer. Diastereomer 19b is then
transformed into the diol 20 in two stereospecific steps.
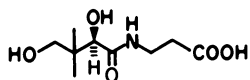
Pantothenic Acid

The present industrial processes used to produce the
crucial intermediate (R)-(-)-pantolactone (22) are based on
resolution of racemic material (3). A different and very
promising approach has been reported by a Japanese group (26).
Independently, Roche workers also investigated this approach
which involves asymmetric reduction of ketolactone 21 using
rhodium catalysts derived from chiral phosphines (27). In
this manner, 22 can be obtained in very high chemical and
optical yields.

D-Biotin

The original synthesis of D-biotin, which involves a
classical resolution with efficient recycling of the unwanted
enantiomer (1), has recently been advantageously modified
(28). The key feature of the new Sumitomo route involves
preparation of the chiral imide 24 from symmetrical diacid 23.
Hydride reduction of 24 occurs with high asymmetric induction,
generating hydroxy amide 25 having excellent optical purity, in
65% yield. Treatment with HCl converts 25 to the corresponding
γ-lactone and ultimately D-biotin by the established route.
The chiral aminopropanediol (R*) is recovered and recycled.
Other novel approaches to D-biotin have been studied at
Hoffmann-La Roche in recent years (29,30).

Vitamin E ((2R,4'R,8'R)-α-Tocopherol)

The development of a practical total synthesis of natural
(2R,4'R,8'R)-α-tocopherol (26) is a major challenge. While
much progress has been made in this area, a technically feasible
synthetic approach to this form of vitamin E remains an elusive
goal and isolation from soybean oil continues to be the major
source of 26 (31).

PANTOTHENIC ACID
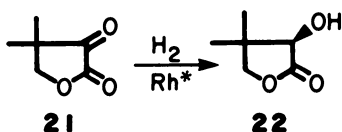
**21** **22**

Ketolactone   (R)-(-)-Pantolactone

D-BIOTIN

**23**   **24**   **25**

$$R^* =$$
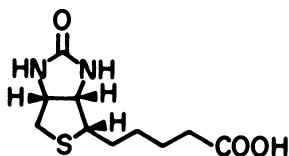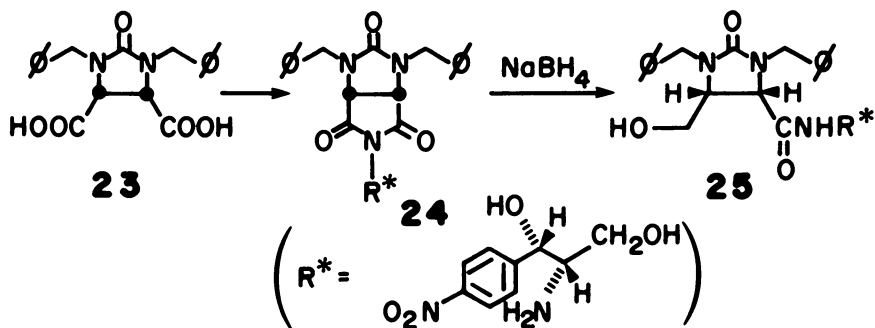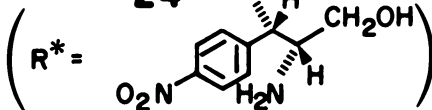
Much of our synthetic work aimed at 26 has been summarized
in a recent review (32) and will not be covered in detail
here. The two homologous strategies employed are depicted by
the bond dissections "a" and "b". In the former, a C_{14}-
chroman unit is coupled with a C_{15}-side chain intermediate in
the penultimate step while in the latter, C_{15}-chroman and C_{14}-
side chain synthons are united.

Regarding the side chain, recent developments in our lab-
oratories involve applications of asymmetric hydride reductions
(e.g., 27 → 29 and 31) to provide chiral Claisen rearrangement
substrates 32, 33, 35, and 36 which, in turn, afford optically
active ester 34 or its enantiomer 37 with essentially complete
chirality transfer (33). In another approach, catalytic asym-
metric hydrogenation of geranic acid (38) yields the C_{10}-
intermediate 40 in 70% e.e. (34). Many other, often quite
ingenious routes to chiral side chain precursors have been
reported recently by various groups (35-39).

Progress has also been made with regard to the accessibility
of key chroman intermediates. Thus methods were developed
which allow utilization of the unwanted enantiomers of chroman-
2-carboxylic and chroman-2-acetic acids (41c, 42c) obtained
along with the desired antipodes (41b, 42b) by classical
resolution of the racemic forms (41a, 42a) (enantioconvergence
40, 41). For example, a four stage inversion sequence provides
a route for transforming 41c into the (S)-enantiomer 41b
required for synthesis of 26 (42). Similarly, the homologous,
unwanted (R)-chroman-2-acetic acid 42c can be utilized by
means of a racemization-recycling process (43). While these
approaches still rely on classical resolutions, the modifica-
tions incorporated substantially improve the overall efficiency
in terms of obtaining optically pure intermediates.

A significant offshoot of our synthetic studies aimed at
26 has been the exploitation of the resulting methodology for
preparing all seven stereoisomers of 26 (44). Employing a
variation of a gas chromatographic method recently developed
for separating the diastereomers of α-tocopherol (45), we were
able to demonstrate that all of our synthetic stereoisomers
were of high (93-99%) diastereomeric purity (44). The avail-
ability of these compounds in pure form will now allow a
precise determination of the relationship between stereo-
chemistry and vitamin E biopotency in the α-tocopherol molecule.
During the course of this work, it was established for the
first time that naturally occurring d-α-tocopherol from soybean
oil is a single enantiomer (2R,4'R,8'R), that synthetic d,l-α-
tocopherol is an equimolar mixture of four racemates, and that
natural (E)-(7R,11R)-phytol is enantiomerically homogeneous
(44).

26

(2R,4'R,8'R) - α - Tocopherol

$$38(\underline{E}) \xrightarrow[\text{39}]{H_2, Rh \text{ cat.}} 40(\underline{R})$$

70 % e.e.
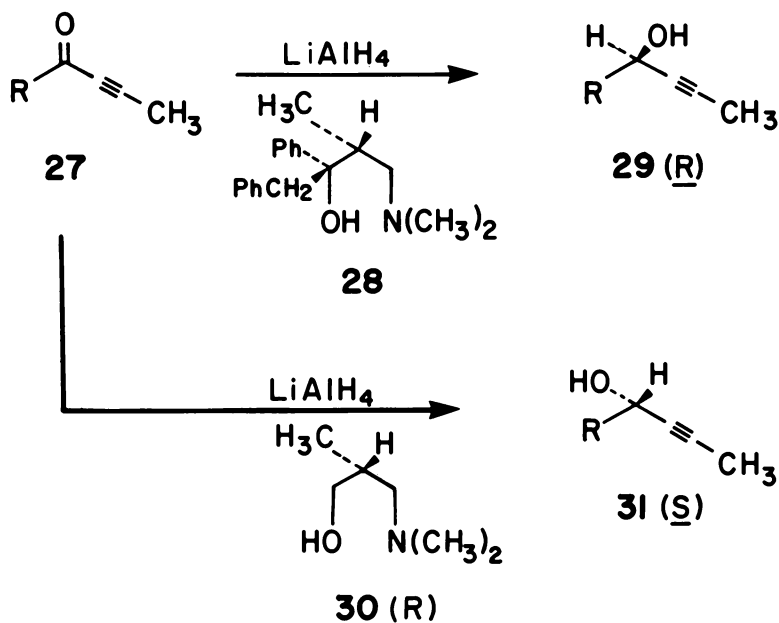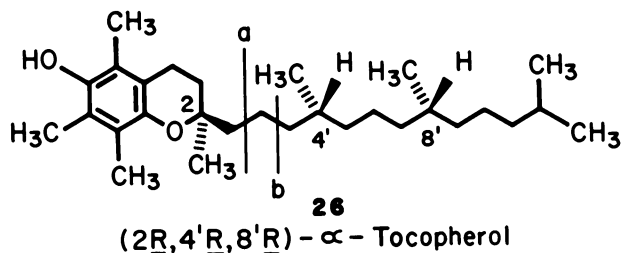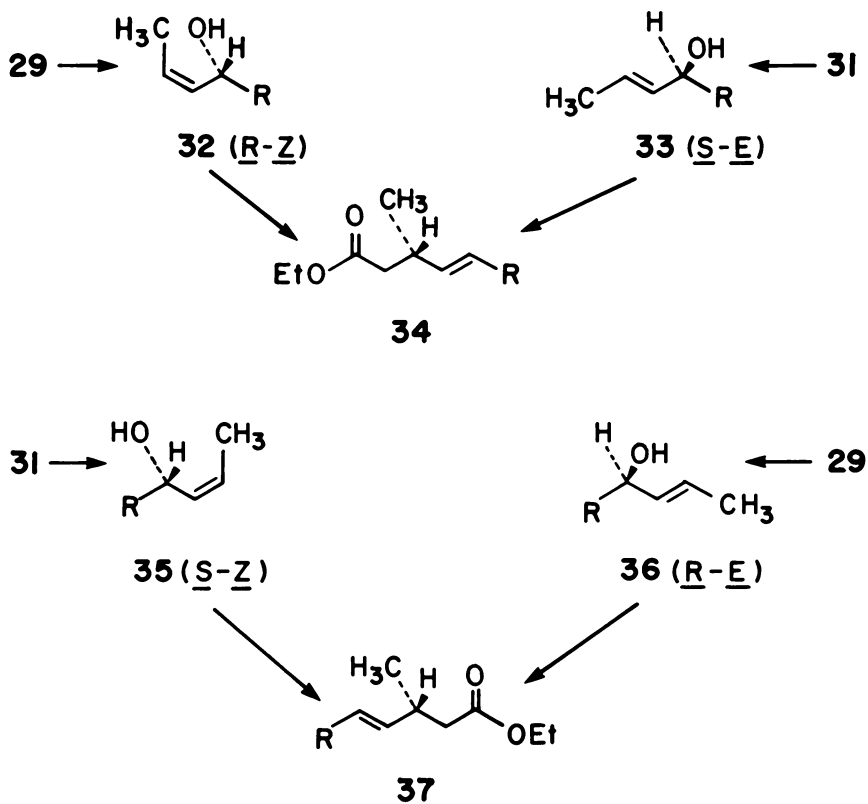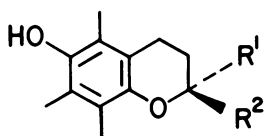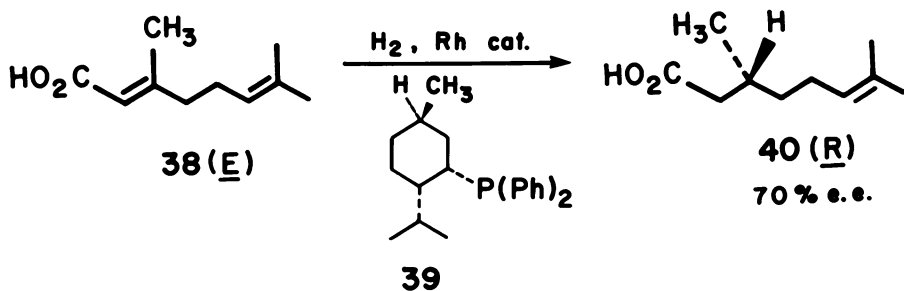
41a; $R^1, R^2 = CH_3, CO_2H$ ($\pm$)
41b; $R^1 = CH_3, R^2 = CO_2H$ ($\underline{S}$)
41c; $R^1 = CO_2H, R^2 = CH_3$ ($\underline{R}$)
42a; $R^1, R^2 = CH_3, CH_2CO_2H$ ($\pm$)
42b; $R^1 = CH_3; R^2 = CH_2CO_2H$ ($\underline{S}$)
42c; $R^1 = CH_2CO_2H; R^2 = CH_3$ ($\underline{R}$)

Conclusions

For many reasons, the pharmaceutical industry will continue to require facile synthetic routes to diastereoisomerically and enantiomerically pure chiral molecules. In order to achieve these goals, new asymmetric processes, especially catalytic asymmetric reactions, will be needed. Alternatively, there is great potential for the development of industrially useful biotransformations to produce complex optically active compounds. Genetic engineering will probably play an important role in such approaches. Nonetheless, the challenge to the organic chemist will remain.

Acknowledgment

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# Stereochemistry of Heterogeneous Asymmetric Catalytic Hydrogenation

KAORU HARADA

University of Tsukuba, Department of Chemistry, Ibaraki 305, Japan

In this paper, the stereochemistry of heterogeneous catalytic hydrogenation of $>C=N-$ and $>C=O$ double bonds of the derivatives of α-keto acids, keto alcohols and diketones is described. The steric course could be explained by the chelation hypothesis.

In 1961, Hiskey et al.(1) reported the successful asymmetric syntheses of α-amino acids. They demonstrated the synthesis of amino acids in 45-70% enantiomeric purity by catalytic hydrogenation of the Schiff bases prepared from α-keto acids and optically active α-methylbenzylamine followed by hydrogenolysis (Scheme 1). When (S)-amine was used, (S)-α-amino acid resulted. This is a highly stereoselective reaction. However, the authors did not discuss the steric course of the asymmetric hydrogenation process.

Scheme 1

R-C-COOH ‖ N | C₆H₅-CH-CH₃ (S) → (H₂, Pd/C) → R-CH-COOH | NH | C₆H₅-CH-CH₃ → (H₂, Pd(OH)₂) → (S) R-CH-COOH | NH₂
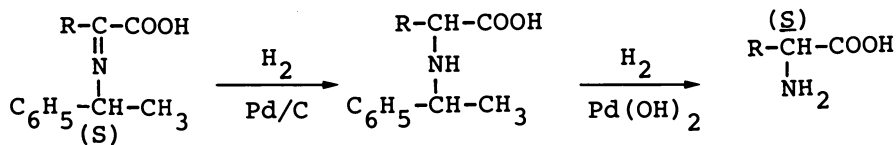
Later Mitsui et al.(2) reported the asymmetric syntheses of phenylglycine by the Hiskey type reaction and proposed a steric course for the asymmetric synthesis as shown in Scheme 2. If it is applicable to all of the Hiskey type reactions, the following may be expected: (a) an increase in optical yield upon substitution of α-methylbenzylamine by α-ethylbenzylamine and (b) a comparable optical yield upon substitution of α-methylbenzylamine by α-(1-naphthyl)ethylamine.

Scheme 2
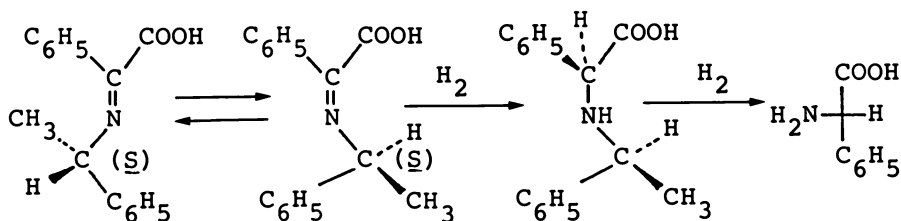
In order to examine the steric course proposed by
Mitsui et al., we have performed asymmetric syntheses
of alanine, α-aminobutyric acid, phenylglycine, phenyl-
alanine and glutamic acid from the corresponding α-keto
acids using (S)-α-methylbenzylamine [Me(-)], (S)-α-
ethylbenzylamine [Et(-)] and (R)-α-(1-naphthyl)ethyl-
amine [Naph(-)] as the chiral adjuvant. The results
are shown in Table I(3,4).
     The results indicate that a) the optical purity of
amino acids obtained with α-methylbenzylamine is always
higher than when α-ethylbenzylamine is used, b) the
optical purity of the amino acids decreases steadily as
the bulk of the alkyl group of the α-keto acids in-
creases, and c) the optical purity increases when (R)-
α-(1-naphthyl)ethylamine is used(4).
     These findings show clearly that the steric course
proposed previously does not explain any of the exper-
imental results. Based on molecular models we pro-
posed a different steric course consistent with the
experiments. Structure I (Scheme 3) represents a con-
formation of the substrate which satisfies all of the

Table I   Asymmetric Synthesis of Amino Acids(3,4)

α-Keto acid R-CO-COOH	Optically active amine		Amino acid	Optical purity(%)
R= CH$_3$	Me (-)	(S)	Alanine	67
	Et (-)	(S)	Alanine	52
	Naph(+)	(R)	Alanine	83
C$_2$H$_5$	Me (-)	(S)	Butyrine	44
	Et (-)	(S)	Butyrine	33
C$_6$H$_5$	Me (-)	(S)	Phenylglycine	30
	Et (-)	(S)	Phenylglycine	24
CH$_2$-C$_6$H$_5$	Me (-)	(S)	Phenylalanine	14
	Et (-)	(S)	Phenylalanine	10
(CH$_2$)$_2$COOH	Me (-)	(S)	Glutamic acid	12
	Et (-)	(S)	Glutamic acid	6

Solvent:EtOH

Scheme 3
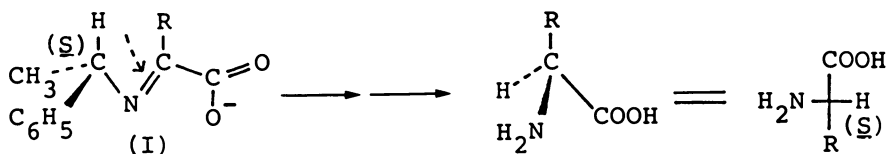
Scheme 4
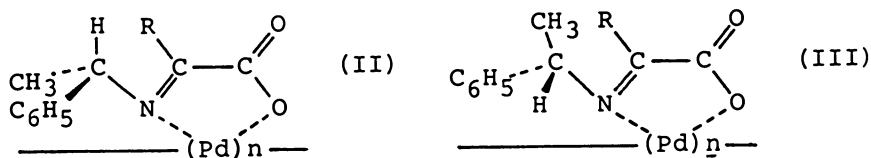
conditions required by the experimental findings(3).
The structure I might be considered to form a sub-
strate-catalyst complex as shown in structure II
(Scheme 4). A molecular model of structure II fits
very well on the surface of the palladium catalyst.
The plane comprising the Schiff base of the α-keto acid
is assumed to be perpendicular to the palladium sur-
face, with the phenyl group lying on the palladium sur-
face as shown in structure II. If the phenyl group was
placed as shown in structure III (Scheme 4), the alkyl
group of the asymmetric moiety and that of the keto
acid would interfere with each other, and the structure
III would be unstable. Thus we assume (A) the sub-
strate initially interacts with the catalyst, to form
a substrate-catalyst complex as shown in structure II
before the catalytic hydrogenation takes place, and
then (B) the structure II is adsorbed on the cata-
lyst from the less bulky side of the molecule, and cat-
alytic hydrogenation takes place. We have called this
hydrogenation process "the chelation hypothesis"(3),
and further studies were undertaken to test this
hypothesis.

Table II shows solvent effects in the asymmetric
synthesis of alanine from pyruvic acid and (S)-α-
methylbenzylamine(4). The optical purity of alanine
decreases with increasing polarity of the solvent. In
the case of the asymmetric synthesis of glutamic acid
from α-keto-glutaric acid and (S)-α-methylbenzylamine,
the configuration of the resulting glutamic acid was
actually inverted by the use of polar solvents. The
substrate appears to interact with the catalyst more
strongly in a less polar than in a more polar solvent.
Thus, the population of the chelated substrate is

Table II   Solvent Effect in the Asymmetric Synthesis
           of Alanine

Solvent	Yield(%)	Optical purity(%)
Hexane	75	75
AcOEt	49	60
DMFA	47	50
i-PrOH	56	46
MeOH	61	38
MeOH:H$_2$O(1:2)	75	35
MeOH:H$_2$O(1:4)	76	29

larger in the less polar solvent than in the more polar
one.
     The unchelated species, which has a stable con-
formation IV (Scheme 5) in solution, could be adsorbed
on the less bulky front -C=N- face of the molecule
(Scheme 5) resulting in an alanine derivative which has
the configuration opposite to that obtained from the
chelated species.
     Asymmetric catalytic hydrogenation of the Schiff
base prepared from ethyl pyruvate and an optically
active amine in different solvents was carried out and
supports the chelation hypothesis. Figure 1 shows
solvent effects in the synthesis of alanine and α-
aminobutyric acid(5). When (S)-benzylic amine was used
as the asymmetric moiety, the optical purity of the
resulting amino acid increased with a decrease in sol-
vent polarity(6,7). A temperature effect was also
observed, and the optical purity of the amino acids
increased upon lowering the reaction temperature(8,9,
10).
     The chelation hypothesis could also be applied to
the catalytic hydrogenation of α-keto acid amides
carried out initially by Hiskey et al., who explained
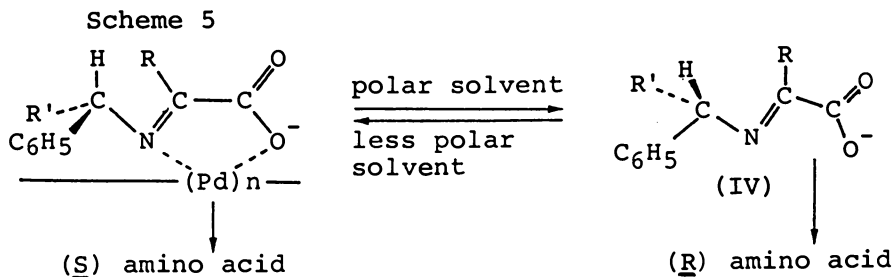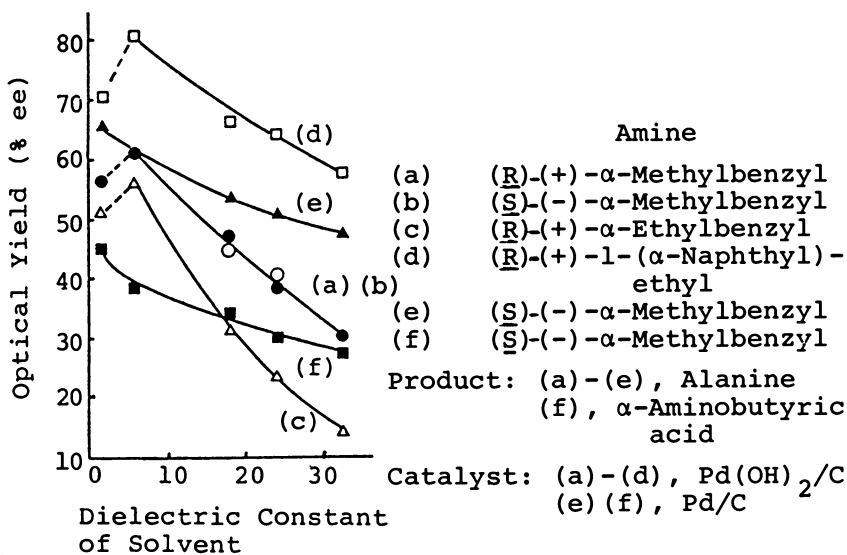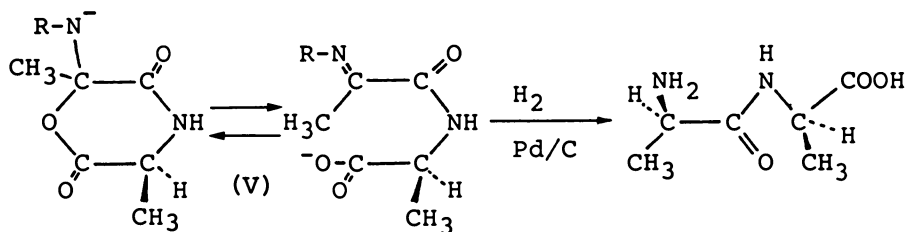the steric course assuming intermediate structure V
(11) (Scheme 6).

     Scheme 5

Figure 1   Solvent Effect in the Asymmetric Synthesis
of Amino Acids from Ethyl Pyruvate(5)

	Amine
(a)	(R)-(+)-α-Methylbenzyl
(b)	(S)-(-)-α-Methylbenzyl
(c)	(R)-(+)-α-Ethylbenzyl
(d)	(R)-(+)-1-(α-Naphthyl)-ethyl
(e)	(S)-(-)-α-Methylbenzyl
(f)	(S)-(-)-α-Methylbenzyl

Product: (a)-(e), Alanine
(f), α-Aminobutyric
acid

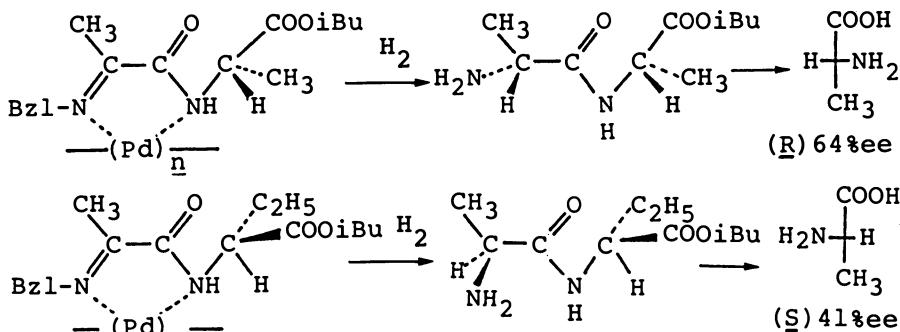Catalyst: (a)-(d), Pd(OH)$_2$/C
(e)(f), Pd/C

Scheme 6

The change in configuration of the resulting amino
acid with the use of different asymmetric moieties is
also explained by the chelation hypothesis(12)
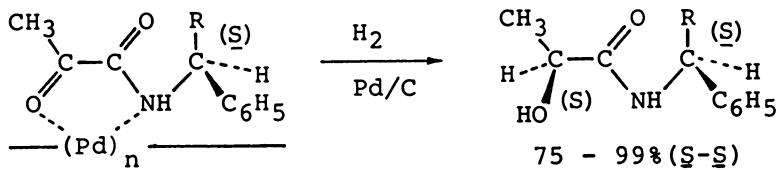(Scheme 7).

