

農

258

1-0

STEREOCHEMISTRY OF
[2,3] AND [3,3] SIGMATROPIC REARRANGEMENTS

YUKIO YAMAMOTO

1978

STEREOCHEMISTRY OF
[2,3] AND [3,3] SIGMATROPIC REARRANGEMENTS

YUKIO YAMAMOTO

1 9 7 8

ACKNOWLEDGEMENT

The author wishes to express his sincerest appreciation to Professor Yuzo Inouye for his encouragement and guidance throughout the course of this investigation. The author is also indebted to Associate Professor Jun'ichi Oda for his valuable advices and suggestions. It is a great pleasure to acknowledge to Dr. Seiji Sawada, Associate Professor of Kyoto University of Education, Dr. Naomichi Baba, and Dr. Minoru Moriwaki for their helpful discussions.

The author is grateful to Mr. Hiroshi Shimoda for his enthusiastic assistance in experiments. The author takes pleasure in making acknowledgement here of the valued help of his laboratory members.

LIST OF CONTENTS

1	INTRODUCTION	
1-1	[3,3] and [2,3]Sigmatropic Rearrangements	1
1-2	Self-Immolative Asymmetric Synthesis	15
2	STEREOCHEMISTRY OF THE REARRANGEMENT OF AN ALLYLIC AMINE OXIDE	
2-1	Objective	21
2-2	Result and Discussion	24
2-3	Experimental	32
3	STEREOCHEMISTRY OF THE REARRANGEMENT OF TRICHLOROACETIMIDATES	
2-1	Objective	42
2-2	Result and Discussion	44
2-3	Experimental	50
4	SUMMARY	59
5	REFERENCES	61

1 INTRODUCTION

1-1 [3,3] and [2,3]Sigmatropic Rearrangements

The investigation of reaction mechanism during the last fifty years or so has provided a satisfying and coherent picture of organic reactions. As ideas of mechanism developed, two broad classes of reactions, involving either ionic species or free radicals, were recognized. Although many reactions could confidently be classified as ionic or radical processes, a third group fell outside this classification; they appeared not to involve intermediates but proceeded by reorganization of electrons through cyclic transition state, and were therefore classified as concerted (one-step) processes.

Concerted reactions have the following general characteristics discriminating themselves from stepwise reactions. And those can be used as criteria for concertedness.

1) Concerted reactions never involve any intermediates contrary to stepwise reactions. In the latter, intermediates can actually be isolated sometimes and may be detected by ir, uv, or nmr spectroscopies. Transient radical intermediates can be detected by esr spectroscopy and the technique of CIDNP. The presence of intermediate can also be proved by trapping them with other reactants.

2) The rates of concerted reactions are, in general, less sensitive to changes in substituents and solvents than are the rates of stepwise reactions.

3) In general, concerted cycloadditions and rearrangements require critical orientations of atoms and therefore show large negative entropy of activation, $\Delta S^\ddagger$. Stepwise processes generally do not require such critical alignment, and smaller activa-

tion entropies are to be expected. Concerted processes usually have small enthalpies of activation, $\Delta H^\ddagger$, since they do not require energies to cleave chemical bonds in transition states.

4) The stereochemical course of concerted reactions is governed by the strict rule which will be referred to later. In the allowed course, additional stereoselectivity is often observed which is inherent to critical alignment in transition state.

The development of a general theory of concerted reactions has been due chiefly to the work of Woodward and Hoffmann.¹⁾ They have taken the basic ideas of molecular orbital theory and used them, mainly in a qualitative way, to derive selection rules which predict the stereochemical course of various types of concerted reactions; electrocyclic reactions, cycloadditions, and sigmatropic rearrangements. These rules are best understood in terms of symmetries of interacting molecular orbitals. The same kind of selection rules have been obtained by various other theoretical approaches; frontier orbital theory by Fukui,²⁾ Dewar-Zimmerman rule³⁾ based on the aromatic transition state concept, and a valence bond treatment.⁴⁾ Woodward and Hoffmann have introduced the term "pericyclic" to cover all those concerted reactions, and have derived the following general selection rule; A ground-state pericyclic change is symmetry-allowed when the total number of $(4q+2)_{\text{supra}}$ and $(4r)_{\text{antara}}$ components is odd.

Uncatalyzed thermal rearrangements occurring intramolecularly and involving a 6-membered cyclic transition state are very common, and include an enormous variety of structural types. Some of these, such as the Cope and Claisen rearrangements and [1,5]hydrogen shifts in conjugated dienes, have been known for many years; others which occur thermally or photochemically in anions, cations, ylides, and carbenes as well as in neutral

molecules have only recently been recognized as being of this type. The unifying features of all these reactions are that they are concerted, uncatalyzed, and involve a sigma bond migration through a cyclic transition state in which an atom or group is simultaneously joined to both termini of a π electron system. Woodward and Hoffmann have given the name sigmatropic rearrangements to such reactions, the adjective "sigmatropic" indicating movement of a sigma bond.

The extent of the migration of a sigma bond is represented by the prepositive of $[i,j]$. The total number of atoms, N , concerning a rearrangement is the sum of i and j . A reaction is neutral, cationic, anionic when the difference $(N-n)$ is 0, +1, or -1 respectively, where n is the total number of electrons concerning the reaction. Selection rules for sigmatropic rearrangements are depicted in Table 1. The stereochemical course of the reaction is governed by the number of electrons participating as are the other pericyclic reactions.

Table 1. Selection rules for sigmatropic rearrangements

n	Ground state	Excited state
$