In the sequel, we will discuss a generalization of
the chelation hypothesis as it applies to reactions
other than hydrogenation of Schiff bases of α-keto
acids with chiral amines. The catalytic hydrogenation
of pyruvic acid amide resulted in the formation of
lactamide in high optical purity (75-99% diastereomeric
excess)(13). This might be explained by the chelate
conformation of the substrate-catalyst complex shown
in Scheme 8.

The catalytic hydrogenation of optically active
benzoin oxime resulted in the stereoselective formation
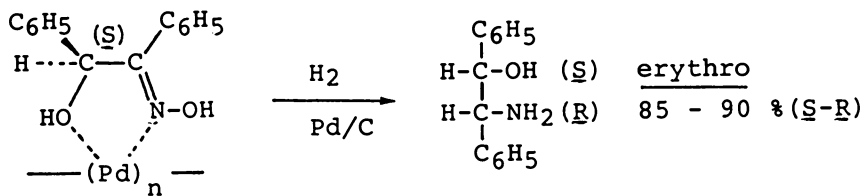of optically active *erythro* diphenylethanolamine in

Scheme 7

$$CH_3 \quad O \quad COOiBu$$
$$C=C \cdots C \cdots CH_3 \quad \xrightarrow{H_2} \quad H_2N-C-C-C\cdots CH_3 \quad \longrightarrow \quad H-C-NH_2$$
$$Bzl-N \quad NH \quad H \qquad H \quad N \quad H \qquad CH_3$$
$$——(Pd)\underset{n}{—} \qquad\qquad H \qquad\qquad (R)\,64\%ee$$

$$CH_3 \quad O \quad C_2H_5$$
$$C=C \cdots C \blacktriangleleft COOiBu \quad \xrightarrow{H_2} \quad C-C-C \blacktriangleleft COOiBu \quad H_2N-C-H$$
$$Bzl-N \quad NH \quad H \qquad NH_2 \quad N \quad H \qquad CH_3$$
$$— (Pd)_{\underset{n}{}} — \qquad\qquad H \qquad\qquad (S)\,41\%ee$$

Scheme 8

$$CH_3 \quad O \quad R \;(S) \qquad CH_3 \quad O \quad R \;(S)$$
$$C=C \cdots C \cdots H \quad \xrightarrow[Pd/C]{H_2} \quad H \cdots C-C \cdots H$$
$$O \quad NH \quad C_6H_5 \qquad HO\;(S) \quad NH \quad C_6H_5$$
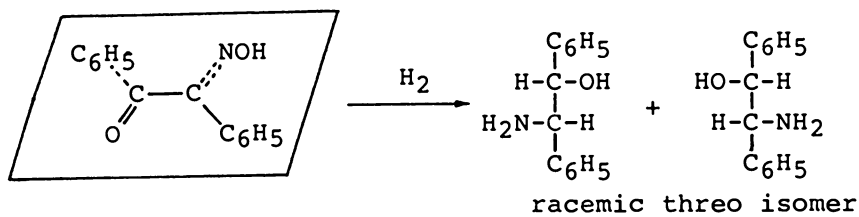$$——(Pd)\underset{n}{} —— \qquad\qquad 75 - 99\%(S\text{-}S)$$

high optical and diastereomeric purity(14) (Scheme 9).
Benzil monoxime was similarly hydrogenated using a
palladium catalyst to form _erythro_ diphenylethanolamine
(15). If the conformation of the substrate in the
reaction is planar, as expected from steric and elec-
tric considerations, the resulting hydrogenation prod-
uct should be the _threo_ isomer(16) (Scheme 10). In

Scheme 9

$$C_6H_5 \;(S) \quad C_6H_5$$
$$H \cdots C-C \qquad \xrightarrow[Pd/C]{H_2} \qquad H-C-OH \;(S) \quad \underline{erythro}$$
$$HO \quad N-OH \qquad\qquad H-C-NH_2\,(R) \quad 85 - 90\;\%(S\text{-}R)$$
$$——(Pd)_{\underset{n}{}} — \qquad\qquad C_6H_5$$

Scheme 10

$$C_6H_5 \quad NOH \qquad\qquad C_6H_5 \qquad\qquad C_6H_5$$
$$C-C \qquad \xrightarrow{H_2} \qquad H-C-OH \qquad HO-C-H$$
$$O \quad C_6H_5 \qquad\qquad H_2N-C-H \quad + \quad H-C-NH_2$$
$$\qquad\qquad\qquad\qquad C_6H_5 \qquad\qquad C_6H_5$$

racemic _threo_ isomer

fact, however, the resulting diphenylethanolamine was found to be predominantly the _erythro_ form.   Similar results have been reported in the synthesis of threonine, phenylserine and ephedrine(17-21) (Scheme 11).

In 1953 Chang and Hartung proposed a mechanism for the hydrogenation of diketone monoxime which explains the formation of a single racemic modification (_erythro_ form) by the formation of a rigid ring-like structure with the catalyst(22).   The explanation could be regarded as a chelation hypothesis preceding the present generalized chelation hypothesis in catalytic hydrogenation.

Recently, support for the chelation hypothesis was obtained by examining the infrared dichroism of the substrate adsorbed on a metal surface using the high-sensitivity reflection method(23-26).   In these investigations the orientation of the substrate on the metal surface is just as assumed by the chelation hypothesis. It was found that the OH, C=O, NH_3, =NOH groups interact with the metal surface and the substrates stand on the catalyst surface vertically.   The observation of the infrared dichroism is considered to be a direct physical evidence for the chelation hypothesis (Scheme 12).

Scheme 11
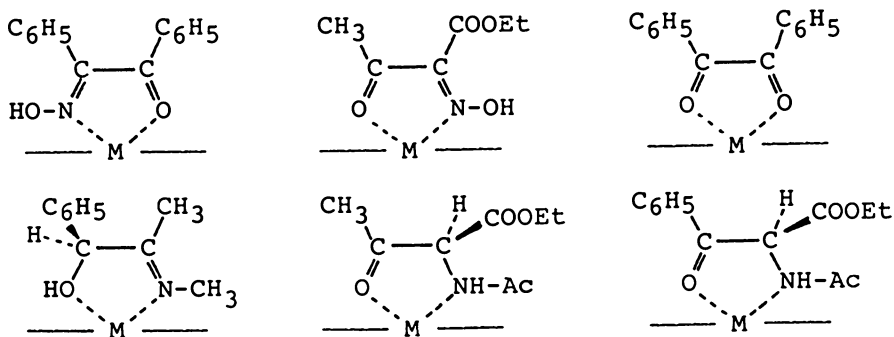
Scheme 12
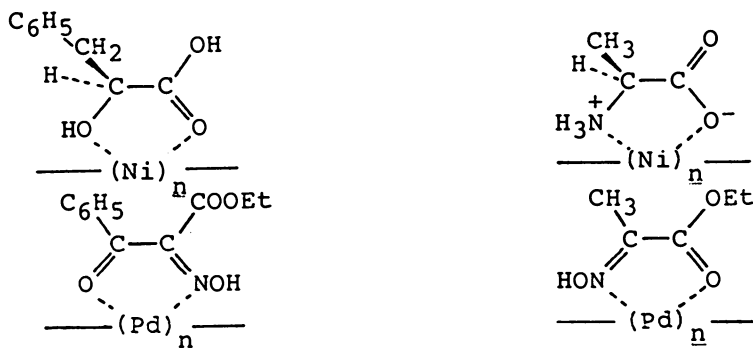
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Asymmetric Grignard Cross-Coupling Catalyzed by Chiral Phosphine–Nickel and Phosphine–Palladium Complexes

TAMIO HAYASHI

Kyoto University, Department of Synthetic Chemistry, Faculty of Engineering, Yoshida, Kyoto, Japan 606

A process of kinetic resolution in the coupling of Grignard reagents R*MgX (having a chiral center at the point of attachment to the metal) with various alkenyl halides under the influence of chiral phosphine-nickel or -palladium complexes is described. Enantiomeric excess of the coupling products depends strongly on the phosphine ligand and ranges up to 94% with e.e.'s in the 60-70% range common. Synthetic applications of the procedure are described.

We have prepared various kinds of optically active phosphines,[1,2] e.g., ferrocenylphosphines and β-aminoalkylphosphines, useful for several catalytic asymmetric reactions, viz., hydrogenation of olefins,[3] ketones,[4] and imines[5] catalyzed by rhodium complexes, hydrosilylation of ketones by rhodium complexes[6] and of olefins by a palladium complex,[7] as well as Grignard cross-coupling by nickel complexes.[2,8] Here, we describe the asymmetric cross-coupling of Grignard and organozinc reagents with organic halides catalyzed by chiral phosphine-nickel and -palladium complexes.

Phosphine-nickel and -palladium complexes have been used as catalysts for the reaction of Grignard reagents (RMgX) with vinyl or aryl halides (R'X') to produce, selectively, cross-coupling products (R-R'). The catalytic cycle of the reaction has been proposed to consist of a sequence of steps involving a diorgano-metal complex ($L_nM(R)R'$) as a key intermediate (Scheme I).

Scheme I
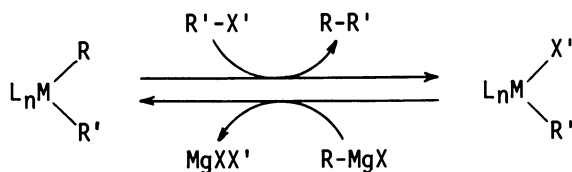
Grignard reagents carrying the magnesium atom attached to a chiral carbon center ordinarily undergo racemization because of the stereochemical instability of the magnesium-carbon bond. Should the inversion at this chiral carbon be much faster than the cross-coupling reaction, however, kinetic resolution of the racemic Grignard reagent under the influence of chiral phosphine-metal complexes might occur, leading to a constant optical yield for the coupling product throughout the reaction (Scheme II).

Scheme II
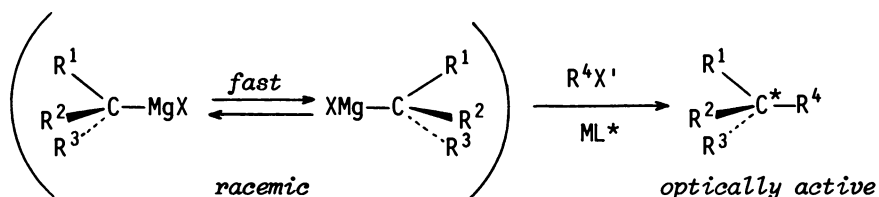
The reaction of 1-phenylethyl-, 2-octyl-, and 2-butyl-magnesium chloride (**1a,b,c**) with vinyl bromide (**2a**), (E)-β-bromo-styrene (**2b**), 2-bromopropene (**2c**), and bromobenzene (**2d**) was carried out in the presence of 0.5 mol% of a nickel catalyst prepared in situ from nickel chloride and a chiral ligand, or a chiral palladium-phosphine complex (eq. 1).

The chiral phosphines used are shown in Figure 1 and representative results are summarized in Table I. Among the ferro-cenylphosphines, (S)-(R)-PPFA was one of the most effective ligands giving the coupling product, 3-phenyl-1-butene (**3a**), in up to 68% ee in the reaction of **1a** with **2a**. The ferrocene planar

Table I. Asymmetric Cross-Coupling of **1** with **2** Producing **3**[a]

Entry No	Chiral catalyst	Product % ee	Entry No	Chiral catalyst	Product % ee
1	(S)-(R)-PPFA/NiCl$_2$	**3a** 63(R)	24	(S)-(R)-PPFA/NiCl$_2$	**3b** 52(R)
2	(S)-(R)-PPFA/NiCl$_2$[b]	**3a** 56(R)	25	PdCl$_2$[(S)-(R)-BPPFA]	**3b** 46(R)
3	(S)-(R)-PPFA/NiCl$_2$[c]	**3a** 66(R)	26	PdCl$_2$[(S)-(R)-BPPFA]	**3c** 5(S)
4	(R)-(S)-PPFA/NiCl$_2$[c]	**3a** 68(S)	27	(S)-(R)-PPFA/NiCl$_2$	**3d** 37(S)
5	PdCl$_2$[(S)-(R)-PPFA][d]	**3a** 61(R)	28	(S)-(R)-BPPFA/NiCl$_2$	**3d** 24(S)
6	(R)-(R)-PPFA/NiCl$_2$	**3a** 54(R)	29	(R)-(S)-PPFA/NiCl$_2$	**3e** 30(R)
7	(S)-FcPN/NiCl$_2$	**3a** 65(S)	30	PdCl$_2$[(R)-(S)-BPPFA]	**3f** 12(R)
8	(R)-PPEF/NiCl$_2$	**3a** 5(S)	31	PdCl$_2$[(S)-(R)-BPPFA]	**3g** 22(R)
9	(S)-(R)-**4a**/NiCl$_2$	**3a** 33(R)	32	(S)-Alaphos/NiCl$_2$	**3a** 38(S)
10	(S)-(R)-**4b**/NiCl$_2$	**3a** 65(R)	33	(S)-Leuphos/NiCl$_2$	**3a** 57(S)
11	(S)-(R)-**4c**/NiCl$_2$	**3a** 65(R)	34	(S)-Phephos/NiCl$_2$	**3a** 71(S)
12	(S)-(R)-**4d**/NiCl$_2$	**3a** 57(R)	35	(R)-PhGlyphos/NiCl$_2$	**3a** 70(R)
13	(S)-(R)-**5a**/NiCl$_2$	**3a** 35(R)	36	(S)-Valphos/NiCl$_2$	**3a** 81(S)
14	(S)-(R)-**5b**/NiCl$_2$	**3a** 7(S)	37	(S)-Ilephos/NiCl$_2$	**3a** 81(S)
15	(S)-(R)-**5c**/NiCl$_2$	**3a** 15(S)	38	(R)-ChGlyphos/NiCl$_2$	**3a** 77(R)
16	(S)-(R)-**5d**/NiCl$_2$	**3a** 62(R)	39	(R)-t-Leuphos/NiCl$_2$	**3a** 83(R)
17	(S)-(R)-**5e**/NiCl$_2$	**3a** 42(S)			(94)[e]
18	(S)-(R)-**5f**/NiCl$_2$	**3a** 17(R)	40	(S)-**8**/NiCl$_2$	**3a** 25(R)[e]
19	(S)-(R)-**5g**/NiCl$_2$	**3a** 65(R)	41	NiCl$_2$[(S)-prophos]	**3a** 0
20	(S)-(R)-**6**/NiCl$_2$	**3a** 57(R)	42	(S)-**9**/NiCl$_2$	**3a** 50(S)
21	(S)-(R)-BPPFA/NiCl2	**3a** 65(R)	43	(S)-**9**/NiCl$_2$ (reused)	**3a** 48(S)
22	PdCl$_2$[(S)-(R)-BPPFA][d]	**3a** 61(R)	44	(S)-**10**/NiCl$_2$	**3a** 53(S)
23	(R)-(S)-**7**/NiCl$_2$	**3a** 17(R)			

[a] The reaction was carried out in ether at 0°C for 24 h unless otherwise noted. 1/2 = 2-4. [b] 1/2 = 1. [c] At -20°C. [d] At 25°C for 60 h. [e] Corrected for the optical purity of the phosphine ligand.

(S)-(R)-PPFA

(R)-(S)-PPFA

(R)-(R)-PPFA

(S)-FcPN

(R)-PPEF

(S)-(R)-BPPFA

(S)-(R)-**4**

Ar =
a   **b**   **c**   **d**

NR_2 = NEt_2 **a**, NPr_2^i **b**, NBu_2^i **c**, N⟩ **d**,

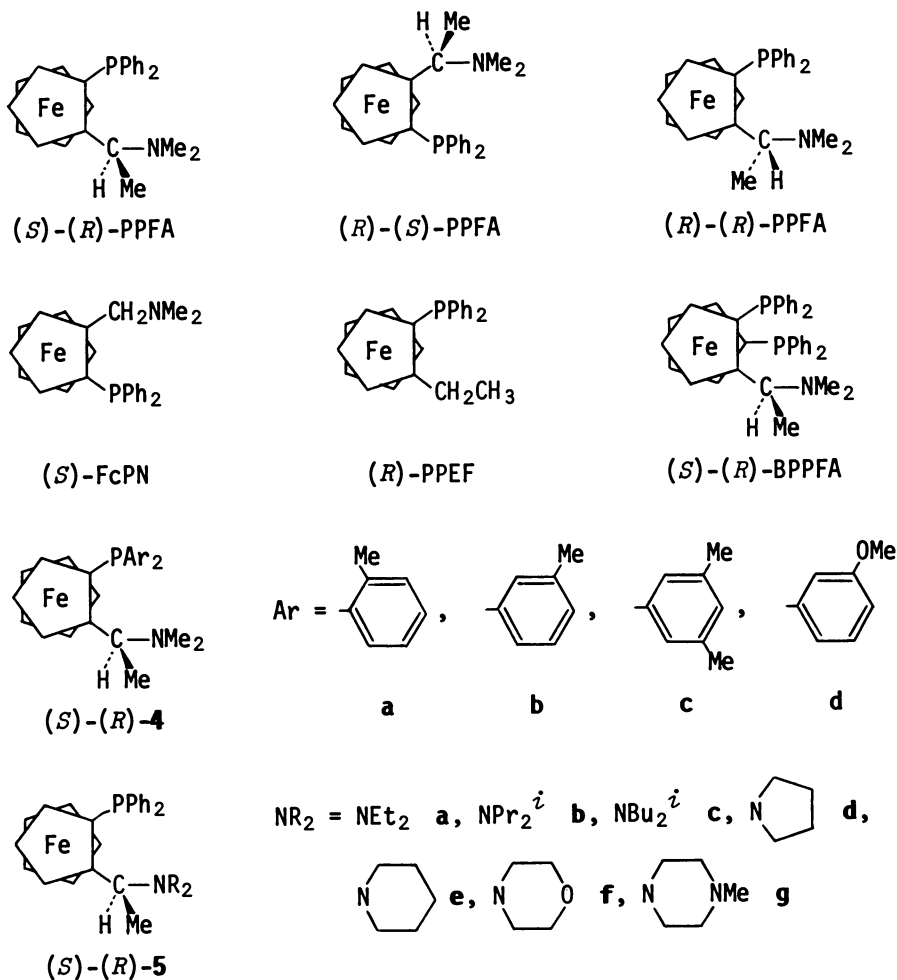N⟩ **e**, N⟩O **f**, N⟩NMe **g**

(S)-(R)-**5**

Figure 1. Chiral phosphine ligands and their palladium complexes. Continued
on next page.

$(S)-(R)-\mathbf{6}$

$PdCl_2[(S)-(R)-PPFA]$

$PdCl_2[(S)-(R)-BPPFA]$

$(R)-(S)-\mathbf{7}$

$(S)-\mathbf{8}$

R =

Me:	Alaphos
i-Bu:	Leuphos
$PhCH_2$:	Phephos
Ph:	PhGlyphos
i-Pr:	Valphos
sec-Bu:	Ilephos
c-Hex:	ChGlyphos
t-Bu:	t-Leuphos

$(S)-\mathbf{9}$

$(S)-\mathbf{10}$
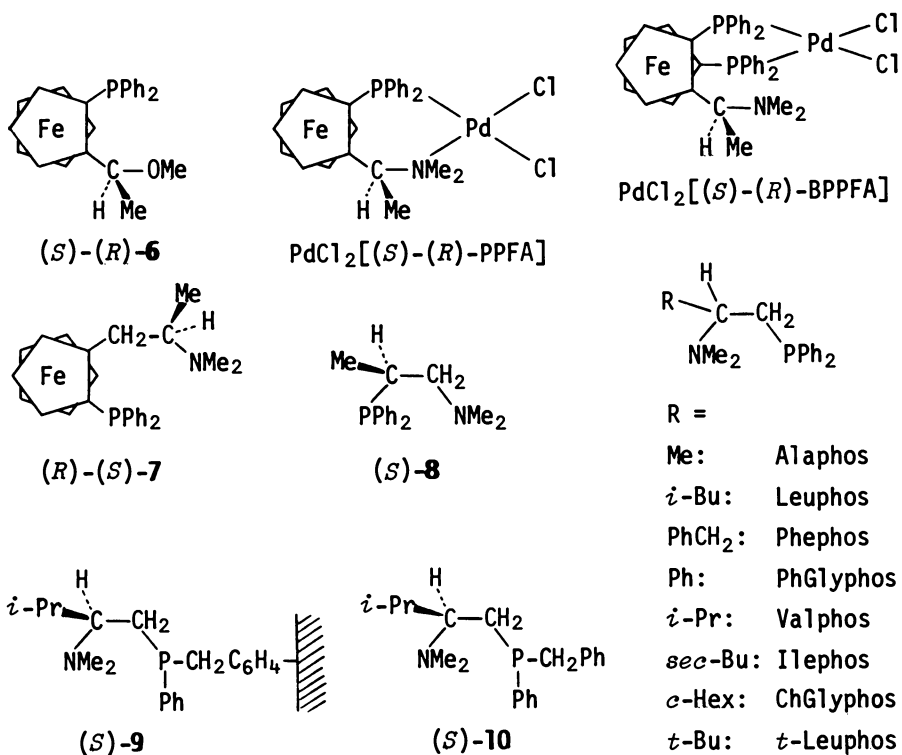
Figure 1 Continued. *Chiral phosphine ligands and their palladium complexes.*

$$R\text{-CH-MgCl} \quad + \quad R'\text{-Br} \quad \xrightarrow[\text{Et}_2\text{O}]{\text{L*M}} \quad \overset{*}{R}\text{-CH-R'} \qquad (1)$$

with Me below the first carbon and Me below the product carbon.
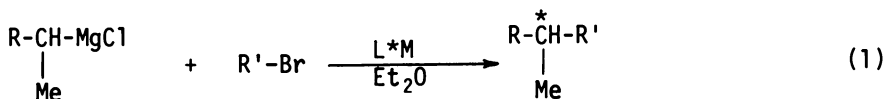
1a: R = Ph   2a: R' = CH=CH₂   3a: R = Ph, R' = CH=CH₂

1b: R = n-HeX   2b: R' = $\diagup\!\!\diagdown\!\!\diagup$Ph   3b: R = Ph, R' = $\diagup\!\!\diagdown\!\!\diagup$Ph

1c: R = Et   2c: R' = CMe=CH₂   3c: R = Ph, R' = CMe=CH₂

                    2d: R' = Ph   3d: R = n-HeX, R' = CH=CH₂

                                           3e: R = Et, R' = CH=CH₂

                                           3f: R = Et, R' = CMe=CH₂

                                           3g: R = Et, R' = Ph

chirality was found to be more important than the carbon central
chirality and the dimethylamino group also appears to be of
primary importance for high stereoselectivity. Thus, (R)-(R)-PPFA
and (S)-FcPN showed an asymmetric induction of comparable effi-
ciency to the (S)-(R)- or (R)-(S)-PPFA ligand (Table I, entries
1∿7), while (R)-PPEF was almost ineffective for the cross-coupling
(entry 8). The stereoselectivity was little changed by introduc-
tion of substituents onto the diphenylphosphino group of the
ligand (Table I, entries 9∿12), but was strongly affected by
changing the steric bulk of the secondary amino group on the
ferrocenylphosphine side chain (entries 13∿19).

   Some of the chiral β–dimethylaminoalkylphosphines derived
from amino acids were more effective than the ferrocenylphos-
phines. (S)-Valphos, (S)-Ilephos, and (R)-t-Leuphos gave the
coupling product **3a** with over 80% ee. It is clear from the
results in Table I that the presence of the dimethylamino group
is, again, important for high stereoselectivity in the reaction
with the β-aminoalkylphosphine-nickel catalyst. We propose a
mechanism involving coordination of the amino group to the magne-
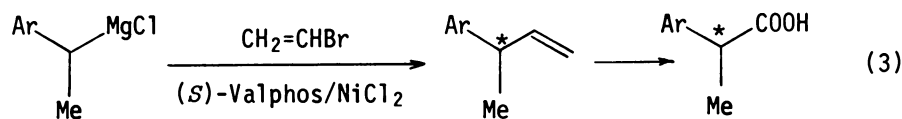sium atom as shown in Scheme III.

Scheme III
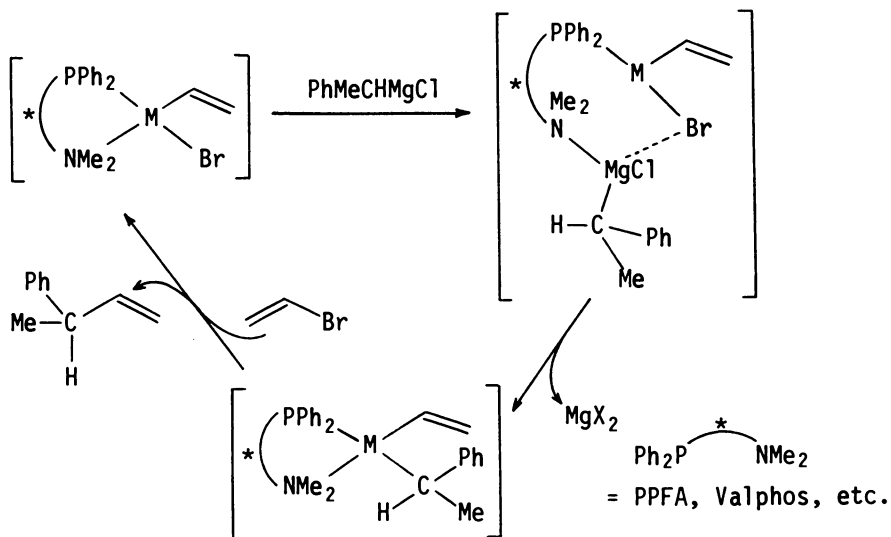
The nickel-catalyzed asymmetric cross-coupling between *sec*-alkyl Grignard reagents with vinyl bromide finds many applications in the synthesis of optically and biologically active substances, e.g. α-curcumene (eq. 2) and 2-arylpropionic acids, (anti-inflammatory drugs) (eq. 3).[8b]
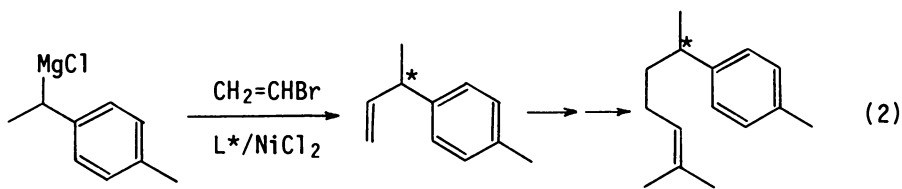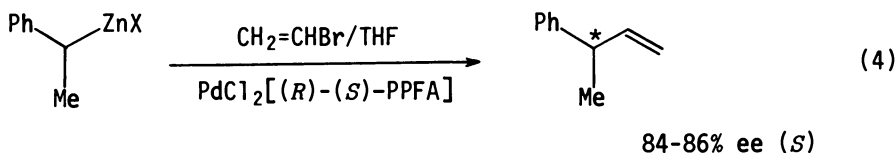

$$L^* = (S)-(R)-PPFA: 66\% \text{ ee } (R)$$
$$L^* = (S)-Valphos: 83\% \text{ ee } (S)$$

$$Ar = p-i-Bu-C_6H_4: 81\% \text{ ee } (R)$$
$$Ar = p-Ph-C_6H_4: 82\% \text{ ee } (R)$$

The asymmetric cross-coupling of organozinc reagents effected with palladium catalysts in THF was found to proceed with higher stereoselectivity than that of Grignard reagent (eq. 4).[9]

$$84-86\% \text{ ee } (S)$$

(4)

Grignard reagents which do not undergo racemization were kinetically resolved by asymmetric cross-coupling in the presence of (S)-Valphos-nickel catalyst. Thus, the reaction of 2-norbornylmagnesium chloride gave olefins of 37% ee (1S,2S,4R), (1R,4S)-Grignard reagent being recovered (eq. 5).[10]

R = H, Ph

(5)
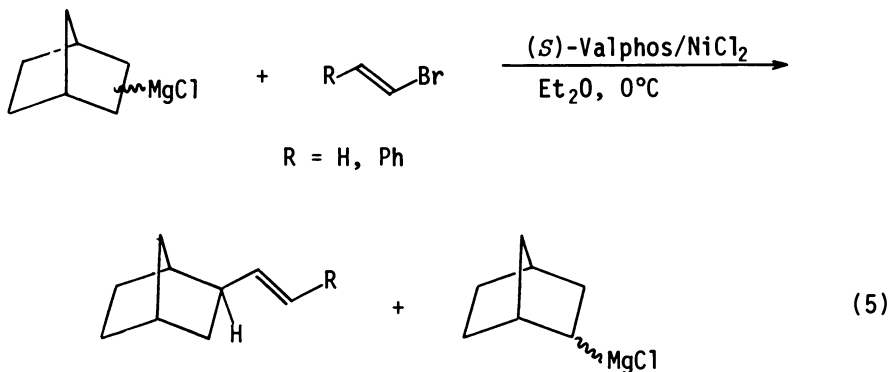
Cross-coupling of α-trimethylsilylbenzylmagnesium bromide with alkenyl bromides catalyzed by the PPFA-palladium complex gave optically active allylsilanes 11 (eq. 6). Allylsilane 11a reacted enantioselectively with the prochiral carbonyl compounds 12 in the presence of TiCl₄ to produce alcohols 13 of over 90% enantiomeric purity (eq. 7).[11]

$$\text{(6)}$$

$$\text{(7)}$$
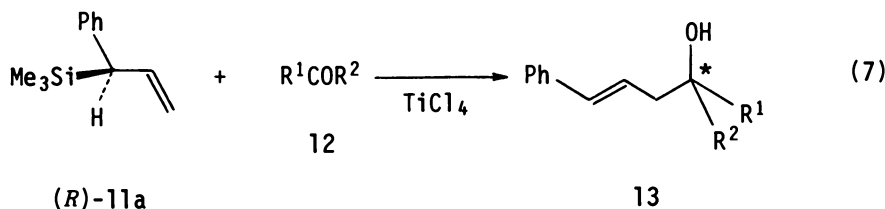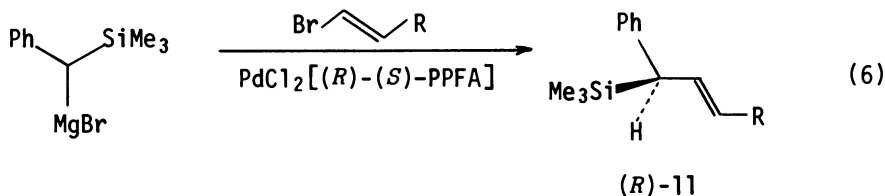
$R^1 = i\text{-Pr}, \ R^2 = H: \quad \sim 90\% \ ee \ (R)$

$R^1 = t\text{-Bu}, \ R^2 = H: \quad \sim 91\% \ ee \ (R)$

$R^1 = Ph, \ R^2 = COOMe: \sim 92\% \ ee$

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Rhodium(I) Catalyzed Enantioselective Hydrogen Migration of Prochiral Allylamines

K. TANI, T. YAMAGATA, and S. OTSUKA—Osaka University, Department of
Chemistry, Faculty of Engineering Science, Toyonaka, Osaka, Japan 560

S. AKUTAGAWA, H. KUMOBAYASHI, and T. TAKETOMI—Takasago
Perfumery Co. Ltd., Central Research Laboratory, 31-36, 5-chome, Kamata,
Ohta-ku, Tokyo, Japan 144

H. TAKAYA and A. MIYASHITA—Institute for Molecular Science,
Chemical Materials Center, Okazaki, Japan 444

R. NOYORI—Nagoya University, Department of Chemistry, Chikusa,
Nagoya, Japan 464

Migration of a multi-substituted inner double bond to a less substituted terminal one occurs when the latter gains relative stability, as seen in functionalized allylic systems(eq. 1).[1,2]

$$R^1_{}R^2 {>} C=CH-CH_2X \longrightarrow R^1_{}R^2 {>} CH-CH=CHX \qquad (1)$$
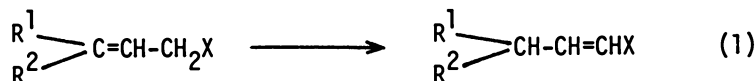
Various complexes of $Fe^{2,3}$, Ru^{2-4}, $Co^{1,2}$, Rh^{2-4}, Ir^5, $Ni^{2,6}$, and Pt^7 have been proposed as catalysts for such allylic migrations. All of them, of course, lead to racemic product. In a recent

communication[1] we have shown that enantioselective hydrogen migration in prochiral allylamines leading to optically active enamines is possible with chiral cobalt catalysts. Both the optical yield and catalytic activity, however, were too low to be of practical use. We have now found better catalysts, namely rhodium(I) chiral diphosphine complexes. In this report we briefly summarize the results of our stereochemical and kinetic studies of such rhodium-catalyzed stereospecific allylamine isomerizations.

As representative $\underline{Z}$ and $\underline{E}$ allylamines we chose diethylnerylamine (1)[8] and its geranyl analog (2).[9] The catalyst was a cationic Rh(I) compound, [Rh(diphos)(diene)]ClO$_4$, prepared from [Rh(diene)Cl]$_2$ (diene=1,5-cyclooctadiene or norbornadiene). For the chiral diphos ligand we employed (2$\underline{R}$, 3$\underline{R}$)-DIOP[10], a tetracyclohexyl analog of (2$\underline{R}$, 3$\underline{R}$)-DIOP [($\underline{R}$)-CyDIOP][11], and ($\underline{R}$)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl [($\underline{R}$)-BINAP].[12]

Typically, a THF solution (10 ml) containing the substrate (5 mmol) and a catalytic amount (0.05 mmol) of [Rh(diphos)(COD)]-ClO$_4$ was stirred under a nitrogen atmosphere at 60° for 17-24h. The isomerization product from 1 and 2 was (3$\underline{R}$)-(3) and (3$\underline{S}$)-citronellal-_trans_-enamine (4), respectively (eq. 2,3). The chemical yields are virtually quantitative, with 94-96% optical yields. A secondary amine, cyclohexylgeranylamine (5) gave the

$$\text{Rh}(\underline{R}\text{-BINAP})^+ \qquad 60°/\ \text{THF} \qquad (2)$$

(R)

NEt$_2$

1

3

94% ee

$$\text{(3)}$$

$$\text{(4)}$$
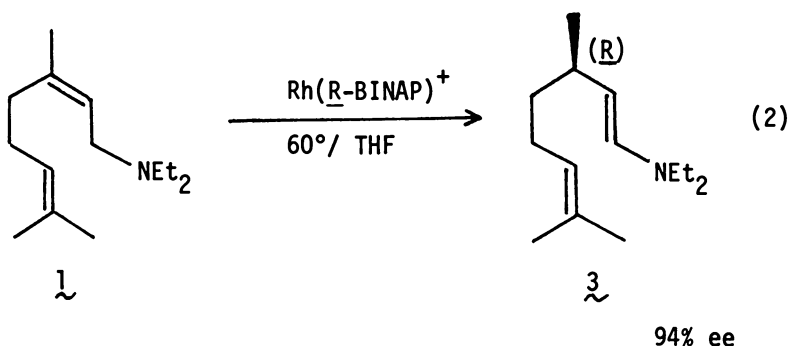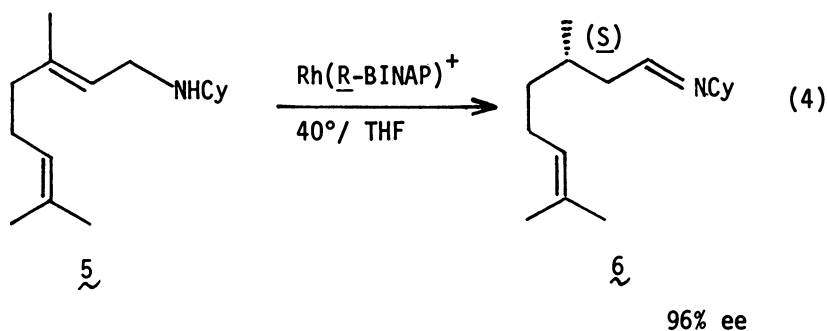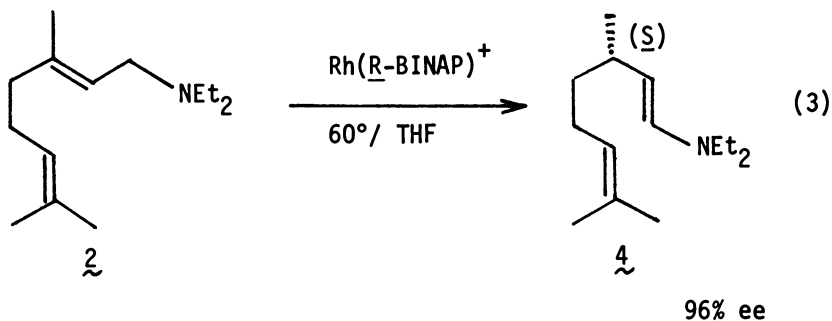
corresponding imine (6) in 96% enantiomeric excess (eq. 4). Optical yields were assessed by transforming the hydrolyzed product (citronellal) via isopulegol into menthol which serves as a reliable reference substance for determining optical purity by specific rotation.

A Rh(I) diphos complex with (S)-BINAP was also prepared to examine the stereochemistry of the isomerization product. The E-allylamine (2) was isomerized (60°, 17h, THF) to (3R)-citronellal-trans-enamine (3) with 96% ee. The stereochemical correlation between the configurations of the Rh(I) ligand and product can now be summarized as shown below.
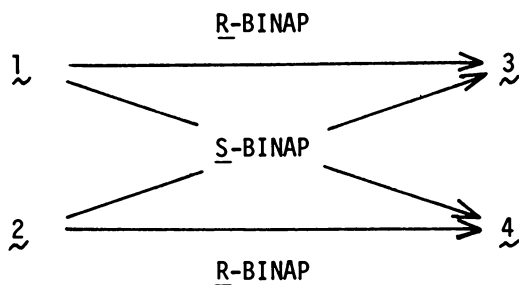
A similar correlation has already been observed for the cobalt catalyst.[1]

Catalysts containing (R)-DIOP and (R)-CyDIOP as the chiral ligand gave lower optical yields. Thus, isomerization of 1 with [Rh(R-DIOP)(COD)]$^+$ and [Rh(R-CyDIOP)(COD)]$^+$ gave 4 in 27% and 68% ee, respectively. The optical yield for the isomerization of 5 with [Rh(R-CyDIOP)(COD)]$^+$ was drastically decreased to only 11%. The reaction rate depends on the nature of the diphos ligand; qualitatively the rate increases in the order of CyDIOP < DIOP < BINAP.

Dimethyl[(E)-3-phenyl-2-butenyl]amine (7) is a slow reacting substrate, presumably because of its styrene type conjugation. Its isomerization, effected with [Rh(R-BINAP)(COD)]$^+$ (60°, 23h, THF), gave the (3R)-trans-enamine (8) in 83% yield with 90% ee (eq. 5). A competitive isomerization of a 9:1 mixture of 7 and its Z-isomer indicated a faster rate for E than for Z.
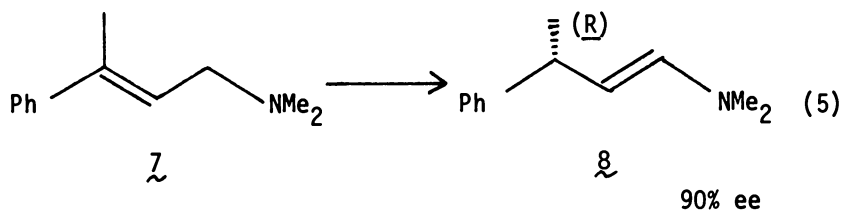
The rate of $[Rh(\underline{rac}\text{-BINAP})(COD)]^+$-catalyzed isomerization of
$\underset{\sim}{1}$ (THF, 40-70°C) was measured by monitoring the ^1H NMR signals of
the methylene protons of the N-ethyl substituents in $\underset{\sim}{1}$ and $\underset{\sim}{3}$.
The substrate concentration range was 0.05-0.55 mol/l, and that
of the Rh(I) catalyst precursor 0.8×10^{-3} - 4.0×10^{-3} mol/l.
The reaction follows the following rate law, at least for the
initial stage ($\lesssim 17\%$ conversion):

$$R = k_{obs} [Rh(I)][Substrate]$$

Compound $\underset{\sim}{2}$ was isomerized a little faster than $\underset{\sim}{1}$ by a factor
of 1.1. tert-Amines and chelating ligands such as COD retard the
rate. 1,3-Dienamines strongly inhibit the reaction.

In order to obtain further mechanistic information, di-
methyl[($\underline{E}$)-3-phenyl-2-butenyl]amine-2,2-$\underline{d_2}$ was prepared via ($\underline{E}$)-
3-methylcinnamyl alcohol-1,1-$\underline{d_2}$ obtained by $LiAlD_4$ reduction of
ethyl ($\underline{E}$)-3-methylcinnamate. The $[Rh(\underline{R}\text{-BINAP})(COD)]^+$-catalyzed
isomerization (60°, 23h, THF) gave exclusively 1,3-dideuterio-
$\underline{trans}$-enamine (95% yield), as established unambiguously by ^1H NMR
spectra. This conclusively shows that stereospecific 1,3-hydrogen
atom migration has occurred and represents the first established
example of a transition metal assisted 1,3-suprafacial hydrogen
migration for linear allylic systems. A stereoselective 1,3-
hydrogen migration has been reported for a cyclic allyl alcohol,
namely, endo-β-1-hydroxydihydrocyclopentadiene ($\underline{9}$) was isomerized
by $Fe(CO)_5$ (10 mol%, 130°) to the ketone ($\underset{\sim}{10}$), while the isomeriz-
ation was not observed for the α-isomer ($\underset{\sim}{11}$).[13]

Any mechanistic proposal should accommodate the results, (1)
100% 1,3-hydrogen migration and (2) 100% $\underline{trans}$-enamine formation.
We postulate an η-allyl-hydride Rh(III) complex as the reactive
intermediate as it accommodates these features and is consistent
with other observations, viz., (1) faster rate for $\underline{E}$- than for
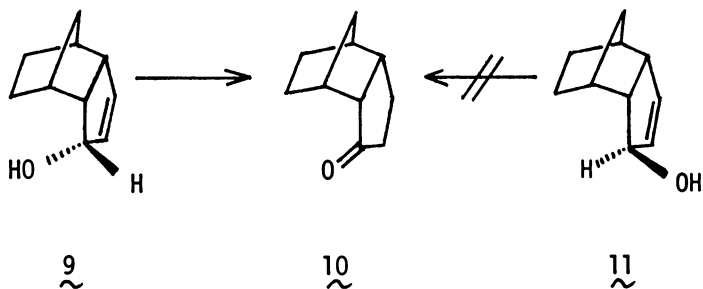
Z-allylamime, (2) inhibition by free amines, diolefins, and con-
jugate dienamines, and (3) stereochemical correlation between the
substrate geometry and product configuration.

    The present rhodium catalyzed isomerization reaction pro-
vides a convenient access to chiral terpenoid enamines and alde-
hydes. Its synthetic utility toward such natural products as
l-menthol, vitamin E, pheromones etc. is obvious.

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Application of Immobilized Enzymes for Asymmetric Reactions

ICHIRO CHIBATA

Tanabe Seiyaku Co., Ltd., Research Laboratory of Applied Biochemistry, 16–89, Kashima-3-chome, Yodogawa-ku, Osaka, Japan

Three immobilized enzyme or microbial cell systems currently used industrially in synthesis of chiral amino acids plus one presently under development are described. L-amino acids are produced by enzymatic hydrolysis of DL-acylamino acid with aminoacylase immobilized by ionic binding to DEAE-Sephadex. *Escherichia coli* cells immobilized by κ-carrageenan crosslinked with glutaraldehyde and hexamethylenediamine are used to convert fumaric acid and ammonia to L-aspartic acid and *Brevibacterium flavum* cells similarly immobilized are used to hydrate fumaric acid to L-malic acid. The decarboxylation of L-aspartic acid by immobilized *Pseudomonas dacunhae* to L-alanine is currently under investigation.

Enzymes are biological catalysts and participate in many chemical reactions occurring in living things. Unlike ordinary chemical catalysts, enzymes have the ability to catalyze a reaction under very mild conditions in neutral aqueous solution at normal temperature and pressure, and with very high substrate specificity. They also have chiral specificity and catalyze asymmetric reactions. However, enzymes are produced by organisms for their own requirements and, though efficient and ef-

fective catalysts, are not always ideal for practical applica-
tions. Thus, in order to obtain superior catalysts for appli-
cations, that is, highly active and stable catalysts having
appropriate specificity, modification of enzymes has been car-
ried out. Among such modifications, immobilization has been
extensively studied in the past fifteen years. If active and
stable immobilized enzymes are prepared, the expected advan-
tages, compared to soluble enzymes, are as follows: (1)
stability of the enzymes is improved, (2) enzymes can be tailor-
made for specific use, (3) enzymes can be reused, (4) continuous
operation becomes practical, (5) reactions require less space,
(6) better control of reactions is possible, (7) higher purity
and yield of products may be attained, and (8) saving of re-
sources with less attendant pollution may be achieved.

      More recently, techniques of direct immobilization of whole
microbial cells have been developed, either to avoid the need to
extract enzymes from microbial cells or to utilize multi-enzyme
systems. Since the early 1960's, we have studied the immobili-
zation of enzymes and microbial cells for industrial applica-
tions and have succeeded in the industrialization of three asym-
metric reactions. In this report, these already industrialized
systems and a potential system for which we are planning indus-
trialization will be described.

I.   IMMOBILIZED AMINOACYLASE — Production of L-Amino Acids
      For the industrial production of L-amino acids, fermentation
and chemical synthetic methods appear to be promising. However,
conventional chemical synthesis leads to a racemic mixture.
Hence resolution of enantiomers is necessary to obtain optically
active L-amino acids. Among many resolution methods, the en-
zymatic method using mold aminoacylase developed by us proved to
be one of the most advantageous procedures. An acyl-DL-amino
acid is selectively hydrolyzed by aminoacylase to give L-amino
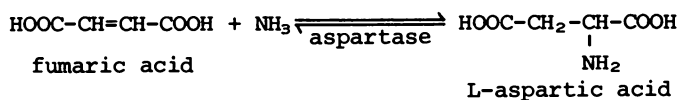acid and unhydrolyzed acyl-D-amino acid.

```
DL-R-CH-COOH                          L-R-CH-COOH     D-R-CH-COOH
      |        + H₂O  ─────────────→        |       +       |
   NHCOR'              aminoacylase        NH₂          NHCOR'
N-acyl-DL-                                             N-acyl-D-
amino acid                            L-amino acid     amino acid
      ↑───────────────  racemization  ───────────────┘
```
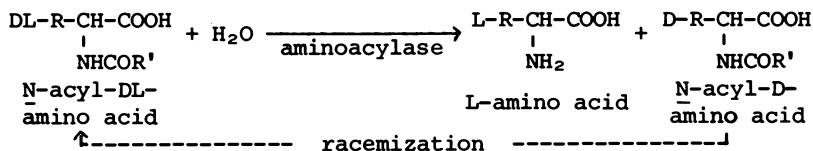
Between 1954 and 1969, this enzymatic resolution method had been employed by Tanabe Seiyaku Co., Ltd. for the production of several L-amino acids. In the 1960s we extensively studied the immobilization of aminoacylase for continuous optical resolution [1,2]. A variety of immobilization methods were tested for industrial purposes, from which aminoacylase immobilized by ionic binding to DEAE-Sephadex was chosen. Through chemical engineering studies on aminoacylase columns we designed an enzyme reactor for continuous production. Since 1969, we have been operating several series of enzyme reactors for the production of L-methionine, L-valine, L-phenylalanine and so forth. With this immobilized enzyme system, L-amino acids can be produced more economically compared to the conventional batch system using native enzyme as shown in Fig. 1.

II. IMMOBILIZED MICROBIAL CELLS

A. Production of L-Aspartic Acid

We attempted continuous production of L-aspartic acid from fumaric acid and ammonia by immobilized *Escherichia coli* having high aspartase activity [3, 4, 5]. Various methods were tested for the immobilization of microbial cells, and a stable and active enzyme system was obtained by entrapping whole microbial cells in a polyacrylamide gel lattice.

```
HOOC-CH=CH-COOH + NH₃ ⇌─────────→ HOOC-CH₂-CH-COOH
                        aspartase                |
   fumaric acid                                 NH₂
                                          L-aspartic acid
```

Using a column packed with immobilized *E. coli* cells, conditions for continuous production of L-aspartic acid were investi-
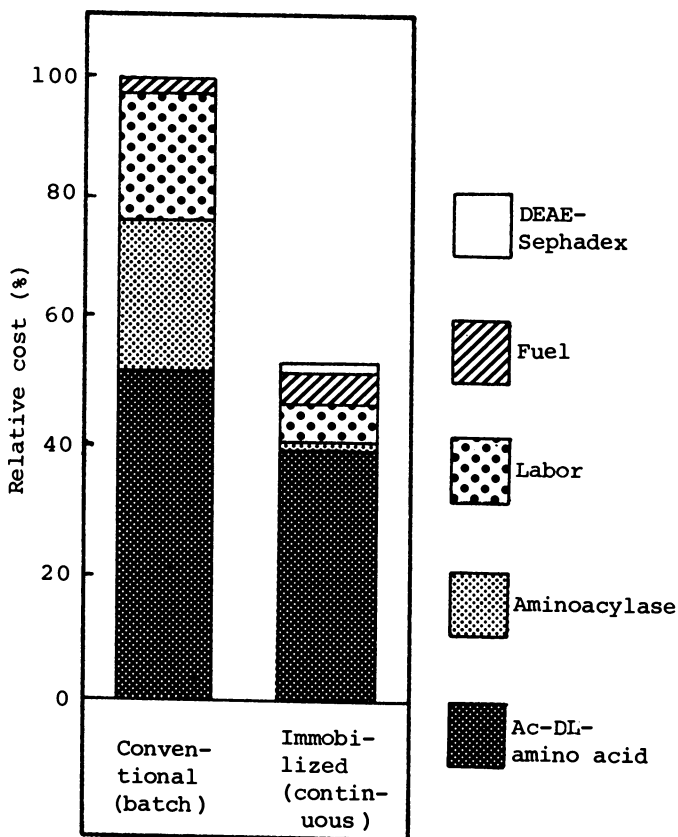
Figure 1.   Cost comparison for production of L-amino acids.

gated in detail, and an aspartase reactor system was designed. The system is essentially the same as that for the immobilized aminoacylase system and has been operated industrially since 1973.

By way of a further improvement of the process, a new technique using κ-carrageenan was discovered for immobilization of *E. coli* [6, 7, 8]. κ-Carrageenan is a kind of polysaccharide prepared from seaweed and has the characteristic of becoming a gel under mild conditions. We compared the efficiency of *E. coli* cells immobilized with polyacrylamide and κ-carrageenan in production of L-aspartic acid, and found that *E. coli* immobilized with κ-carrageenan and then treated with glutaraldehyde and hexamethylenediamine shows the highest productivity (Table 1). Therefore, we considered that this preparation is most advantageous for continuous production of L-aspartic acid, and in 1978 we replaced the conventional polyacrylamide gel method by the new carrageenan method.

Table 1
COMPARISON OF PRODUCTIVITY OF *E. coli* IMMOBILIZED
WITH POLYACRYLAMIDE AND WITH CARRAGEENAN
FOR PRODUCTION OF L-ASPARTIC ACID

Immobilization method	Aspartase activity (unit/g cells)	Stability at 37°C (half-life, days)	Relative productivity*
Polyacrylamide	18,850	120	100
Carrageenan	56,340	70	174
Carrageenan (GA)	37,460	240	397
Carrageenan (GA+HMDA)	49,400	680	1,498

GA:glutaraldehyde, HMDA:hexamethylenediamine

* Productivity = $\int_0^t E_0 \exp(-k_d \cdot t)\,dt$

E_0=initial activity, k_d=decay constant, t=operational period

B. Production of L-Malic Acid

In 1974 we succeeded in the industrial production of L-malic acid from fumaric acid by *Brevibacterium ammoniagenes* cells immobilized by the polyacrylamide gel method [9, 10]. The asymmetric reaction catalyzed by the fumarase activity of the cells is shown below.

$$HOOC-CH=CH-COOH + H_2O \xrightleftharpoons[\text{fumarase}]{} HOOC-CH_2-\underset{\underset{\displaystyle OH}{|}}{CH}-COOH$$

fumaric acid   L-malic acid
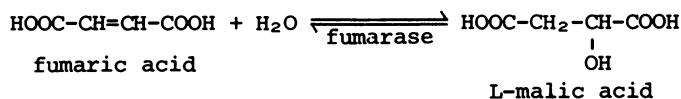
As in the case of L-aspartic acid production, we investigated the carrageenan method to improve the productivity for L-malic acid. After screening various microorganisms for maximal fumarase activity, *Brevibacterium flavum* was found to show a higher enzyme activity after immobilization with κ-carrageenan than the formerly used *B. ammoniagenes*, as shown in Table 2 [11]. Therefore, this polyacrylamide method was also changed to the carrageenan method in 1977. The new method gives satisfactory results for industrial production of L-malic acid.

Table 2
COMPARISON OF PRODUCTIVITIES OF *Brevibacterium ammoniagenes*
AND *Brevibacterium flavum* IMMOBILIZED WITH POLYACRYLAMIDE
AND WITH CARRAGEENAN FOR PRODUCTION OF L-MALIC ACID

Immobi-lization method	B. ammoniagenes			B. flavum		
	Activity (unit/ g cells)	Half-life at 37°C (day)	Relative productivity	Activity (unit/ g cells)	Half-life at 37°C (day)	Relative productivity
Polyacryl-amide	5,800	53	100	6,680	94	204
Carra-geenan	5,800	75	142	9,920	160	516

* activity after treatment with bile extract

Productivity $= \int_0^t E_0 \exp(-k_d \cdot t) dt$

E_0=initial activity, k_d=decay constant, t=operational period

C. Production of L-Alanine and D-Aspartic Acid

Besides these two industrial applications of immobilized microbial cells for asymmetric reactions, we are presently studying the continuous production of L-alanine from L-aspartic acid. At present, L-alanine is produced by a batch process. A continuous production system using immobilized *Pseudomonas dacunhae* cells with high L-aspartate β-decarboxylase activity is currently under investigation [12]. The reaction proceeds as shown below.

$$L-HOOC-CH_2-CH-COOH \xrightarrow[\beta\text{-decarboxylase}]{L\text{-aspartate}} L-CH_3-CH-COOH + CO_2$$

$$\underset{NH_2}{} \qquad\qquad\qquad \underset{NH_2}{}$$

L-aspartic acid   L-alanine
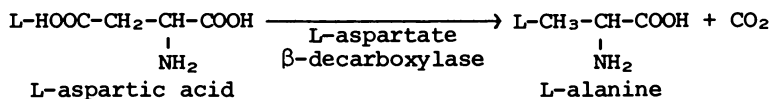
In this continuous system using immobilized cells, there are problems associated with evolution of CO_2 gas during the reaction. It is difficult to maintain the plug-flow of the substrate solution under normal pressure, and to keep a constant pH of reaction mixture in the reactor because of the CO_2 effervescence. We therefore designed a closed column reactor which performs the enzyme reaction at an elevated pressure such as 10 Kg/cm^2. Using this reactor, since liberated CO_2 gas is melded into reaction mixture, the complete plug-flow of the substrate solution is maintained and the pH of reaction mixture is not appreciably changed. Therefore, as shown in Table 3, the efficiency of immobilized cells for production of L-alanine in the closed column system (at high pressure) is much higher than that in the conventional column system at normal pressure.

The decarboxylase enzyme shows high enantiomer selectivity reacting only with L-aspartic acid. Thus, L-alanine and D-aspartic acid can be produced from DL-aspartic acid at the same time.

D-Aspartic acid is used as an important intermediate for synthetic penicillin, whose synthesis has been developed by Tanabe Seiyaku Co.

Table 3

COMPARISON OF EFFICIENCIES AND STABILITIES
OF CONVENTIONAL AND CLOSED COLUMN
REACTORS FOR L-ALANINE PRODUCTION

	Conventional (normal pressure)	Closed (high pressure)
Efficiency μmole/hr/ml of reactor at 99% convension	250	360
Stability half-life, days at 37°C	46	46

We are planning industrialization of these continuous L-alanine and D-aspartic acid production systems using immobilized *P. dacunhae* in the near future.

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Asymmetric Synthesis Using Cofactor-Requiring Enzymes

GEORGE M. WHITESIDES, CHI–HUEY WONG, and ALFRED POLLAK

Massachusetts Institute of Technology, Department of Chemistry, Cambridge, MA 02139

The use of cofactor-requiring enzymes as catalysts for large-scale requires efficient and economical procedures for *in situ* regeneration of these co-factors. This manuscript summarizes the procedures which are now available for cofactor preparation and regeneration. ATP can be effectively regenerated from ADP (and AMP) using acetyl phosphate and acetate kinase (and adenylate kinase), and it can be prepared inexpensively from RNA. Use of ATP-requiring enzymes is now routine (at least as far as the ATP regeneration is concerned). The use of the nicotinamide cofactors is more difficult, because these materials decompose in solution. The best procedure for regenerating NAD(P)H from NAD(P)$^+$ are those based on formate/formate dehydrogenase, glucose 6-phosphate/glucose-6-phosphate dehydrogenase, and ethanol/alcohol dehydrogenase/aldehyde dehydrogenase. The best procedures for regenerating NAD(P)$^+$ from NAD(P)H use dioxygen/methyl viologen or ketoglutarate/glutamic dehydrogenase.

Although enzymes can be effective catalysts for enantio-selective reactions, they have been relatively little used for this purpose in practical organic synthesis. The relative indifference of synthetic chemists to the potential of this group of catalysts is a consequence of a number of circumstances. First, enzymes are unfamiliar: they require aqueous environments; they are prepared, characterized, and manipulated using specialized techniques having little in common with techniques used in other areas of synthetic organic chemistry; and they appear to be unstable. Second, certain generally interesting classes of enzymatic reactions (including many reactions which *form* bonds between organic molecules and most reactions which involve oxidation or reduction) involve cofactors; these reactions are expensive. Third, the substrate selectivity

of enzyme-catalyzed reactions often limits the generality of their application. Nonetheless, in these reactions in which they are applicable, they can be very efficient catalysts, and their ability to catalyze reactions of naturally-occurring substances (which are, of course, products of and reactants in the reactions which take place in life) makes them of particular interest in pharmaceutical, food, and agricultural chemistry.

The research summarized in this manuscript was directed toward one particular problem in enzymology: that is, the development of techniques which would make possible the use of cofactor-requiring enzymes in organic synthesis. The central problem in this area has been one of expense. ATP costs approximately $800/mole when purchased in mole quantities; the costs of the nicotinamide cofactors range from $1500/mole (for NAD^+) to $250,000/mole (for NADPH). There are few organic reactions which can tolerate costs of this magnitude for stoichiometric reagents. The solution to this problem of cost is, in principle, straightforward, and has been the subject of extensive previous work. The most efficient way of lowering the effective cost of the cofactors is to develop procedures which make possible their regeneration from inexpensive reagents *in situ* (Figure 1)

Among the considerations which determine the usefulness of a synthetic sequence which involves a cofactor-requiring enzymatic step are:

1) The character of the reaction used for regeneration of the cofactor. The reagent A should be readily available, inexpensive, and stable; the product B should not complicate workup; the equilibrium constant for the reaction $A + X \rightleftharpoons B + Y$ should lie far to the right; the enzymes used (if any) should have low cost, high stability, and high specific activity.

2) The intrinsic stabilities of the cofactors X and Y under the conditions of the reaction.

3) The original cost of the cofactor.

4) The operational simplicity of the regeneration scheme.

Here we divide the discussion of approaches to cofactor regeneration into three sections: one each for ATP, oxidized nicotinamide cofactors (NAD^+ and NADP), and reduced nicotinamide cofactors (NADH and NADPH). Most of the other cofactors which appear in biochemistry are either easily regenerated or of little importance, and we shall not discuss their regeneration here.

Although either purely chemical or enzymatic procedures might be used to effect the regeneration reactions, in general enzymatic procedures are superior. To be able to recycle the cofactors a large number of times it is necessary to have high yields for the reactions which regenerate them. Thus, to have 50% of the cofactor remaining after 100 cycles of reaction and regeneration, the yield for each cycle must be 99.3% (100 log 0.993 = log 0.50), and for 1000 cycles, the corresponding yield must be 99.9%. This type of selectivity is most easily obtained by enzymatic catalysis, and we have therefore used only enzymatic methods in our work.
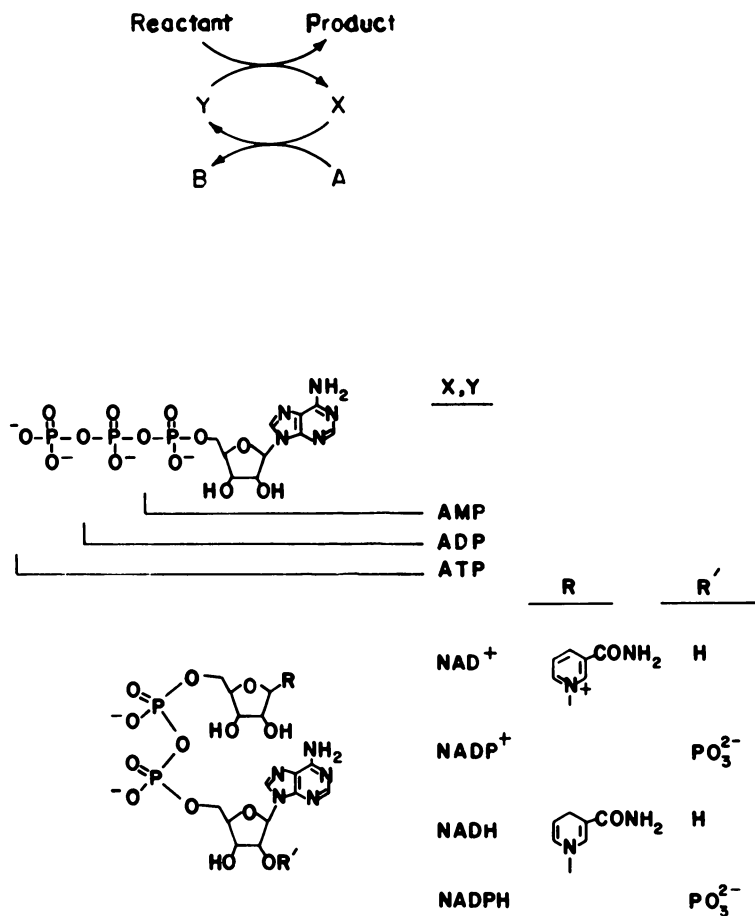
Figure 1. General scheme for cofactor regeneration (top) and structures of adenosine and nicotinamide cofactors (bottom). Key: X, Y, cofactors; A, regenerating agent; and B, product from this reagent.

ATP

Regeneration. Most biochemical reactions which involve ATP
as a cofactor convert it to ADP or AMP; adenosine itself is impor-
tant only as a product of the small group of reactions which pro-
ceed through S-adenosyl methionine. Thus, it is necessary to have
regeneration procedures which will convert both AMP and ADP to
ATP. Chemical methods for these phosphorylation reactions can be
rejected out of hand: they are incompatible with the enzymes
which would be present in the system as catalysts for reactions
which *use* the ATP, and lack the specificity required to give high
yields and high total turnover numbers (TTN) for the ATP (TTN =
moles of product produced in the reaction per mole of cofactor or
enzyme present). The stability of ATP is good: the hydrolysis of
ATP at pH 6-8 is slow compared with any synthetic reaction of
practical interest.

The choice of phosphorylating agents which might, in princi-
ple, be used to convert AMP or ADP to ATP is limited. Table I
summarizes values of $\Delta G^{\circ\prime}$ for the reaction XP + ADP $\rightleftharpoons$ X + ATP for
those compounds XP which are (relatively) readily available and
exergonic with respect to phosphorylation of ADP. Of these, PEP

Table I.   Free energy of phosphorylation of ADP to ATP

XP	$\Delta G^{\circ\prime}$ (kcal/mole)
Phosphoenolpyruvate (PEP)	-7.5
Carbamyl phosphate	-5.0
Acetyl phosphate (AcP)	-3.0
Pyrophosphate (PP_i)	-0.7

is relatively expensive (although regeneration systems based on
PEP have many advantages in simplicity), carbamyl phosphate has
very poor stability in solution, and pyrophosphate is only a weak
phosphorylating agent and requires enzymes which are available
only with difficulty. Acetyl phosphate (AcP) is a reagent which
offers a practical combination in its characteristics: it is
prepared easily from inexpensive reagents; the enzymes it requires
for use in ATP regeneration are commercially available and accept-
ably stable; it is a good phosphorylating agent. In this manu-
script we focus attention on procedures for ATP regeneration based
on AcP. The only other procedure which seems useful for labor-
atory-scale is that based on PEP; details of this procedure will
be published elsewhere.

AcP can be prepared easily by acylation of phosphoric acid
with acetic anhydride or with ketene, and isolated as a fairly

stable ammonium salt (1,2). Acetate kinase (the enzyme which catalyzes the reaction of acetyl phosphate with ADP) and adenylate kinase (the enzyme which catalyzes phosphate transfer between ATP and AMP) are readily available and inexpensive. The ATP regeneration schemes based on these enzymes are shown in Figure 2 (3,4,5).

These schemes have now been used to prepare organic materials on scales of several moles. An example relevant to asymmetric synthesis is the glycerol kinase-catalyzed phosphorylation of glycerol (equation i) (6).

$$\text{(i)}$$
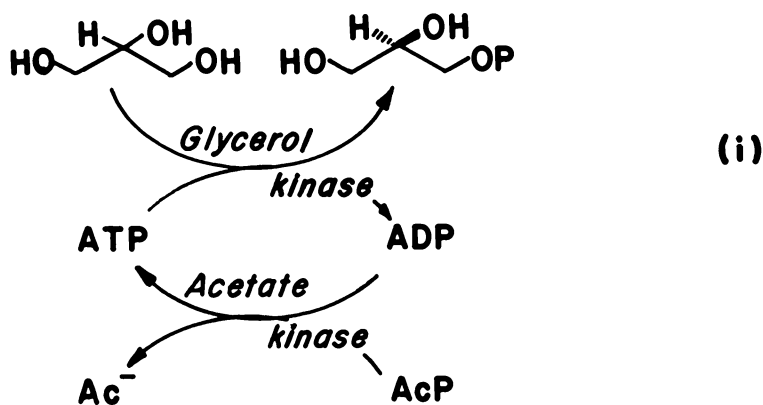
This reaction yields enantiomerically pure sn-glycerol-3-phosphate ((R)-glycerol-1-phosphate, a compound having the correct configuration to serve as the basis for the synthesis of phospholipids). The turnover numbers (TTN = moles product per mole cofactor) achieved in these syntheses (TTN $\simeq$ 100) have been limited primarily by convenience: we normally use a relatively large quantity of ATP, to keep reaction rates high. The ATP is, however, essentially all still present at the conclusion of the reaction. For laboratory-scale synthesis of fine chemicals, the methods shown in Figure 2 represent an effective solution to the problem of ATP regeneration.

Synthesis. A final problem related to ATP utilization is that of obtaining the initial quantity of ATP to be used in the reaction. ATP as a pure biochemical is expensive. A material suitable for use in recycling can be obtained from RNA (approximately $80/kg) by the process outlined in equation ii (7).

$$AcP = CH_3\overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{O}}\overset{O}{\overset{\|}{P}}(O^-)_2$$
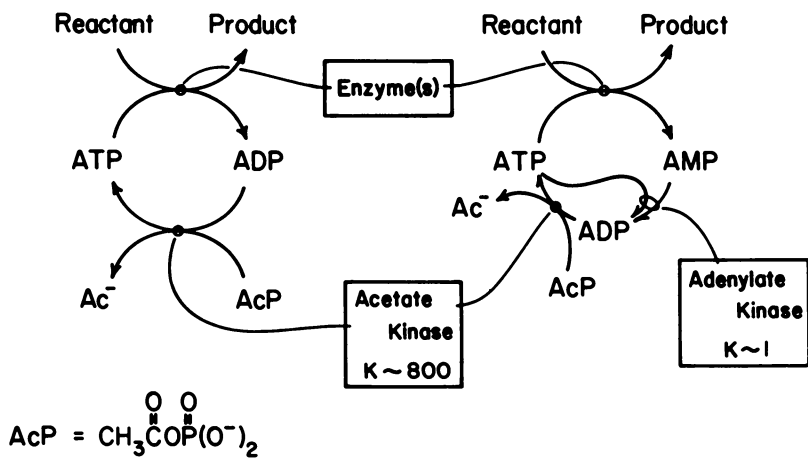
Figure 2. Schemes used for regenerating ATP from ADP (left) and AMP (right).

RNA

$\downarrow$ *Nuclease P$_I$*

AMP + UMP + GMP + CMP

AcP. $\rangle$ *Acetate kinase*   **(ii)**

Ac$^-$ $\rangle$ *Adenylate kinase*

ATP + UMP + GMP + CMP

Cleavage of RNA using nuclease P$_1$ yields a mixture of nucleoside monophosphates, contaminated with oligonucleotides and other materials. The AMP present in this mixture can be converted selectively to ATP by treatment with acetyl phosphate and a mixture of adenylate kinase and acetate kinase. The resulting mixture can be used directly, *without purification*, to supply ATP for use in cofactor recycling.

NAD(P)$^+$

Regeneration. The oxidized nicotinamide cofactors (NAD(P)$^+$) are considerably more difficult to work with than ATP, but are more tractable than the reduced nicotinamide cofactors (NAD(P)H). The oxidized cofactors are sensitive to nucleophiles (8), but are relatively stable at pH 7; the reduced cofactors decompose by acid-catalyzed processes involving protonation at C-5 of the dihydropyridine ring as the rate-limiting step (equation iii) (9,10).

Other products   **(iii)**

Phosphate, a common component of enzymatic systems and an integral part of NADP$^+$ and NADPH, is a particularly effective acid catalyst for this reaction.

The efficient utilization of the nicotinamide cofactors requires not only a scheme for their recycling but also a method for dealing with their limited lifetime in solution. A number of approaches to recycling have been considered, and some appear to be quite satisfactory. The only obvious approach to the economic problem posed by limited lifetime is to lower the initial cost of the cofactor, and we can only offer suggestions concerning this problem.

The recycling of NAD(P)H to NAD(P)$^+$ can be accomplished by any of several methods. If dioxygen can be used in the system, the most straightforward recycling method involves methyl viologen (MV)-catalyzed oxidation (equation iv). The details of the several
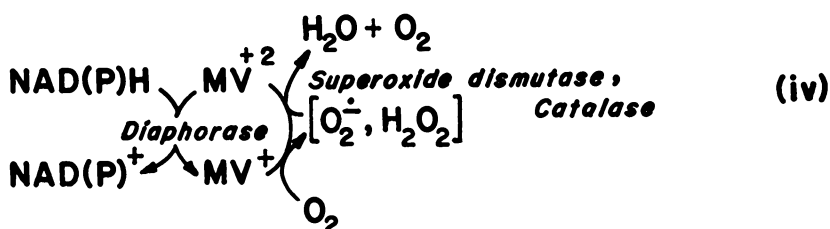
reactions which may be involved in this recycling scheme are not known, but in practice, it has proved to be a useful synthetic method. When *anaerobic* recycling is required, a procedure based on glutamic dehydrogenase works well (equation v) (11).
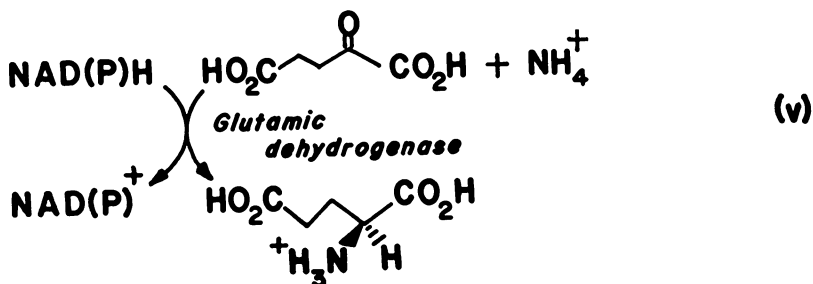
We defer discussion of the problem of *synthesizing* NAD(P)$^+$ to the next section.

NAD(P)H

Regeneration. A large number of systems have been tested for utility in regeneration of reduced nicotinamide cofactors. Of these, only three seem likely to be useful in the short term. Here we briefly describe those systems which, in our opinion, have the practicality required for use in mole-scale organic synthesis.

Formate/Formate Dehydrogenase. This system (equation vi) (12) has several advantages: it requires only one enzyme, and this enzyme is readily available in quantity (although it is still moderately expensive when purchased commercially); formate is inexpensive, and removal of CO_2 causes no problem during workup; formate is a strong reducing agent. The principal disadvantages

$$HC\overset{O}{\underset{O^-}{\diagdown}} \quad NAD^+$$

Formate dehydrogenase   (vi)

$$CO_2 \quad NADH$$
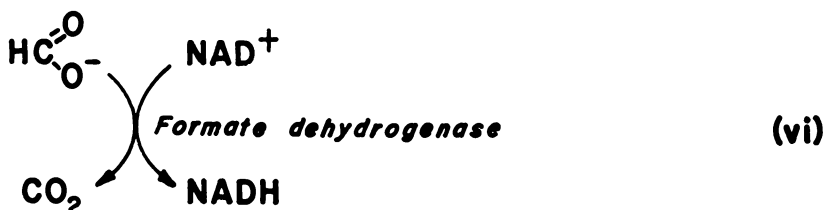
of the system are that it is specific for NAD$^+$ (and thus requires a transhydrogenase for use with NADP$^+$), that the specific activity of the enzyme (3 U/mg; 1 U = 1 μmole of NAD$^+$ consumed/min) is only modest (13) (thus large reactor volumes are required when immobilized enzymes are being used), and that the enzyme is sensitive to autoxidation.

Glucose-6-Phosphate/Glucose-6-Phosphate Dehydrogenase. The advantage of this system (equation vii) are that it requires a single enzyme (10), that this enzyme is stable and available with high specific activity (700 U/mg for NAD$^+$; 500 U/mg for NADP$^+$) (14), that the same enzyme catalyzes the reduction of both NAD and NADP, and that the reaction is irreversible because 6-phosphogluconolacetone hydrolyzes rapidly to 6-phosphogluconate. Its disadvantages are that glucose-6-phosphate is not commercially available (although it is relatively readily prepared), that 6-phosphogluconate may cause significant problems in workup, and that glucose-6-phosphate and 6-phosphogluconate both catalyze the decomposition of NAD(P)H (10). In practice, the convenience of having an easily manipulated, stable, active enzyme outweighs the disadvantages of having to prepare glucose-6-phosphate and of suffering a short lifetime for NAD(P)H. Overall, the method is a useful one in laboratory-scale preparations.

(vii)
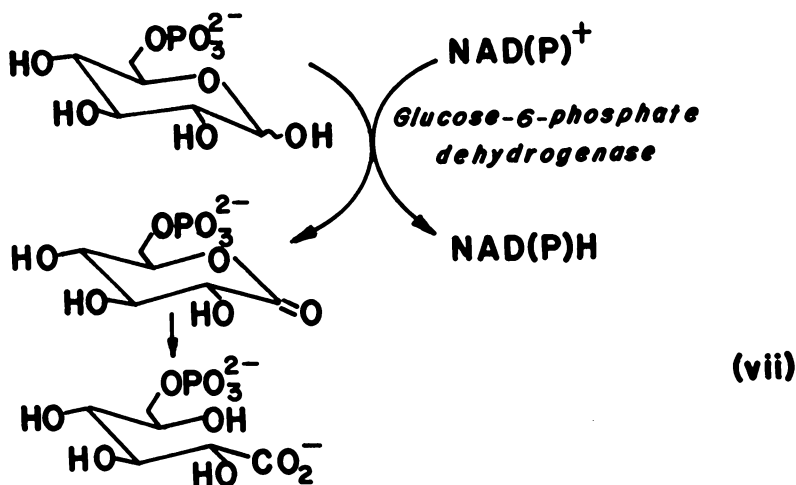
Ethanol/Alcohol Dehydrogenase/Aldehyde Dehydrogenase. The combination of ethanol and alcohol dehydrogenase has been used extensively to reduce NAD^+ to NADH (15,16). This system is un-satisfactory for two reasons: it is only weakly reducing, and the acetaldehyde produced deactivates many enzymes. By adding an excess of aldehyde dehydrogenase (equation viii) the system becomes a very good one (17,18). Its advantages are that ethanol is

(viii)
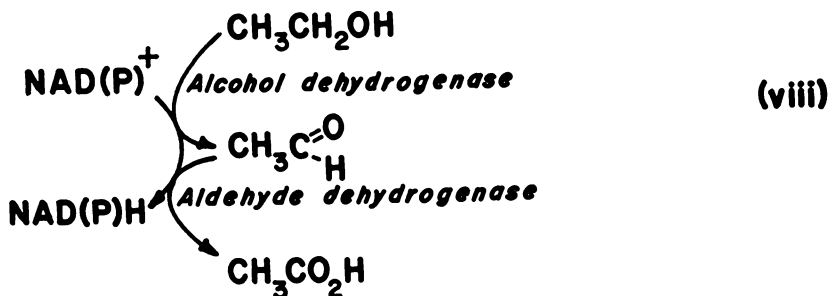
inexpensive, the coupled system is strongly reducing, the enzymes have high specific activities (19) (alcohol dehydrogenase: 400 U/mg for ethanol; aldehyde dehydrogenase; 80 U/mg for acetaldehyde), and acetate seldom complicates workup. Its disadvantages are that the system requires two enzymes, that the enzyme which must be in excess (aldehyde dehydrogenase) is the more expensive and the more sensitive, and that it is more reactive toward NAD^+ than $NADP^+$. A similar system which works well for NADH regeneration is based on methanol as substrate and three combined enzymes, including alcohol dehydrogenase, aldehyde dehydrogenase and formate dehydrogenase, as catalysts (18). The side product (CO_2) in this system does not complicate the work-up and methanol is less expensive than ethanol, but the specific activities of the rate-limiting enzymes of this system are less than those based on ethanol as ultimate reducing source.

Others. In addition to these procedures, a number of others have been established to be effective in reducing $NAD(P)^+$. Many of these methods have been reviewed (15,16). Recently a promising procedure based on a secondary alcohol dehydrogenase has been described by Zeikus (20), and methods which use dihydrogen (21) and electrons from a cathode (22,23) have been described. With the exception of the procedure of Zeikus, these methods are not as convenient for laboratory-scale work as those described above.

There are many examples of the use of NAD(P)H to effect organic syntheses in systems in which the reduced nicotinamide cofactor is regenerated *in situ* (15,16,24). Recent examples include syntheses of D-lactic acid (10,12), isocitric acid (10,21) and other α-hydroxy acids (D or L) on scales of 0.1 to 0.5 mole (equation ix). The turnover numbers for NAD(P)(H) in these reactions are TTN ≃ 1000 - 2000.
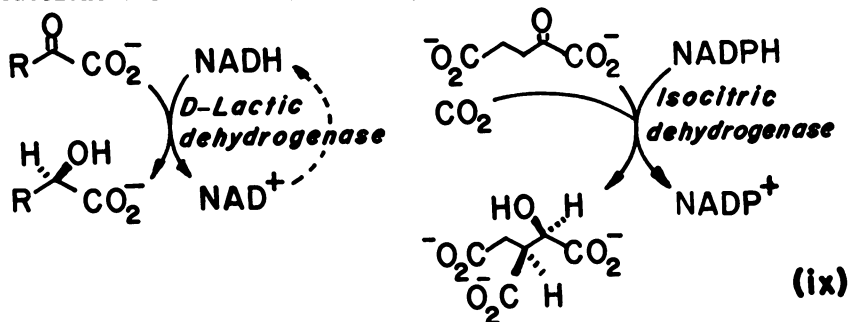
Synthesis of NAD^+ and $NADP^+$. The nicotinamide cofactors are now isolated from yeast (25,26). A major difficulty in this preparation is simply that of separation of the NAD(P)(H) from the other components in the cell. To reduce the cost of these materials, either the yield must be improved from the yeast preparation, the isolation must be simplified, or some type of synthesis must be developed. We have taken a step toward developing a new synthesis by the combined enzymatic/conventional synthetic procedure summarized in Figure 3 (27). The overall conversion from
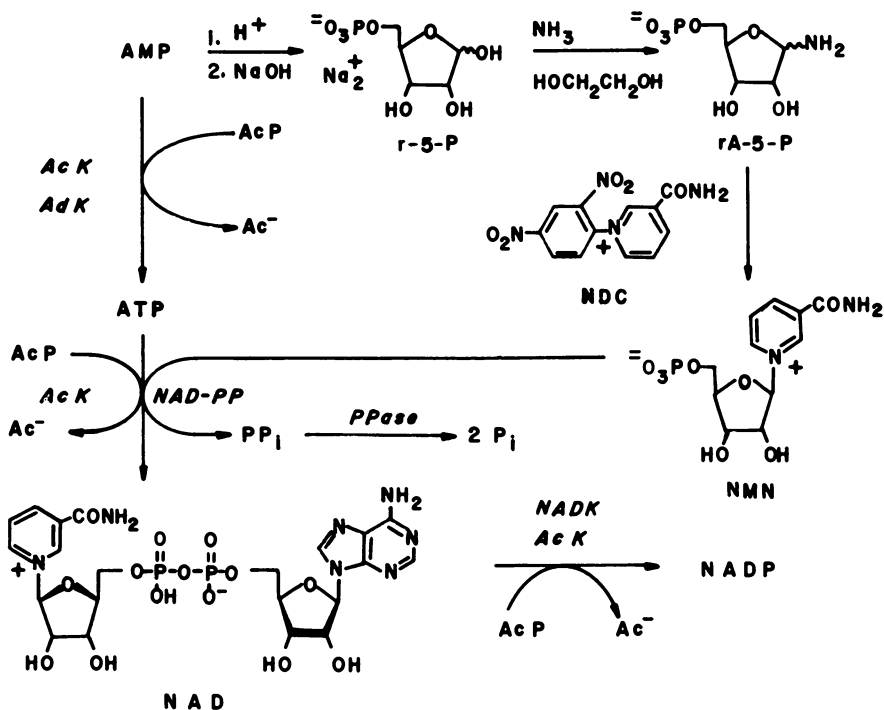
Figure 3. Combined chemical and enzymatic synthesis of NAD⁺ (27).
Key: AcK, acetate kinase; AdK, adenylate kinase; NAD–PP, NAD pyrophosphorylase; PPase, pyrophosphorylase; NADK, NAD kinase; r-5-P, ribose-5-phosphate; rA-5-P, ribosylamine-5-phosphate; NMN, nicotinamide mononucleotide; AcP, acetyl phosphate; PP$_i$, pyrophosphate; and NDC, N$_r$-(2,4-dinitrophenyl)-3-carbamoylpyridinium chloride.

ribose-5-phosphate to NAD$^+$ in this procedure is approximately 60% on small scale; that from AMP to NAD$^+$ via ATP is essentially quantitative. The procedure involves only one isolation (that of ribose-5-phosphate). The solution containing the NAD$^+$ can be used directly for cofactor recycling: whatever components are present as impurities in this solution apparently do not inactivate or inhibit enzymes. This procedure (after development) or some related procedure may provide the best hope for reducing the cost of the nicotinamide cofactors.

Acknowlegements

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Mechanistic Considerations of Biomimetic Asymmetric Reductions

ATSUYOSHI OHNO

Kyoto University, Institute for Chemical Research, Kyoto, Japan

As shown in Table 1, the reduction of ethyl benzoylformate by a 1-substituted-1,4-dihydronicotinamide, a model of NADH or NADPH, in acetonitrile occurs in the presence of a bivalent metal ion such as magnesium(II) or zinc(II)(1)(Scheme 1). When one of the amide-hydrogens is substituted by a chiral group, asymmetric reduction takes place. The stereospecificity of this reduction is also affected by magnesium ion as shown in Table 2 (2,3). Although it is not clear why such a remote chiral center affects the stereochemistry of the reduction, the presence of a nitrogen atom on the side chain appears to play an important role in the stereospecificity, as shown in Table 3(4). The optical yield is still ·unsatisfactory compared with the enzymic reductions. Expecting that the enantioselectivity would be improved with a model compound having the chiral center and reacting hydrogen at the same position, we synthesized all four possible optical isomers of N-α-methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotin-amide (Me₂PNPH, Scheme 1)[1]. Results for the reduction of various substrates with some of these model compounds are summarized in Table 4.

$$PhCCO_2Et + \text{(pyridine ring)} CONH_2 \xrightarrow[\text{in MeCN}]{Mg^{2+}} PhCHCO_2Et + \text{(pyridinium ring)} CONH_2$$

Scheme 1

PNPH

Me₂PNPH

R = Pr: PNAH
R = PhCH₂: BNAH
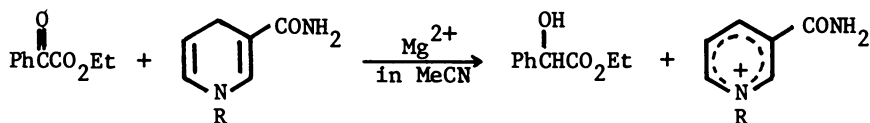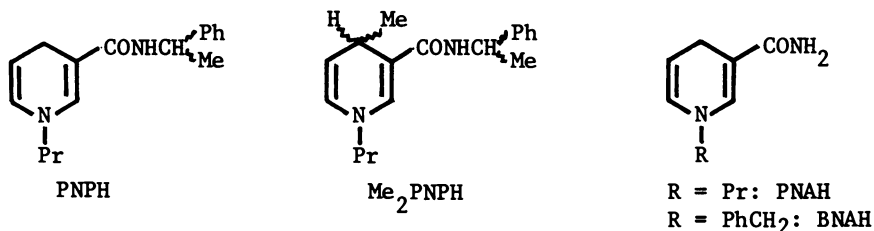
[1] Hereafter, the author will denote XY-Me₂PNPH for an isomer of Me₂PNPH which has configurations X at the ring C_4 and Y at the benzylic carbon.

Table 1. Reduction of Ethyl Benzoylformate by 1-Benzyl-1,4-di-hydronicotinamide (BNAH) [a]

BNAH, mmol	Metal ion,[b] mmol	Isolated Yield,% Recovered Keto ester	Ethyl mandelate
1.06	none	90	0
1.11	Mg^{2+} 1.08[c]	6	86
1.09	Mg^{2+} 1.13	0	100[d]
1.09	Zn^{2+} 1.25[e]	8	66
1.09	Li^{+} 1.25	92	2

[a] The reactions were run with 1 mmol of keto ester in 15 mL of acetonitrile for 17 hr at room temperature in the dark. [b] Perchlorate. [c] Reaction time: 44 hr. [d] Oxidized BNAH (BNA^{+}) was isolated in 90% yield. [e] Hydrated salt was used.

Table 2. Asymmetric Reduction of Ethyl Benzoylformate by Optically Active N-α-Methylbenzyl-1-propyl-1,4-dihydronicotin-amide (PNPH) [a]

Config. of PNPH, mmol		Mg^{2+}, mmol[b]	$[Mg^{2+}]/[PNPH]$	Ethyl mandelate Yield,%	e.e.,%
R	1.00	0.26	0.3	86	6.6
	1.02	0.52	0.5	82	8.6
	2.05	1.05	0.5	95	9.9
	0.99	1.04	1.1	94	19.6
	0.98	1.99	2.0	95	18.1
S	1.14	0.96	0.8	96	-18.6[c]

[a] Reactions were run with 1 mmol of the keto ester in 15 mL of acetonitrile for 44 hr at room temperature in the dark. [b] Perchlorate. [c] S-Mandelate was obtained in excess.

Table 3. Effect of Substituent on the Stereospecificity of the Reduction of Ethyl Benzoylformate [a)]

X in Model	Ethyl mandelate Isolated,[b)] e.e.,%
NH	26
CH$_2$	9
O	2

[a)] Reaction conditions are the same as described in Table 2. The structure of the model is:
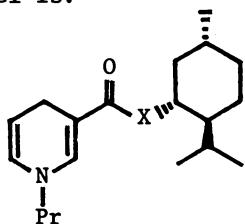
[b)] Chemical yields are quantitative.

Table 4. Reduction by Chiral N-α-methylbenzyl-1-propyl-2,4-di-dimethyl-1,4-dihydronicotinamide (Me$_2$PNPH)

Substrate	Config. of Me$_2$PNPH[a)]	Conv.,%[b)]	Product Structure	Yield,%	e.e.,%
	RR	100		100	97.6(R)
	SR	100		100	96.5(S)
	SS	100		100	94.7(S)
	RR[c)]	100		100	52.5(R)
	RR	95		99	>99 (R)
	RR	60		100	92.0(R)
	SR	56		100	92.0(S)
	RR[c)]	68		68	71.3(R)
	SR[c)]	79		66	41.4(S)

Table 4 Continued
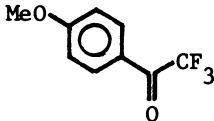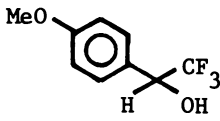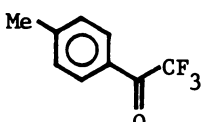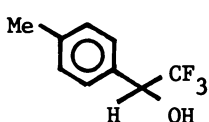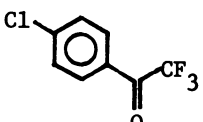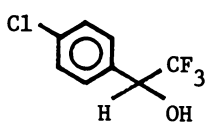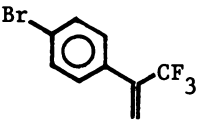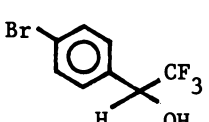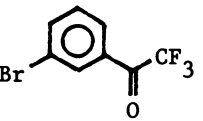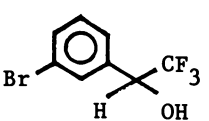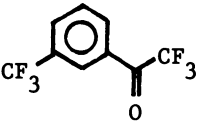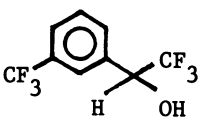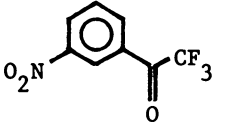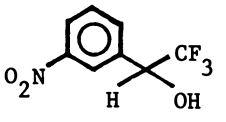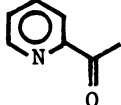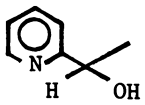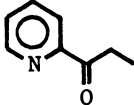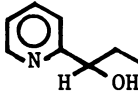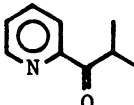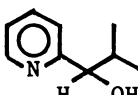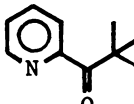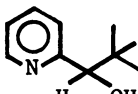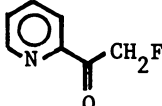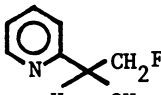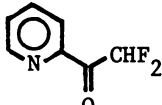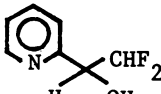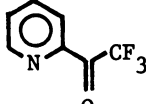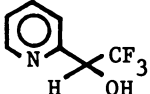
Substrate	Config.	Yield	Product		
MeO–C6H4–CO–CF3	RR[c)]	97	MeO–C6H4–C(H)(OH)–CF3	78.4	80.2 (R)
Me–C6H4–CO–CF3	RR	74	Me–C6H4–C(H)(OH)–CF3	100	95 (R)
	RR[c)]	95		33.6	76.4 (R)
Cl–C6H4–CO–CF3	SS	75	Cl–C6H4–C(H)(OH)–CF3	100	>95 (S)
	RR[c)]	99		55.3	82.5 (R)
Br–C6H4–CO–CF3	RR[c)]	100	Br–C6H4–C(H)(OH)–CF3	52.5	82.2 (R)
Br–C6H4–CO–CF3 (meta)	RR	77	Br–C6H4–C(H)(OH)–CF3 (meta)	100	90 (R)
CF3–C6H4–CO–CF3 (meta)	RR[c)]	99	CF3–C6H4–C(H)(OH)–CF3 (meta)	58.0	85.9 (R)
O2N–C6H4–CO–CF3 (meta)	SS	85	O2N–C6H4–C(H)(OH)–CF3 (meta)	100	>99 (S)
pyridin-2-yl–CO–CH3	RR	100	pyridin-2-yl–C(H)(OH)–CH3	50.1	62.8 (R)

Table 4 Continued

pyridyl C(=O)CH$_2$CH$_3$	RR	76	pyridyl CH(OH)CH$_2$CH$_3$	45.2	52.1(R)
pyridyl C(=O)CH(CH$_3$)$_2$	RR	92	pyridyl CH(OH)CH(CH$_3$)$_2$	78.3	~0
pyridyl C(=O)C(CH$_3$)$_3$	RR	47	pyridyl CH(OH)C(CH$_3$)$_3$	40.3	43.4(R)
pyridyl C(=O)CH$_2$F	RR	98	pyridyl C(OH)(CH$_2$F)	43.3	53.5(S)
pyridyl C(=O)CHF$_2$	RR	100	pyridyl C(OH)(CHF$_2$)	39.4	30.3(S)
pyridyl C(=O)CF$_3$	RR	100	pyridyl C(OH)(CF$_3$)	35.7	16.5(S)

a) See Note 5 for the notation.   b) Amount of substrate consumed.
c) Reaction without magnesium perchlorate.

The results show several interesting characteristics;
1.   Introduction of two methyl groups on the dihydropyridine ring
(Me$_2$PNPH) enhances the reactivity compared to PNPH, as exhibited
by the reduction of α,α,α-trifluoroacetophenone without magnesium
ion.
2.   The predominant enantiomer of the product is determined by
the configuration at the C_4-position of Me$_2$PNPH in the presence of
Mg^{2+}.   However, in the absence of magnesium ion, the configuration
at the benzylic carbon exerts a secondary effect on the stereo-
chemistry.
        For enzymic reactions, it was proposed that the carbonyl
oxygen of the substrate points toward the dihydropyridine ring
nitrogen of NAD(P)H in the transition state(6).   Based on the
same assumption the stereochemistry of the product in the mimetic
reduction can be predicted as shown in 1.

R$_p$: polar substituent

R$_n$: nonpolar substituent

1
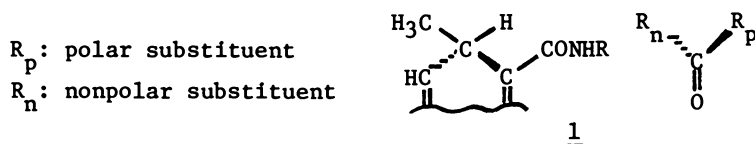
The relative bulk of the substituents in the substrate exerts no
contribution, at least not a primary one.
        In order to obtain information on the transition-state
stereochemistry, we studied the reduction of camphoroquinone (CQ)
with Me$_2$PNPH.   Products from the reduction of (-)- and (+)-CQ's
are shown in Scheme 2 and the results are listed in Table 5.

Scheme 2

(-)-CQ   X-2a   D-2a

X = exo
D = endo   X-3a   D-3a

(+)-CQ X-**2b** D-**2b**

X-**3b** D-**3b**

Scheme 3

D-**2** ⟵ *exo*-C_2 *exo*-C_3 ⟶ D-**3**
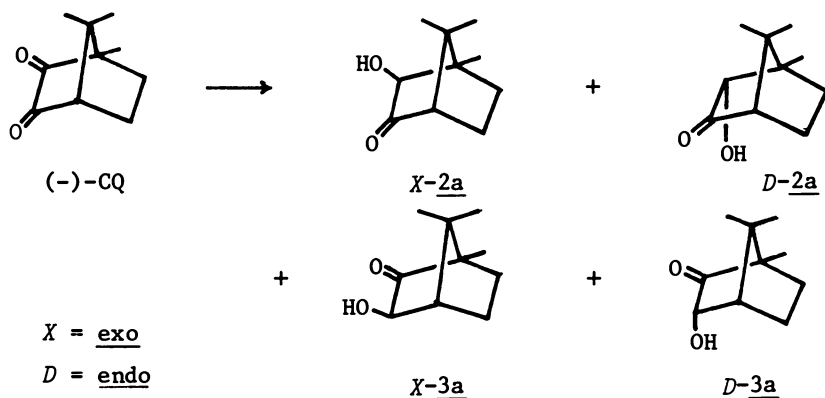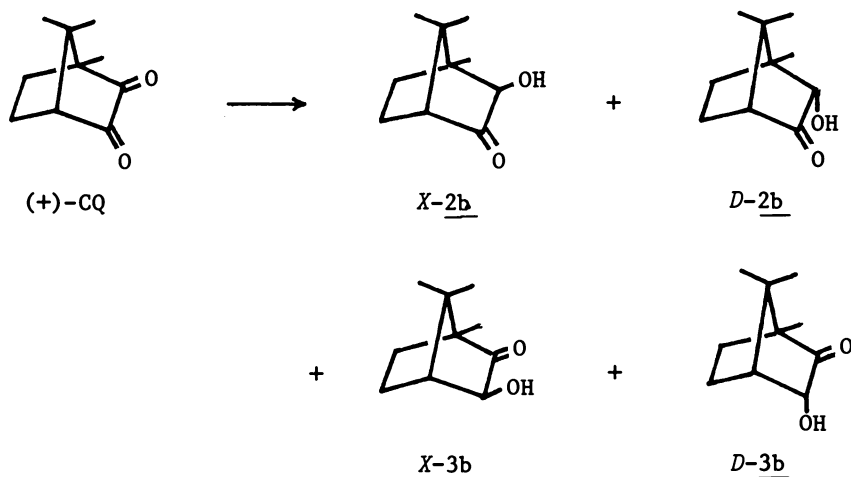
X-**2** ⟵ *endo*-C_2 *endo*-C_3 ⟶ X-**3**
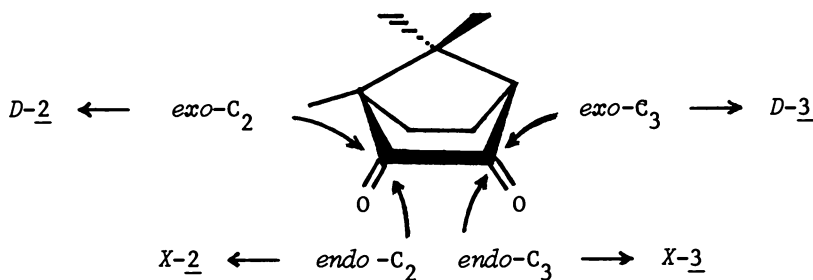
Similar results from the reduction with BNAH, PNAH, and R-PNPH are summarized in Table 6, which indicates that *exo*-C_3-attack (see Scheme 3) is the most preferential course of the reduction with C_4-achiral dihydronicotinamide derivatives. The chirality in the side-chain of R-PNPH plays no important role in determining the stereochemistry of the product. In contrast, the stereochemistry in the reduction with Me_2PNPH reflects mainly the configuration at C_4 of this model compound, and the intrinsic reactivity of each position in CQ, observed above, has only a minor influence now. The result indicates that there is a preference in the orientation of the substituents in CQ with respect to the diastereotopic faces of Me_2PNPH.

    The most preferred mode of attack of SS-Me_2PNPH is *exo*-C_3 for (−)-CQ (Table 5, entry 2). In this mode the amide moiety in SS-Me_2PNPH has to face the carbonyl (electronegative) group of the substrate. Thus, the intermolecular arrangement at the transition state is most likely to be similar to that shown in **1**, polar groups facing each other. A magnesium ion probably assists their assembly.

Table 5.   Reduction of Camphoroquinone with N-α-methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (Me$_2$PNPH)[a]

Substrate	Config. of Me$_2$PNPH	Recov'd CQ,%[b]	Product Yield, %[c]	Product Ratio[c]			
				X-2a	D-2a	X-3a	D-3a
(−)-CQ	RR	57.7	40.6	8	19	68	5
(−)-CQ	SS	36.2	67.6	20	16	6	58
				X-2b	D-2b	X-3b	D-3b
(+)-CQ	RR	53.1	47.3	21	14	7	58
(+)-CQ	SS	50.9	58.7	7	21	62	10
				X-2[e]	D-2[e]	X-3[e]	D-3[e]
(±)-CQ[d]	SS	46.0	54.1	14	16	27	43

[a] Reaction was run for 52 hr with each 1 mmol of reagent.
[b] Isolated yields.   [c] Relative intensities of ^{1}H-NMR signals.
[d] Racemic camphoroquinone.   [e] A mixture of a and b.

Table 6.   Reduction of Camphoroquinone with NAD(P)H-Models

Substrate	Model	T, hr[a]	Recov'd CQ, %[b]	Product Yield, %[b]	Product Ratio[c]			
					X-2a	D-2a	X-3a	D-3a
(−)-CQ	BNAH	235	42.3	7.3	14	13	16	57
(−)-CQ	PNAH	48	65.6	4.3	13	11	24	52
(−)-CQ	R-PNPH	91	50.2	8.6	15	9	14	62
					X-2b	D-2b	X-3b	D-3b
(+)-CQ	R-PNPH	91	61.6	6.8	8	10	20	62

[a] Reaction time.   [b] Isolated yields.   [c] Relative intensities of ^{1}H-NMR signals.

        Based on the above results, steric and electronic effects of
the substituents of a substrate have been studied further.
Results from the reduction of a series of 2-fluoroacylpyridines
and 2-acylpyridines indicate that substituent effects are such
that the stereospecificity of the reduction is mainly governed by
electronic effects.   However, the steric bulk of the substituents
exerts a certain effect on the conformation of these substrates(7
- 11).
        The stereospecificity remains almost constant (>90% e.e.) for
the reduction of substituted and unsubstituted α,α,α-trifluoro-
acetophenones in the presence of magnesium ion.   On the other
hand, the specificity changes with a change in electronic effect
of the substituent for the reduction without magnesium ion.   Both
electron-releasing and -withdrawing substituents increase the
specificity.   The results cannot be accounted for by simple
steric or electronic substituent effects in a one-step reaction.
However, a multi-step mechanism with an initial electron-transfer
process(12, 13) explains the variation of the specificity.   An
electron-releasing substituent reduces the electron-affinity of a
substrate and the electron-transfer to a substrate of this sort
requires a high activation energy, as illustrated in Scheme 4a.
A substrate in this category would form an electron-transfer
complex with Me$_2$PNPH, which is unstable.   The subsequent proton-
transfer takes place almost spontaneously.   The stereochemistry
of the net reduction will be defined in the initial electron-
transfer step.
        The selectivity-reactivity relationship predicts that the
less the electron-releasing power of a substituent on the subst-
rate, or the less the activation energy for the electron-transfer
process, the less the difference in energy between preferred and
other conformations.   Consequently, the reduction becomes less
stereospecific.
        With a strongly electron-withdrawing substituent on a subst-
rate, on the other hand, the electron-transfer takes place quite
rapidly and the intermediate electron-transfer complex becomes
more stable than the reactant system as shown in Scheme 4c.   The
preferential course of reduction in this category is, therefore,
controlled by the thermodynamic stability of the intermediate,
which makes strongly electron-demanding substrates more stereo-
specific than weakly electron-demanding ones.   The stereo-
chemistry of the net reduction is now defined in the second step.
Scheme 4b represents the intermediate category, in which both the
initial and second steps affect the stereospecificity of the
reduction.   In Scheme 4, full lines indicate the reduction
without magnesium ion and dotted lines represent the reduction
with magnesium ion.   Since magnesium ion catalyzes the initial
electron-transfer process, the stereochemistry of the net reduc-
tion in the presence of magnesium ion is controlled by energetics
of the second step.

Scheme 4

$$\Delta G^{\ddagger}$$

(a)   (b)   (c)
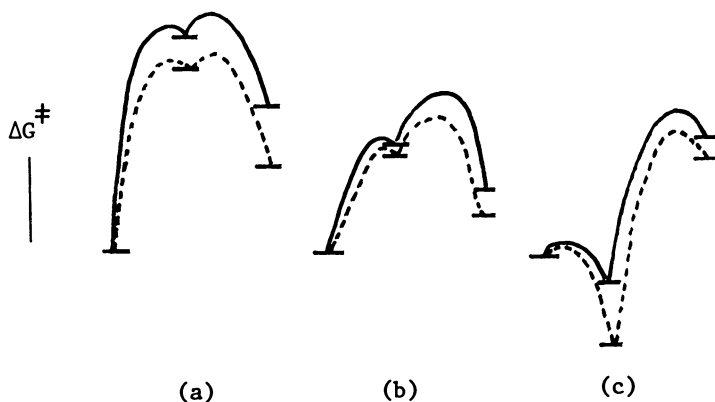
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Stereochemistry of One-Carbon Transfer Reactions

HEINZ G. FLOSS

Purdue University, Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, West Lafayette, IN 47907

The steric course of a number of biological one-carbon transfer reactions has been studied by means of stereo-specifically isotope-labeled substrates. These reactions include the transfer of the methylene group of serine to tetra-hydrofolate catalyzed by serine transhydroxymethylase, the further utilization of the methylene group of methylene-tetrahydro-folate for the generation of the methyl group of thymidylic acid catalyzed by thymidylate synthetase, the transfer of the S-meth-yl group of S-adenosylmethionine to various acceptors catalyzed by a number of different methyltransferases, and the transfer of a methyl group from dimethylnitrosamine to DNA or model nucleo-philes, a process thought to initiate carcinogenic cell trans-formation.

As part of a broader interest in stereochemical aspects of biological processes, our laboratory has recently carried out a variety of studies on the stereochemistry of biological one-carbon transfer reactions. Since biologically important single carbon units, like methyl groups, are not per se chiral, this work has required the use of one-carbon centers made chiral by virtue of isotopic substitution; for example, methyl groups which are chiral by virtue of the presence of normal hydrogen, deuterium and tritium. The synthesis of such species is not particularly difficult; it can be accomplished essentially by an extension of methods used widely to generate stereospecifically labeled prochiral centers. However, the configurational analysis, i.e., the determination whether an unknown sample represents a methyl group of R- or S- configuration presented a conceptually new problem. This was solved by the pioneering work carried out in the laboratories of Cornforth (1) and Arigoni (2). These authors developed a method which involves conversion of the methyl group in the form of acetic acid into acetyl-CoA followed by condensation with glyoxylate, catalyzed by malate synthase, to give malate, and equilibration with fumarase. Based on an isotope effect in the malate synthase reaction, the percentage tritium retention in the fumarase reaction, called the F value, indicates

the configuration and degree of purity of the acetate methyl group. An F value of 79 corresponds to an optically pure R methyl group, an F value of 21 is shown by a chirally pure S methyl group (3). This analytical methodology was employed in most of the studies to be reported here.

Our first study of an enzymatic one-carbon transfer reaction actually involved not the transfer of a methyl group but rather of a methylene group and was carried out in collaboration with the laboratory of Benkovic (4). The pyridoxal phosphate enzyme serine transhydroxymethylase catalyzes the conversion of serine and tetrahydrofolate into glycine and methylene-tetrahydrofolate as shown in Scheme I. Mechanistic considerations suggested that free or enzyme-bound formaldehyde must be a reaction intermediate. To probe this question, we carried out the reaction with serine stereospecifically tritiated in the 3 position and trapped the methylene-tetrahydrofolate generated immediately by further dehydrogenation to methenyl-tetrahydrofolate catalyzed by methylene tetrahydrofolate dehydrogenase. The stereospecific removal of one hydrogen from the methylene group by this enzyme simultaneously served to determine the tritium distribution between the two methylene hydrogens of methylene-tetrahydrofolate. Starting from serine carrying 100% of its tritium in one diastereotopic hydrogen we obtained, under single turnover conditions, methylene-tetrahydrofolate containing 76% of its tritium in one methylene hydrogen and 24% in the other. If the label in serine was in the other diastereotopic hydrogen, the mirror image tritium distribution in methylene-tetrahydrofolate was generated. If the reaction was allowed to go back and forth several times, the methylene group was randomly labeled. This characteristic reaction-dependent scrambling can be explained in either of two ways. Formaldehyde may be a reaction intermediate which remains enzyme bound during its transient existence except for a few molecules which dissociate from the enzyme and rebind before reacting with tetrahydrofolate. Alternatively, the enzyme may bind serine in two conformations around the α,β bond with each conformation reacting stereospecifically as illustrated in Scheme II. It is not possible at the moment to distinguish between these two alternatives, although circumstantial evidence favors the second possibility. The absolute steric course of the reaction was not apparent at the time but can now be written as shown in Scheme III based on the recent determination of the absolute configuration of tetrahydrofolate and additional studies in the laboratory of Benkovic.

Scheme III shows the experimental arrangement to study the second one-carbon transfer reaction we investigated, the formation of thymidylic acid from uridylic acid catalyzed by thymidylate synthetase. In this reaction, the methyl group of thymidylate is derived from the carbon and the two hydrogens of the methylene bridge plus H-6 of methylene-tetrahydrofolate. To study the stereochemistry of this reaction, we (5) synthesized serine stereospecifically labeled with tritium and deuterium at
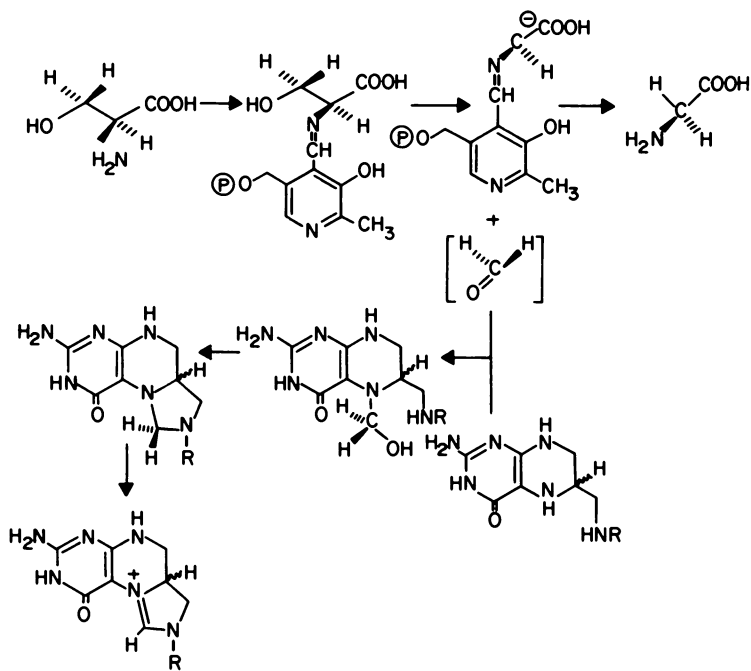
Scheme I. Serine transhydroxymethylase mechanism and experimental setup for stereochemical analysis.
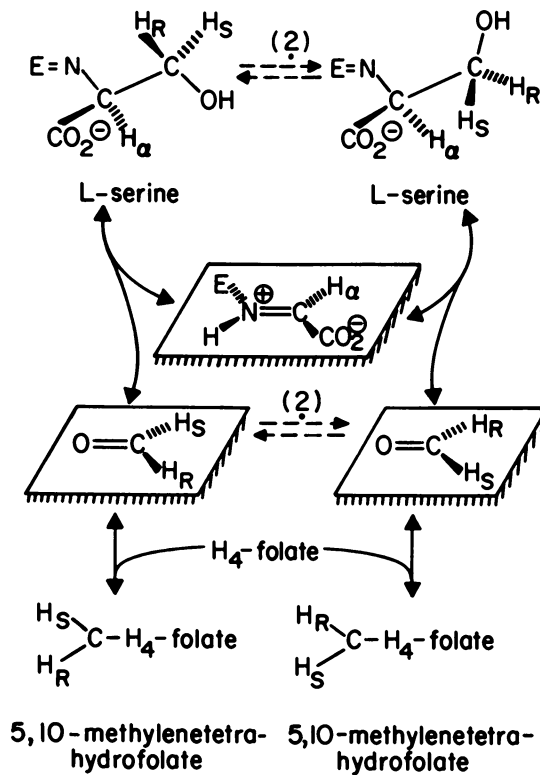
Scheme II. *Stereochemical mechanism of serine transhydroxymethylase.*
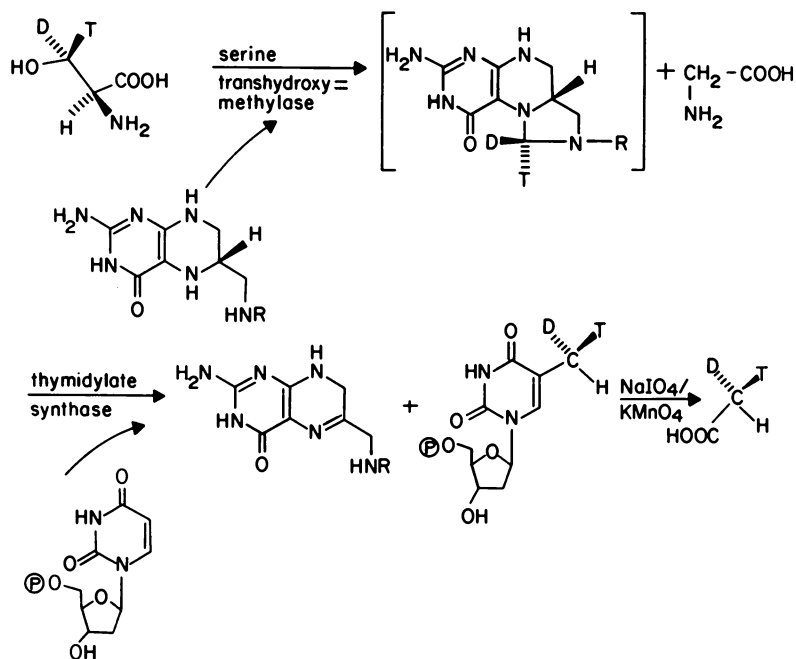
Scheme III. Stereochemistry of serine transhydroxymethylase and thymidylate synthetase.

C-3 and converted it in a coupled reaction sequence into thymi-
dylic acid which was then degraded to recover the methyl group as
acetic acid. Chirality analysis of the acetic acid showed that
it was indeed chiral and had the configuration shown in Scheme
III. Generation of the methyl group of thymidylate from methy-
lene-tetrahydrofolate involves four sequential bond breaking and
forming steps at the stereospecifically labeled one-carbon unit;
the results show that each of these steps occurs in a highly
stereospecific manner. However, because of the multitude of
steps involved, the result does not yet allow us to describe the
steric course of each individual step.
    The mode of formation of a methyl group seen in thymidylate
is exceptional; most methyl groups in biological molecules arise
from the S-methyl group of methionine. Our next goal was to de-
termine the steric course of the transfer of a methyl group from
methionine or S-adenosylmethionine (AdoMet) to various C-, N-, or
O-atoms in biological molecules catalyzed by methyltransferase
enzymes. Pursuit of this goal involved the following tasks:
    1) Synthesis of methionine and AdoMet carrying a chiral
methyl group of known configuration.
    2) Enzymatic transfer of the methyl group to the substrate.
    3) Degradation of the product to carve out the chiral meth-
yl group and convert it into a compound suitable for configura-
tional analysis, using only stereospecific reactions of known
steric course.
    4) Configurational analysis of the methyl group.
    The synthesis of methionine and AdoMet carrying a chiral
methyl group started from chiral acetate, which had been prepared
as shown in Scheme IV (6). The conversion into methionine
(Scheme V) involved a Schmidt reaction, known to proceed with
retention of configuration, to give methylamine, which, in the
form of its ditosylimide, was then used to alkylate the S-anion
of homocysteine (6). The latter reaction was expected to proceed
with inversion of configuration of the methyl group; the only
plausible alternative, racemization due to an S_N1 mechanism, is
ruled out by the subsequent finding that the methyl group was in-
deed still chiral. Enzymatic activation of the two samples of
methionine (7) then gave AdoMet.
    The first transmethylation studied was that catalyzed by
catechol-O-methyltransferase (COMT) using either epinephrine (1a)
or 3,4-dihydroxybenzoic acid (1b) as substrate. The products,
metanephrine (2a) and 4-hydroxy-3-methoxybenzoic acid (2b), were
degraded by the stereospecific reaction sequence shown in Scheme
VI to give acetic acid carrying the chiral methyl group. It will
be noted that the degradation sequence involves one inversion of
the configuration of the methyl group in the cyanide displacement
step (8).
    Configurational analysis of the various acetic acid samples
showed that AdoMet synthesized from acetate of F=28 gave 2a and
2b which, upon degradation, produced acetate of F=68 and 67, re-
spectively. In the other enantiomeric series, the values were

Scheme IV. Synthesis of chiral acetate.
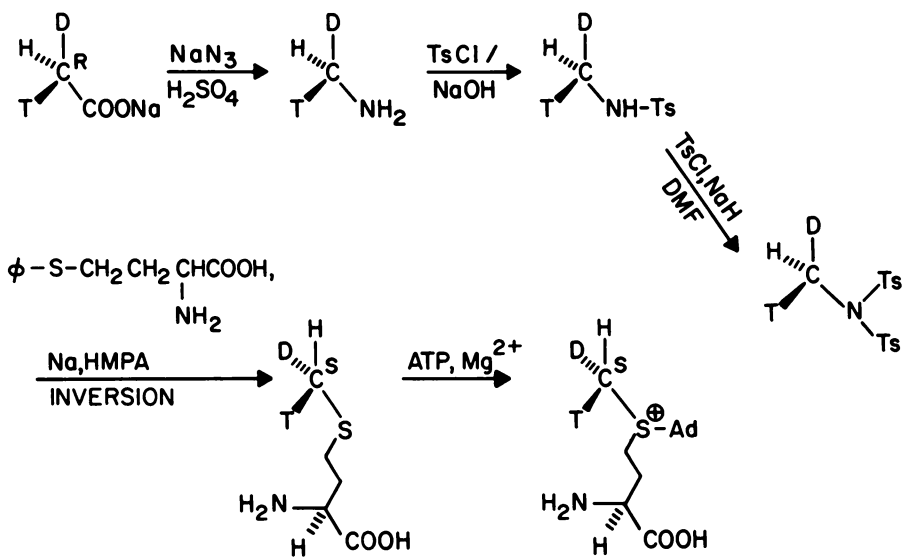
Scheme V. Synthesis of chiral (S)-adenosylmethionine from chiral acetate.
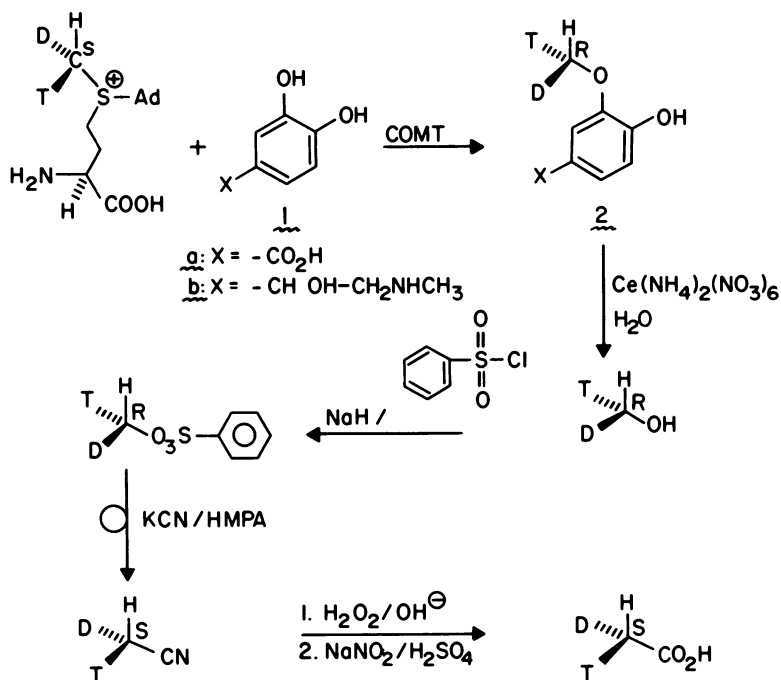
Scheme VI.   Degradation of the products from the COMT reaction to recover the chiral methyl group as acetic acid.

F=68 for the starting acetate, and F=39 and 44 for the acetate samples from the degradation of 2a and 2b, respectively. Thus, there is an odd number of inversions in going from the starting acetate (Scheme V, upper left) to the final product (Scheme V, lower right). Since both the synthesis and the degradation each involve one inversion, it follows that the enzymatic transfer of the methyl group catalyzed by COMT must have occurred with inversion of configuration (8).

The same stereochemical course was also observed for another methyl transfer to oxygen, the methylation of the polygalacturonic acid carboxyl groups of pectin catalyzed by an enzyme preparation from mung bean shoots. The methyl group in this case was recovered by direct cyanolysis of the pectin to give acetonitrile (with inversion), which was then converted to acetate for analysis. Again, the starting and the final acetate samples had opposite configurations (F=28 → F=62; F=68 → F=32) (9).

In a microbial system, Streptomyces griseus, we studied simultaneously two methyl transfers, one to carbon and one to nitrogen, which are involved in the biosynthesis of the antibiotic indolmycin (10). In this case, chiral methionine was added directly to the cultures and the resulting indolmycin and indolmycenic acid were degraded as shown in Scheme VII. The results again indicated enzymatic transfer of the methyl group, both to carbon and to nitrogen, with inversion of configuration (6). Earlier work from our laboratory had shown that, in the C-methylation reaction leading to indolmycin, a hydrogen at C-3 of indole-pyruvate is replaced by the methyl group in a retention mode (11). Thus the stereochemistry of indolmycin biosynthesis in Streptomyces griseus can be summarized as shown in Scheme VIII.

In conclusion, all enzymatic methyl transfer reactions studied so far proceed with net inversion of configuration of the methyl group. All these methyl transferases therefore involve an uneven number of transfers of the methyl group, most likely a single, direct transfer from the sulfur of AdoMet to the acceptor atom in an S_N2-type reaction. Ping-pong mechanisms in which a group in the enzyme active site is transiently methylated can be excluded. The two substrates must be oriented in the enzyme active site such that in the transition state the sulfur, the methyl carbon and the acceptor atom form a linear array.

Methyl transferases are not only important in various metabolic processes, but also in the processing of informational macromolecules; for example, DNA by restriction methylases. Aberrations in this processing, as occur in the methylation by carcinogens like dimethylnitrosamine, are probably involved in the transformation of the cell into a tumor cell. This process involves metabolic activation of dimethylnitrosamine, in the manner shown in Scheme IX, to generate the ultimate carcinogen, a methyldiazonium ion which then transfers its methyl group to various nucleophilic sites on DNA. This latter process is presumably not enzyme-controlled and should therefore follow the same rules as the same process in an abiological system. Keeping
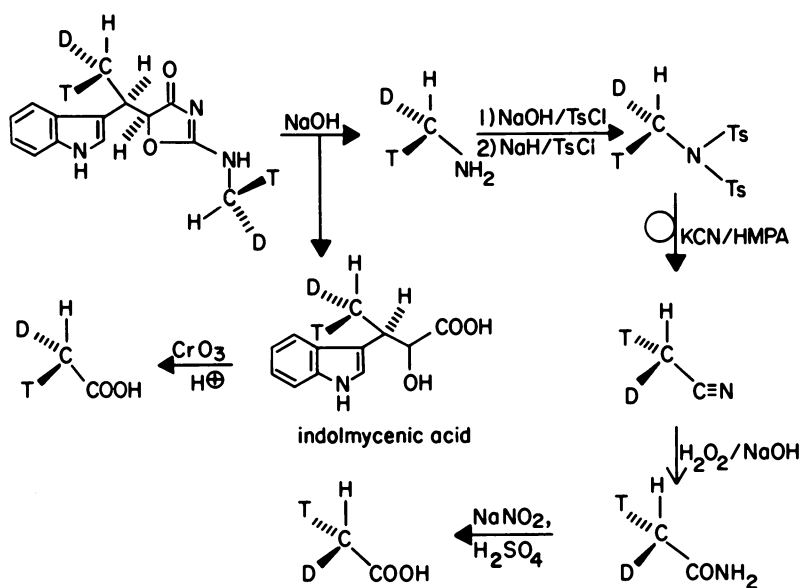
Scheme VII. *Degradation of indolmycin and indolmycenic acid to recover the chiral methyl groups as acetic acid.*
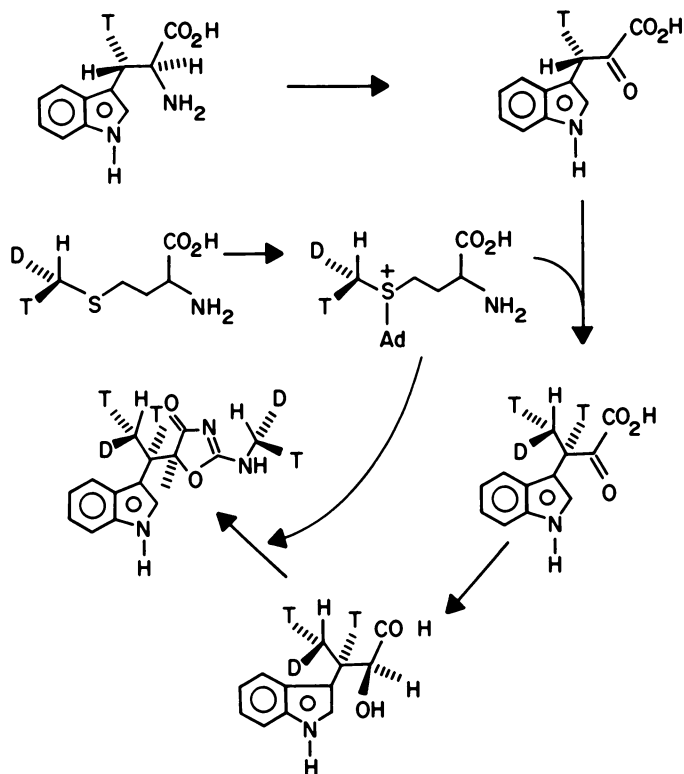
*Scheme VIII.   Steric course of indolmycin biosynthesis.*
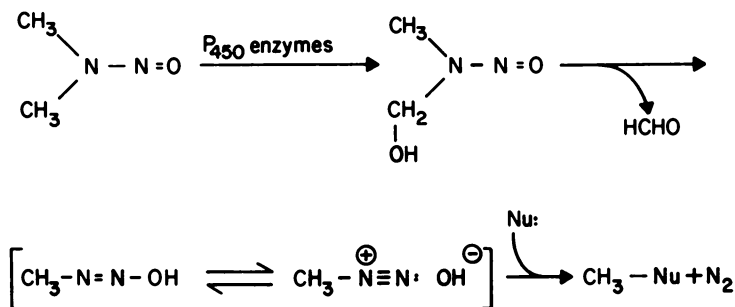
*Scheme IX.   Metabolic activation of dimethylnitrosamine.*

all other factors constant, the stereochemistry of this methyl transfer should be sensitive to the polarity of the reaction environment. Therefore, a comparison of the in vitro and the in vivo process should enable us to probe whether the reaction in the intact cell takes place in a hydrophobic environment, like the nuclear membrane, or in an aqueous surrounding. To lay the groundwork for experiments probing this question, we synthesized dimethylnitrosamine carrying a chiral methyl group by the reaction sequence shown in Scheme X. Methods for the alkylation of DNA and for the recovery of the methyl group from the most prominent modified base, 7-methylguanine, have been worked out, but results from the stereochemical analysis of these samples are not yet available. We have, however, completed the stereochemical analysis of the alkylation of a model nucleophile, 3,4-dichlorothiophenol, by dimethylnitrosamine activated with rat liver microsomes (12). The reaction sequence is shown in Scheme XI. Based on the structure of the alkyl group in this reaction and the nature of the nucleophile, we expected to see transfer of the methyl group with a high degree of inversion of configuration. However, the first set of analyses of the acetate samples from the degradation of the alkylated material shown in Table I suggests transfer of the methyl group with complete retention of configuration. This surprising result may indicate that even in this in vitro system, the reaction takes place entirely in the lipophilic microsomes and therefore proceeds exclusively by an ion pair mechanism with internal return. Alternatively, the mechanism of dimethylnitrosamine activation and alkyl transfer may be more complex than is currently envisioned and may, for example, involve a double displacement process. Further experiments are under way to verify the initial result and to study this problem further.

Table I. Stereochemical analysis of the alkylation of 3,4-dichlorothiophenol by metabolically activated dimethylnitrosamine.

	F-VALUE	CONFIGURATION	F-VALUE	CONFIGURATION
STARTING ACETATE	28	S	68	R
DIMETHYLNITRO-SAMINE	--	S	--	R
3,4-DICHLORO-THIOPHENOL METHYL ETHER	--	S	--	R
ACETATE FROM DEGRADATION	71	R	33	S
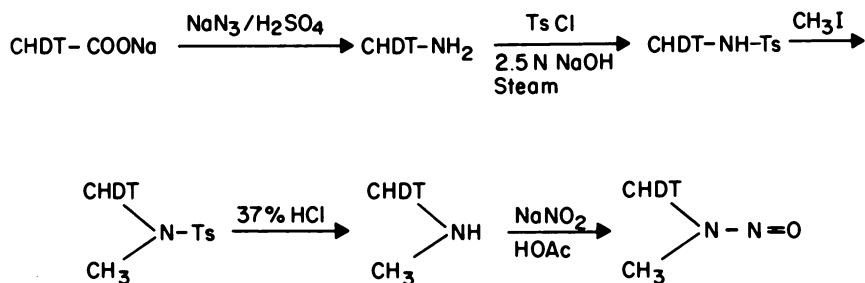
Scheme X.   *Synthesis of dimethylnitrosamine carrying a chiral methyl group.*
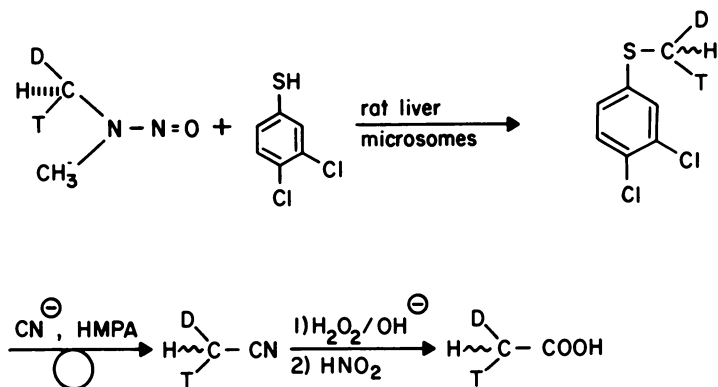
Scheme XI.   *Alkylation of 3,4-dichlorothiophenol by chiral dimethylnitrosamine.*

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A Useful and Conveniently Accessible Chiral Stationary Phase for the Liquid Chromatographic Separation of Enantiomers

WILLIAM H. PIRKLE, JOHN M. FINN, BRUCE C. HAMPER, JAMES SCHREINER, and JAMES R. PRIBISH

University of Illinois, School of Chemical Sciences, Urbana, IL 61801

The use of a simply prepared high efficiency chiral HPLC column capable of separating the enantiomers of thousands of compounds is described, documentation being provided by more than 120 specific examples covering 19 classes of compounds. Chiral recognition models are presented to account for elution orders of the enantiomers. Practical applications of the chiral column, including preparative separations, are described.

It has long been perceived that chromatography of enantiomers upon a chiral stationary phase (CSP) might, in principle, result in separation of the enantiomers. Owing to the potential utility of such a resolution procedure, a great many workers have attempted to so effect resolutions. Most early attempts involve empirically chosen, readily accessible CSP's (e.g., starches, modified celluloses, wool) with varying degrees of success. More recently, synthetic CSP's (coupled with modern HPLC technology) have begun to afford impressive examples of chromatographically effected resolutions. Several recent reviews of this work are available (1-4).

The development of CSP's for the direct chromatographic separation of enantiomers is revolutionizing stereochemical analysis and will considerably alter future synthetic approaches to chiral compounds. From the analytical standpoint, an effective chiral HPLC column makes possible the accurate determination of enantiomeric purity upon as little as nanogram quantities of sample, absolute configurations being obtained simultaneously. From the preparative standpoint, multigram quantities of racemate can be resolved per pass through large chiral columns. Automation of this process will enable hundreds of grams of racemate to be resolved daily. Hence, a wide variety of chiral precursors will be available for the synthesis

of more complex chiral materials. In many cases, the final
products will themselves be chromatographically resolvable.
Finally, chromatographic resolution conveniently provides both
enantiomers for biological evaluation.

The critical point in the preceding Utopian prediction is
whether or not chiral columns can be devised which will indeed
efficiently and predictably separate the enantiomers of a wide
array of solutes. Work conducted in our laboratory in Urbana
leads us to believe that such "Broad Spectrum" CSP's are clearly
possible, that their chiral recognition mechanisms can be
discerned, and that an understanding of these mechanisms can be
used for the rational design of still more effective CSP's
(5-10). To support this belief, let us describe a simply
prepared chiral chromatography column capable of separating the
enantiomers of thousands of compounds of diverse functional
types.

Results and Discussion
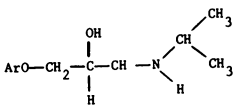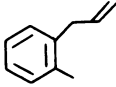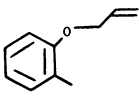
Treatment of γ-aminopropylsilanized silica with a THF
solution of R-N-3,5-dinitrobenzoylphenylglycine affords CSP 1,
a CSP in which the chiral moiety is ionically bonded to the
achiral support. This treatment may be performed either upon a
prepacked HPLC column or upon bulk material (8, 9).
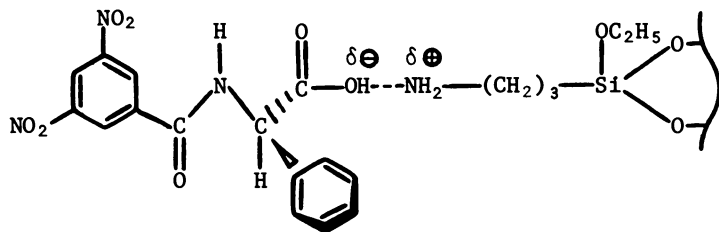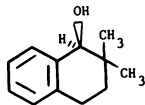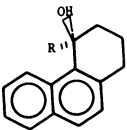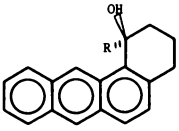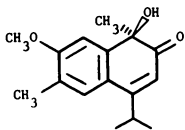
CSP 1

For analytical (and small scale preparative) applications,
we modified a Regis 4.6 mm x 250 mm 5 μ Spherisorb NH$_2$ column.
Using hexane-isopropyl alcohol as a mobile phase, we have been
able to resolve the enantiomers of the types of compounds
indicated in Tables I-IV. It can be seen from Figure 1 that
this column is of high efficiency, enabling one to accurately
determine enantiomeric purity (by peak area comparison) for
compounds having an enantiomeric separability factor of 1.05 or
greater (the enantiomeric separability factor, α, is simply the
ratio of retention times of the enantiomers measured, not from
injection, but from the elution point of a non-retained
compound.)   For compounds having an α value between unity and
1.05, multiple column or recycle techniques may have to be

Table I. Resolution of Some Alcohols Upon CSP 1
Using 1-10% 2-Propanol in Hexane.

BENZYL ALCOHOLS

Ar	R	α
Ph	Me	1.05*
Ph	t-Butyl	1.08*
α-Naph	Me	1.14*
α-Naph	CF$_3$	1.08*
9-Anth	CF$_3$	1.33*
9-Anth	n-Butyl	1.48
9-Anth	CH$_2$COOC$_2$H$_5$	1.27

PROPANOLOL ANALOGS
(AS N-LAUROYL DERIVATIVE)

Ar	α
	1.08
	1.08
α-Naph	1.07

CYCLIC ALCOHOLS

R	α
	1.04*
H	1.17
Me	1.37
n-Butyl	1.73
H	1.17
Me	1.39
n-Butyl	1.50
	1.11

Table I. (continued).

| HYDROXY SULFIDES | | | ARYL–SUBSTITUTED HYDROXY PHOSPHONATES | | |

R_1	R_2	α	Ar	R	α
H	Me	1.03	Ph	Ph	1.07
H	$\underline{n}\text{-}C_{12}H_{25}$	1.04	α–Naph	Et	1.19
Me	Me	1.03	p–Anisyl	Et	1.12
$\underline{n}\text{-}C_6H_{13}$	$\underline{n}\text{-}C_{10}H_{21}$	1.07/1.10			
$\underline{n}\text{-}C_{12}H_{25}$	H	1.06			
H	Ph	1.06 (first?)			
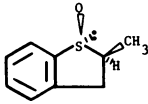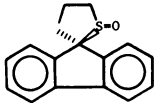
Table II. Resolution of Some Bi-β-naphthols Upon CSP 1 Using 10-20% 2-Propanol in Hexane.

BI-β-NAPHTHOLS
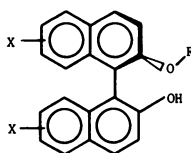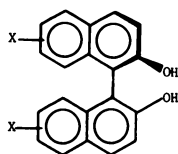
X	α	X	R	α
H	1.45*	H	CH_3	1.75*
6,7-(Me)$_2$	2.40*	H	C_2H_5	1.23*
6-Br	1.41*	6,7-(Me)$_2$	CH_3	3.67*
7-OCH$_3$	1.51			

Table III. Resolution of Some Sulfoxides Upon CSP 1
Using 5-20% 2-Propanol in Hexane.

ARYL ALKYL SULFOXIDES   DIARYL SULFOXIDES

Ar	R	α		Ar	Ar'	α
Ph	Me	1.05*		p-Tolyl	Ph	1.09
Ph	t-Butyl	1.09*		p-Tolyl	o-Tolyl	1.04
p-Tolyl	i-Propyl	1.10*		9-Anth	Ph	1.59
α-Naph	Me	1.09*		9-Anth	p-Anisyl	1.57
9-Anth	Me	1.19*		9-Anth	$p-NO_2-C_6H_4$	1.40
9-Anth	i-Propyl	1.22*		9-Anth	$2,4-(NO_2)_2C_6H_3$	1.20
9-Anth	$CH_2COOC_2H_5$	1.20				

SPIRO-2,2-DITHIOLANE-1-OXIDES

CYCLIC SULFOXIDES

R	α
	1.06*

Y	α	α
H	1.09	
α-Me	1.16	1.14
β-OMe	1.08	1.09 (first)
β-OH	1.0	1.30

	R	α
	H	1.16
	cis Me	1.17
	trans Me	1.18

	α
	1.14

1.33   1.15

Table III. (continued)

| β-HYDROXY SULFOXIDES | β-HYDROXY SULFOXIDES CONTINUED |

$$Ar-\overset{O}{\underset{\cdot}{S}}\cdots CH_2-\overset{OH}{C}HR$$

$$9\text{-Anth}-\overset{O}{\underset{\cdot}{S}}\cdots R$$

Ar	R	α		R	α
9-Anth	H	1.31		$-\overset{Ph}{C}HCH_2\overset{OH}{C}HCH_3$	1.42, 1.22, 1.13
9-Anth	Me	1.38/1.22		(cyclooctane with OH)	1.15/?
9-Anth	$n\text{-}C_{18}H_{37}$	1.52/1.28		(cyclohexane with HO)	1.22, 1.26, 1.07, 1.11
9-Anth	Ph	1.18/1.04			

1-ARYL-1-ALKYL-2,2-DITHIOLANE-1-OXIDES

Ar	R	α
Ph	Et	1.06/NS
Ph	$n\text{-}C_{11}H_{23}$	1.10/NS
(naphthalene ring)		1.13/1.04
(indane ring)		1.10/≈1.01
(methylindane ring)		1.24/NS

Note: Multiple entries for α are those of diastereomers. If in parentheses, α values refer to other positional isomers.

Table IV. Resolution of Some Amides Upon CSP 1.
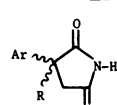
| ARYL-SUBSTITUTED SUCCINIMIDES | ARYL ACETAMIDES |

$$\text{(Ar, R succinimide with N-H)}$$

$$Ar-\overset{Y}{\underset{H}{C}}-CONH_2$$

Ar	R	α		Ar	Y	α
Ph	H	1.13		Ph	i-Propyl	1.08
Ph	Me	1.07		Ph	Methoxy	1.13
Ph	Et	1.13		Ph	i-Propoxy	1.30
p-Anisyl	H	1.24		Ph	SPh	1.03

Table IV. (continued)

ARYL-SUBSTITUTED LACTAMS
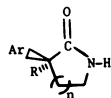
Ar	R	n	α
Ph	H	1	1.18* (1.02) (1.03)
p-Anisyl	H	1	1.33*
α-Naph	H	1	1.14
p-Anisyl	H	2	1.30
α-Naph	H	2	1.23

PHTHALIDES
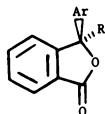
Ar	R	α
Ph	H	1.03
Ph	Et	1.03*
p-Anisyl	H	1.07
α-Naph	H	1.13
α-Naph	Me	1.37
9-Anth	CF$_3$	1.20

OXAZOLIDONES
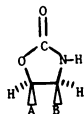
A	B	α
H	Ph	1.05*
H	α-Naph	1.04
Ph	Ph	1.02*

DIELS-ALDER ADDUCTS OF ACRYLAMIDES AND ANTHRACENES
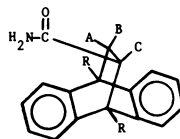
R	A	B	C	α
H	H	H	H	1.13
Me	H	H	H	1.40
Me	H	Ph	H	1.42
Me	H	Cl	H	1.56
Me	H	Br	H	1.80
Me	H	Br	Br	1.96

ARYL-SUBSTITUTED HYDANTOINS
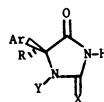
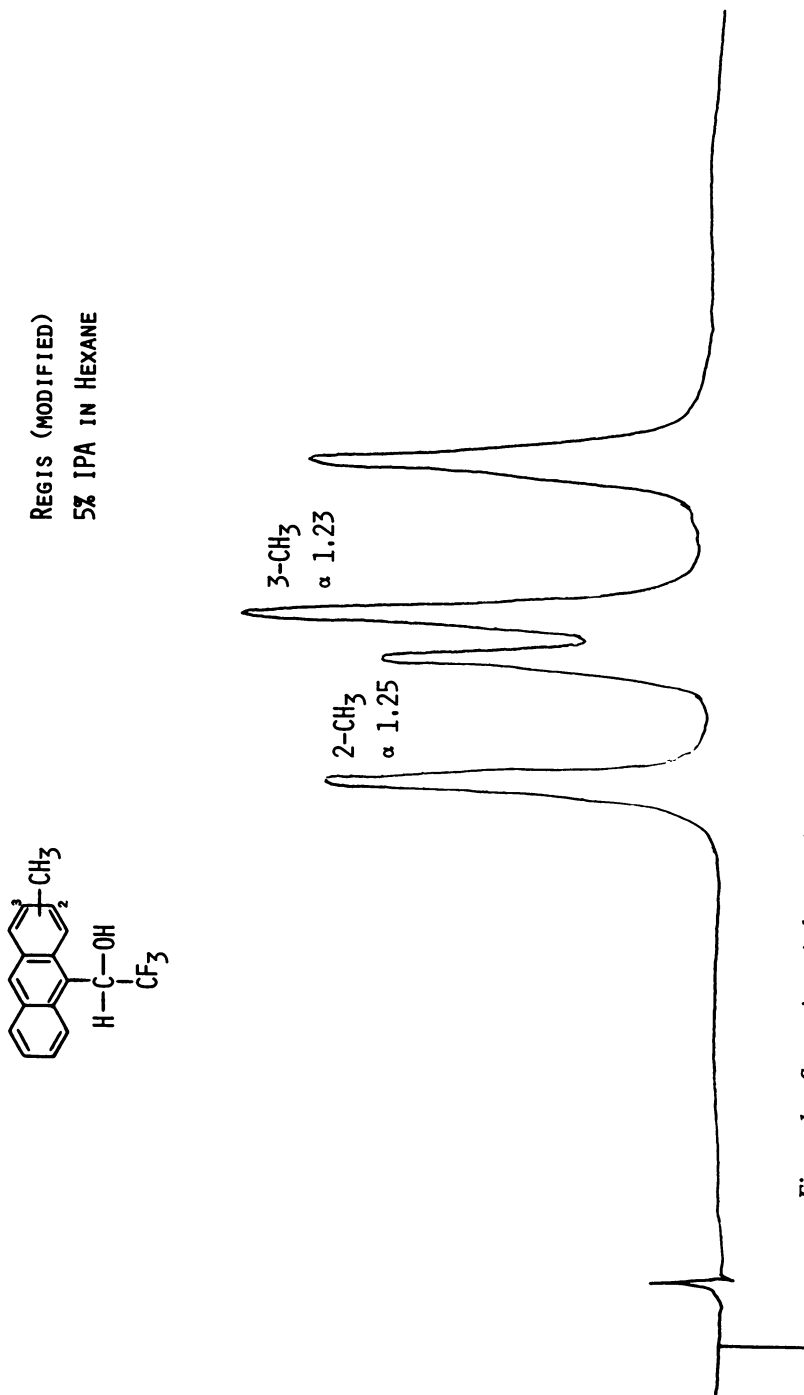| Ar	R	Y	X	α
Ph	H	H	O	1.13
Ph	Et	H	O	1.26
p-Anisyl	i-Propyl	H	O	1.50
α-Naph	Me	H	O	1.35
α-Naph	(CH$_2$)$_2$CH=CH$_2$	H	O	1.48
β-Naph	CH$_3$	H	O	1.39
β-Naph	(CH$_2$)$_2$CH=CH$_2$	H	O	1.33
Ph	H	COCH$_3$	S	1.27
β-Naph	CH$_3$	CH$_3$	O	1.53

Figure 1. *Separation of the enantiomers of two isomeric alcohols on an analytical column containing (R)-CSP 1.*

employed. Each Table indicates the magnitude of α noted upon
the chiral analytical column for the indicated solute. As a
rule, many more compounds have been resolved within each class
than are presented, great generality being encountered.

Elution order from the column is diagnostic of the absolute
configuration of the enantiomers. When a stereochemical
representation is shown for a generalized solute type, that
enantiomer is either known (indicated by an asterisk) or
believed (for mechanistic reasons) to be last eluted. Elution
orders were determined either by chromatographing enriched
samples of known configuration or through use of a polarimetric
detector (Figure 2), the sign of rotation afforded by each
enantiomer being noted as it eluted. These rotational signs
were then compared to literature assignments of stereochemistry.

Chiral Recognition Mechanisms

The conformation depicted in CSP 1 is analogous to the
solution conformations preferentially populated by amides of
primary amines having a single α-hydrogen. This conformation is
used in our present chiral recognition mechanisms. A minimum of
three simultaneous interactions, at least one of which must be
stereochemically dependent, is required for chiral recognition.
CSP 1 uses the following types of interactions. The DNB group
is used to π-complex to a π-base (usually an aryl group) in the
solute, the amide hydrogen bonds to a basic site in the solute,
the third stereochemically dependent interaction being either hy-
drogen bonding of the carboxylate group by an acidic solute site
or steric repulsion between the phenyl of CSP 1 with a "steric
barrier" contained within the solute. Steric repulsions are
notably less effective for chiral recognition than are bonding
interactions involving the carboxylate group. Solutes
containing two acidic sites (and a π-base) but no suitable basic
site can substitute a hydrogen bond to the DNB carbonyl oxygen
for the hydrogen bond from the amide hydrogen. Figures 3-8
illustrate these multiple interactions between R-CSP 1 and the
most strongly retained enantiomer for several solute types.

For benzyl alcohols, one can see from Figure 3 the
simultaneous occurrence of a π-π interaction, a conventional
hydrogen bond, and a weaker "carbinyl hydrogen bond" (8, 11) to
the carbonyl oxygen of the DNB group. Altering the
configuration of either chiral center breaks one of these
bonding interactions, hence a stability difference occurs for the
diastereomeric solvates. Figure 4 shows recognizably similar
interactions between bi-β-naphthol and CSP 1. Increasing the
π-basicity of the naphthol system or increasing the basicity of
one of the oxygens by methylation increases the magnitude of α
(Table II). Two of the interactions shown in Figure 5 are
analogous to those just discussed.   The third stereochemically
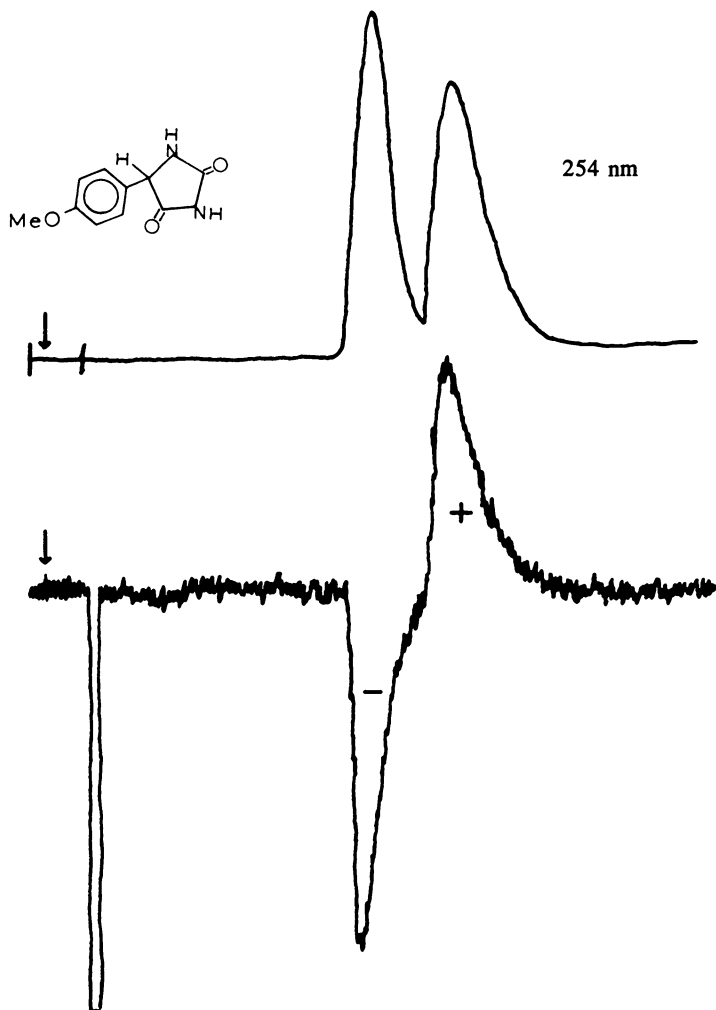dependent interaction seems to be repulsion between the steric

Figure 2.   Separation on (R)-CSP 1 of the enantiomers of 5-anisylhydantoin employing UV (254 nm) and polarimetric (589 nm) detectors.
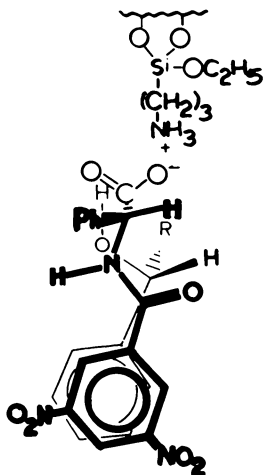
Figure 3. Chiral recognition model showing the relative arrangement for three simultaneous bonding interactions between (R)-CSP 1 and the most retained enantiomer of an alkyl aryl carbinol.
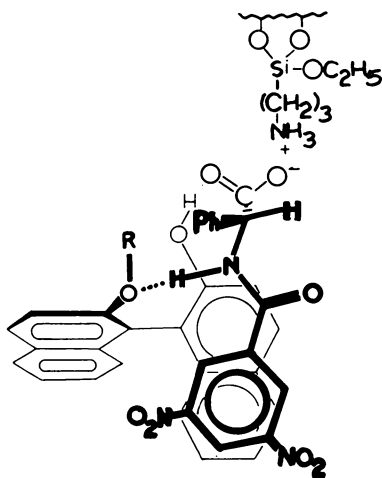

Figure 4. Chiral recognition model showing the relative arrangement for three simultaneous bonding interactions between (R)-CSP 1 and the most retained enantiomer of bi-β-naphthol.

barrier of the alicyclic ring and either the carboxylate or
phenyl group of CSP 1, depending upon relative configuration.
The interaction with phenyl is the most severe. Figure 6 shows
rather similar interactions with aryl alkyl sulfoxides, the
stereochemically dependent interaction being, at least in part,
steric repulsion with the alkyl group. A similar model accounts
for the resolution of diaryl sulfoxides, the π-π interaction
occurring at the most π-basic aryl group, the steric barrier
being the least π-basic aryl group. Note from the data in
Table III that incorporation of a hydroxyl group into the alkyl
group of 9-anthryl alkyl sulfoxides can enhance α by allowing
hydrogen bonding to the carboxylate group to augment steric
repulsion with the phenyl group. Consequently, SN_2 ring opening
of an epoxide with 9-anthryl thiol followed by oxidation to the
sulfoxide appears to offer promise in terms of HPLC enantiomeric
purity determinations of epoxides. Figure 9 shows separation of
the eight entities so derived from racemic disparlure, the Gypsy
moth sex attractant.

    Figures 7 and 8 show that chiral recognition of hydantoins
and lactams by CSP 1 utilizes the same, now familiar, three
bonding interactions. Table IV shows resolution data for these
and other amide-like compounds.

    The foregoing discussion makes clear that CSP 1 requires
that solutes contain structural subunits capable of undergoing
the required multiple simultaneous interactions employed by
CSP 1 in effecting enantiomer separation. It should be obvious
that not only must appropriate "complementary functionality" be
present but that it must be arrayed so that it can effectively
contribute to the chiral recognition process. Because HPLC can
effectively reveal quite small stability differences between
diastereomeric "solvates", the conformational behavior of both
solute and stationary phase must be considered in advancing
chiral recognition models to account for observed chromatographic
behavior. One is seldom in a position to fully describe the
conformations assumed by conformationally mobile molecules.
Nevertheless, our work indicates that chiral recognition
rationales of rather broad scope can be formulated and can be
used in assigning absolute configurations to a variety of
compounds. Moreover, the rationales can be used to formulate
still more effective chiral chromatography columns.

Preparative Resolutions

    Larger scale resolutions have been accomplished using a
2" x 30" column filled with CSP 1 derived from J. T. Baker 40 μ
irregular "amino" silica. This column is considerably less
efficient (in terms of total plates) than the analytical column
but affords somewhat larger α values owing to the use of a
different type of silica. Used in conjunction with a homemade
automated prep chromatography system, we have been able to
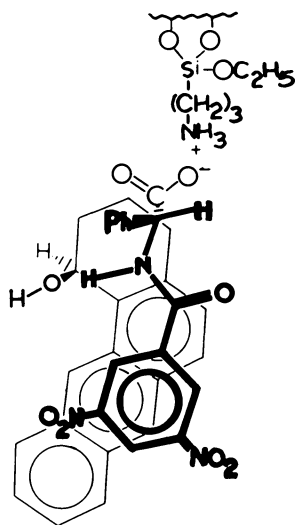
Figure 5.   Chiral recognition model showing the relative arrangement for two simultaneous bonding and one (least) repulsive interaction between (R)-CSP 1 and the most retained enantiomer of 1,2,3,4-tetrahydrobenz[a]anthracen-1-ol.
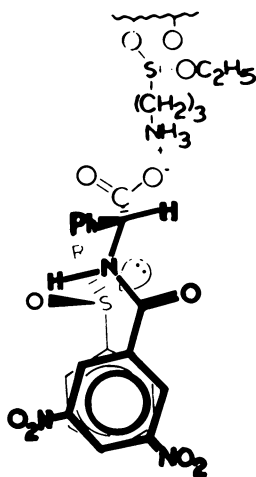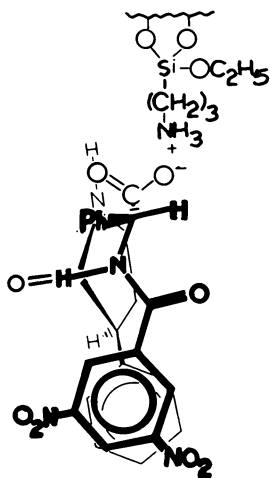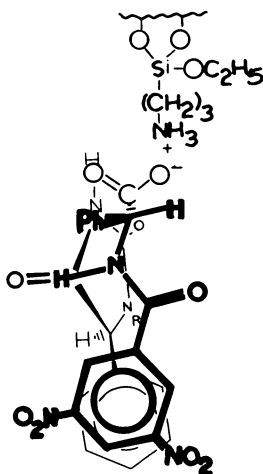

Figure 6.   Chiral recognition model showing the relative arrangement between (R)-CSP 1 and the most retained enantiomer of an alkyl aryl sulfoxide.

Figure 7.   Chiral recognition model showing the relative arrangement for three simultaneous bonding interactions between (R)-CSP 1 and the most retained enantiomer of a 3-aryllactam.

Figure 8.   Chiral recognition model showing the relative arrangement for three simultaneous bonding interactions between (R)-CSP 1 and a 5-arylhydantoin.
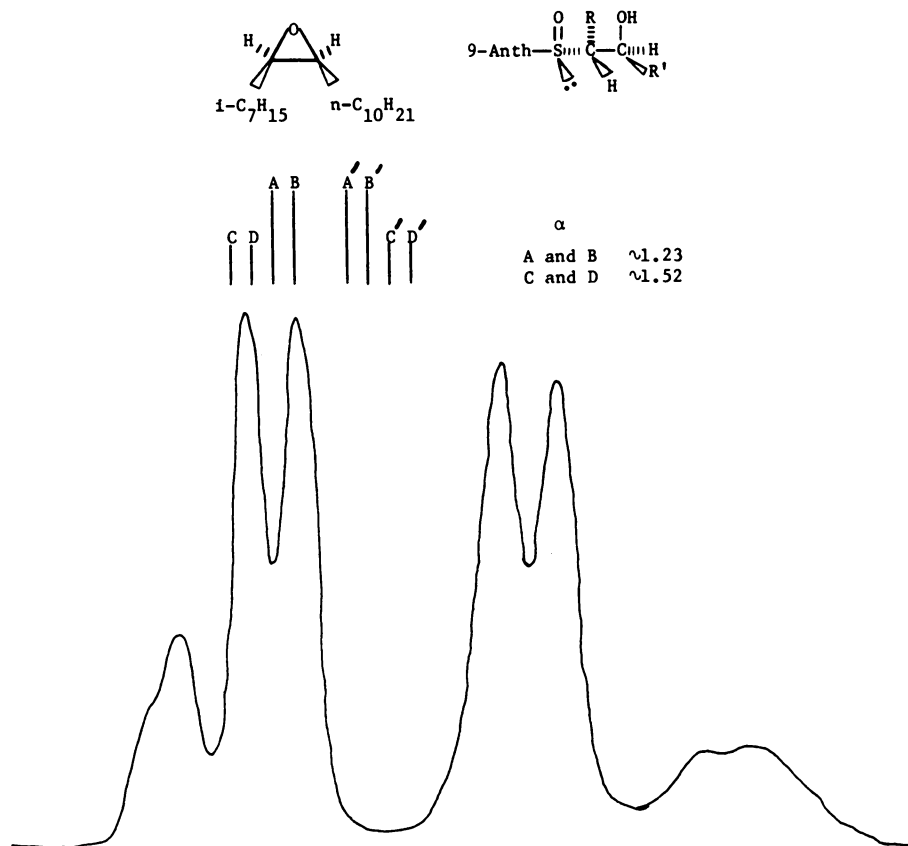
Figure 9. Chromatogram showing the separation on CSP 1 of the eight possible β-hydroxy sulfoxides derived from racemic disparlure. Bands bearing the same letter designation arise from enantiomers. A and B differ in relative stereochemistry from C and D. A and B (and C and D) are identical stereochemically but are regioisomers.

effect essentially total resolution of multigram samples of racemates having an α value of 1.4 or greater. For example, 4.0 g samples of racemic 2,2,2-trifluoro-1-[9-(10-methyl)-anthryl]ethanol [the precursor of another type of CSP (6, 7)] have been so separated into "first" and "second" chromatographic bands, the enantiomeric purities being 99 and 86%, respectively. Eight-gram samples of this racemate have been similarly resolved with only slightly poorer results. For samples having α values of 1.05 to 1.25, a more efficient prep column derived from 5 μ particles would be desirable.

Acknowledgement

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New Asymmetric Reactions Using (S)-2-Aminomethylpyrrolidine Derivatives

MASATOSHI ASAMI

University of Tokyo, Department of Chemistry, Faculty of Science,
Tokyo, Japan 113

A new chiral auxiliary reagent, (S)-2-substituted-amino-methylpyrrolidine 1, has been designed based on the fundamental assumption that a conformationally restricted cis-fused five-membered bicyclic structure would be effective for asymmetric induction. The effectiveness of the new reagent was realized in the following highly stereoselective reaction:

Asymmetric reduction of prochiral ketones. A chiral hydride reagent formed by treating the chiral diamine 1 with LiAlH$_4$ was postulated to assume a cis-fused five-membered bicyclic ring structure 2. Highly enantiomerically pure alcohols were obtained when the reaction was carried out in ether at low temperature (-100°C) by employing diamines 1 having 2,6-xylyl or phenyl substituents on nitrogen.[1]
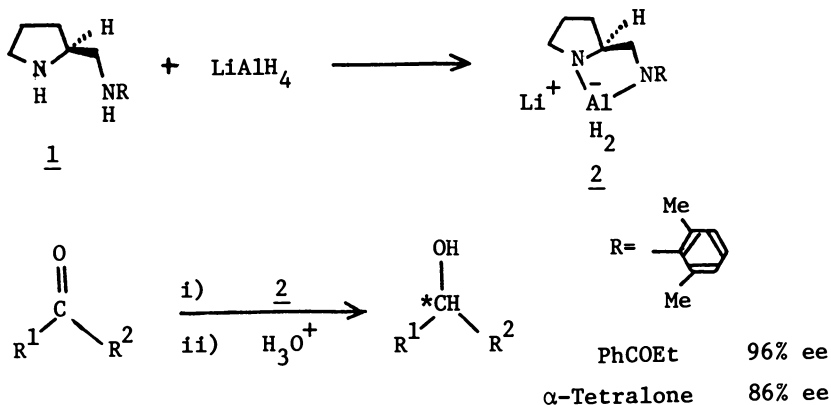

PhCOEt	96% ee
α-Tetralone	86% ee

  <u>Asymmetric synthesis of optically active aldehydes</u>. The
idea was extended to the synthsis of various synthetically useful
optically active aldehydes utilizing aminals having a similar
rigid structure as <u>2</u>. The first example is an asymmetric 1,2-
addition of Grignard reagents to a chiral keto aminal leading to
various α-hydroxyaldehydes.[2] The utility of the aminal structure
was also shown in an asymmetric 1,4-addition of Grignard reagents
to an aminal <u>3</u>, prepared from the diamine <u>1</u> (R=Ph) and fumar-
aldehydic acid methyl ester. Various 3-alkylsuccinaldehydic acid
methyl esters were thus obtained with high optical yields.[3]

85-93% ee
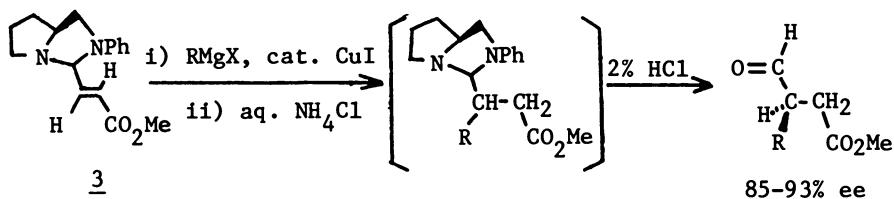
  Another highly enantioselective addition was achieved by
using the chiral aryllithium derived from <u>4</u>. Presumably the
lithium compound assumes structure <u>5</u>. Highly optically pure
lactols <u>6</u> were obtained by its reaction with aldehydes. The
resulting lactols <u>6</u> were successfully converted to optically
active 3-alkylphthalide, e.g., (<u>S</u>)-3-butylphthalide, an essential
oil of celery.[4]
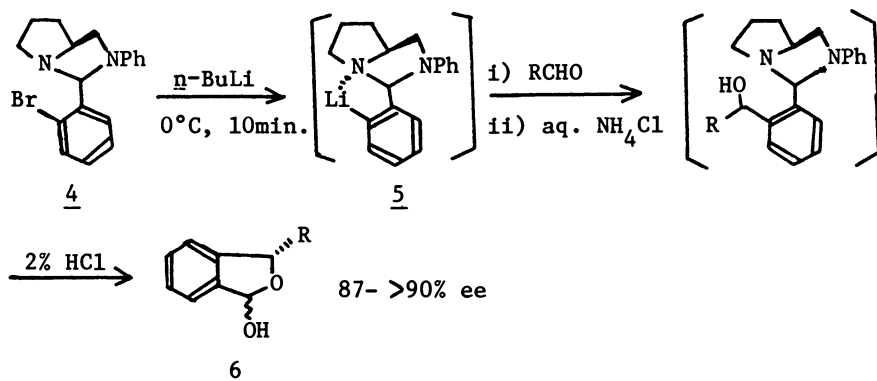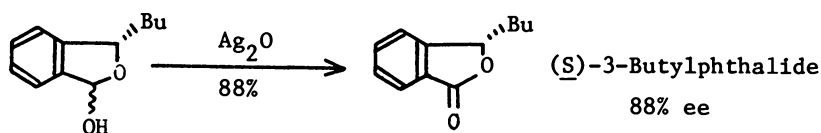
87- >90% ee

(S)-3-Butylphthalide

88% ee

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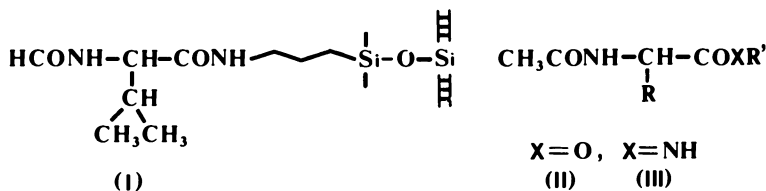
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Liquid Chromatographic Resolution of Enantiomeric α-Amino Acid Derivatives Employing a Chiral Diamide Phase

SHOJI HARA, AKIRA DOBASHI, and MASAKATZU EGUCHI

Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

Liquid chromatographic resolutions based on highly selective host-guest, metal chelate and charge-transfer complexations have been described (1,2). Recently, a chiral diamide-bonded stationary phase (I) has been prepared, which relies entirely on hydrogen bond associations for the material to be resolved. Despite the weak and flexible interaction in this system, direct resolution of enantiomeric N-acyl-ɑ-amino acid esters (II) was accomplished with the advent of a highly efficient column technology (2-4).

Amide derivatives of ɑ-amino acid solutes (III) were tested for resolution. An increase in the bulkiness of the N-alkyl moiety R' improved the separation factors (ɑ), i.e., the enantioselectivity. The highest ɑ value (1.43; 2(v/v)% 2-propanol in n-hexane) was obtained for N-tert-butylamides. Thus, enantiomeric N-tert-butylamide derivatives of N-acyl-ɑ-amino acids were separated with larger ɑ values than corresponding O-alkyl ester derivatives.

$$\text{HCONH-CH-CONH}\sim\!\!\!\sim\!\!\!\sim\text{Si-O-Si}$$
$$\overset{|}{\underset{\underset{CH_3 CH_3}{CH}}{}}$$

(I)

$$CH_3CONH-\underset{\underset{R}{|}}{CH}-COXR'$$

X = O, X = NH

(II)   (III)

For characterization and exploitation of the diamide-phase system, a chiral diamide, e.g., (III) was examined as a modifier in the mobile phase (solvent) in conjunction with a non-bonded (bare) silica.   Such a chiral carrier separated enantiomeric N-acyl-α-amino acid esters and amides with separation factors comparable to those for bonded stationary phase systems.   The resolution can be ascribed to diastereomeric complexation through amide-amide hydrogen bonding between the amide additive and enantiomeric solute molecules in the carrier solvent, followed by separation of the diastereomeric   complexes by the (achiral) silica phase.   This process should be applicable as widely as that involving chiral diamide-bonded stationary phase systems.

Analytical high resolution of enantiomers was achieved with high sensitivity by using glass capillary micro-column technology based on these diamide-phase systems.

The amide phase systems are also applicable to preparative scale separations.   A semi-preparative bonded column (10 mm i.d. x 25 cm) was prepared, yielding a loading capacity of ca. 1 mg per 1 g packing material.   Enantiomeric and diastereo-meric pairs of benzyloxycarbonyl and tert-butyloxycarbonyl protected di- and tri-peptides were resolved successfully using this chiral amide-bonded column system.

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Asymmetric Reduction with Chiral NADH Model Compounds

YUZO INOUYE

Kyoto University, Institute for Chemical Research, Uji, Kyoto, Japan 611

Novel chiral bis(1,4-dihydronicotinamide) derivatives bearing an S-prolinamide moiety were prepared and used to reduce ethyl phenylglyoxylate and other substrates. High optical yields of the reduction product R-mandelate (95.6-98.1%) were obtained with the p-xylylene- and hexamethylene-bridged bis(NAH) reductants.[1]

The e.e. was unaffected by an excess of Mg and also did not change at all during the course of reduction. Upon addition of Mg to bis(NAH), the carbonyl absorption band at 1680^{-cm} shifted to lower frequency, whereas the C-N band at 1605^{-cm} moved to a higher value. This shows[2,3] that Mg ion complexes to the primary amide carbonyl oxygen of prolinamide. The mole ratio method[4] showed the formation of a 1:1 complex between the bis(NAH) and Mg.

The Table shows the outcome of this reaction and the related ones. The spectral evidence, when combined with the stereochemical outcome that the e.e. was at a maximum when equimolar quantities of bis(NAH) and Mg were employed, shows that the present reduction with bis(NAH) is a single kinetically controlled process in contrast to that with the mono-derivatives.[5,6,7] The stereochemical requirements are well accommodated in a stoichiometric intramolecular chelation complex which assumes a C_2-conformation (I) with one specific diastereotopic face of the dihydropyridine moiety disposed toward the outside for the attack on substrates.

The chiral bis(NAH) reductants were easily regenerated by reduction of the resulting oxidized forms with aqueous solutions of

Table. Asymmetric Reductions with Chiral NADH Model Compounds

bis-NAH
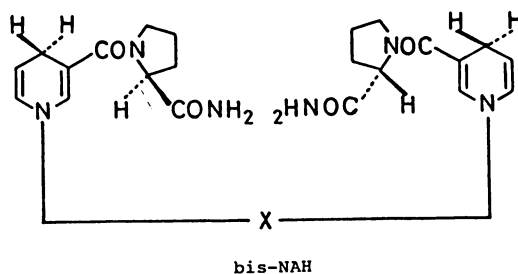
-X-	Substrate	Reaction		Product			
		Temp.(°C)	Period(hr)	% Yield	$[\alpha]_D^{25}$(°)	Config.	% ee
o-xylylene	PhCOCOOEt	25	23	69.5	-38.0	R	36.4
m-xylylene	PhCOCOOEt	25	23	61.5	-35.4	R	34.0
p-xylylene	PhCOCOOEt	25	1	66.6	-102.4	R	98.1
	PhCOCOOEt	50	2	79.8	-97.8	R	93.5
	(pyridyl)COMe	60	16	66.9	+50.8	R	89.7
	(pyridyl)COPh	50	100	71.5	-123.3	-	99.7
	Ph(Me)C=C(CN)$_2$	25	192	16.8	+4.1	R	23.2
	(anhydride)	25	67	100	-19.3	R	38.1
-(CH$_2$)$_4$-	PhCOCOOEt	20	19	50.4	-41.7	R	39.9
-(CH$_2$)$_5$-	PhCOCOOEt	20	17	73.4	-44.9	R	43.0
-(CH$_2$)$_6$-	PhCOCOOEt	20	17	63.5	-99.8	R	95.6
	(pyridyl)COMe	50	23	84.3	-37.8	R	66.7
	(pyridyl)COPh	50	23	67.0	-114.6	-	92.7
	Ph(Me)C=C(CN)$_2$	50	96	59.2	+4.3	R	24.5
	(anhydride)	50	23	65.7	-17.2	R	33.9
-(CH$_2$)$_7$-	PhCOCOOEt	20	15	57.9	-61.3	R	58.7
-(CH$_2$)$_8$-	PhCOCOOEt	20	15	63.2	-84.8	R	81.2
mesitylene (tris-NAH)	PhCOCOOEt	20	16	16.5	+18.3	S	17.6

(I)
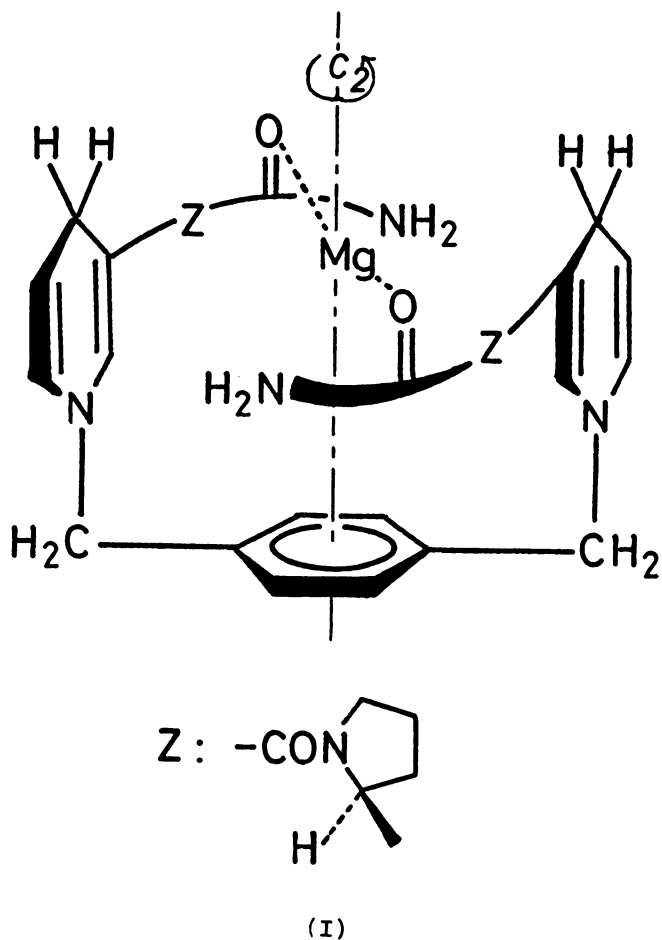
sodium hydrosulfite in 42-60% recovery and can be recycled with the optical yields remaining unchanged.

The mesitylylene-bridged tris(NAH) derivative of *S*-prolinamide and the *p*-xylylene-bridged bis(NAH) derivative of *S*-prolinol switched the steric course of reduction so as to give the enantiomeric *S*-mandelate in lower e.e.

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# Asymmetric Hydrogenation of Cyclic Dipeptides Containing α,β-Dehydroamino Acid Residues and Subsequent Preparation of Optically Pure α-Amino Acids

NOBUO IZUMIYA

Kyushu University, Laboratory of Biochemistry, Faculty of Science,
Higashi-ku, Fukuoka 812, Japan

AM-Toxin I (I, Scheme 1) is a host specific phytotoxin. To elucidate the role of the double bond in the ΔAla^2 residue, we planned to prepare [L-Ala^2]- or [D-Ala^2]-AM-toxin I (II) by hydrogenation of AM-toxin I. By way of a preliminary study we hydrogenated cyclo(ΔAla-L-Leu) (III) and observed unexpectedly high asymmetric induction, affording pure cyclo(L-Ala-L-Leu) (IV).
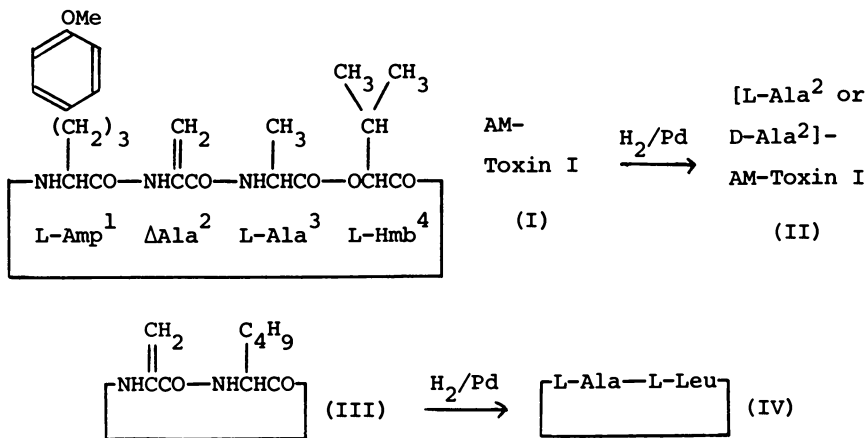
Scheme 1

Cyclo(L-Ser-L-AA) (AA=Ala, Val, Phe or Lys(ε-Ac)) was converted by the Photaki method (1) into the corresponding cyclo (ΔAla-L-AA) and subsequently hydrogenated with Pd black in methanol at 25°C affording cyclo(Ala-L-AA) (2). Generally high chiral inductions defined as %L-Ala minus %D-Ala in the cyclo(Ala-L-AA) were observed, ranging from 92 to 98% with yields of 63-75%. Similarly high chiral inductions (96-99%) were observed for

hydrogenation of a series of cyclo(ΔAA'-L-AA) (ΔAA'=ΔAba, ΔVal or ΔLeu) prepared from cyclo(Gly-L-AA) and appropriate aldehydes (3). Hydrogenation of ΔPhe or ΔTrp in cyclo(ΔPhe or ΔTrp-L-AA) resulted in a slightly lower asymmetric induction at 25°C (3). Hydrogenation of a series of its higher homologs (e.g. cyclo(ΔHomophe-L-Ala)), however, afforded high induction (4). Cyclo(ΔPhe-L-Ala) was hydrogenated with high chiral induction at a low temperature, 0°C (4).

Optically pure α-amino acids can be prepared by this route. For example, pure cyclo(L-Aba-L-Lys(ε-Ac)) obtained from cyclo (ΔAba-L-Lys(ε-Ac)) was hydrolyzed by 6 M HCl to give pure L-Aba (L-2-aminobutanoic acid) (3). Pure L-App (L-2-amino-5-phenyl-pentanoic acid) was prepared from cyclo(ΔApp-L-Ala) and used for the synthesis of AM-toxin II (5). $^2H_2$-D-Phe was prepared from cyclo(ΔPhe-D-Lys(ε-Ac)) and deuterium at 0°C, and synthesis of [$^2H_2$-D-Phe$^{4,4'}$]-gramicidin S (cyclic decapeptide) for NMR investigation is under study.

The mechanism of the chiral inductions has been discussed (2-4). In cyclo(ΔAla or ΔLeu-L-AA), the rigid and planar structure of the diketopiperazine ring and the side chain containing the double bond is an important factor inducing high asymmetry. In cyclo(ΔPhe or ΔTrp-L-AA), however, the diketopiperazine ring and the aromatic ring cannot be coplanar; a somewhat poorer stereo-selectivity in the adsorption of the diketopiperazine ring on Pd is assumed to lower the degree of asymmetric hydrogenation.

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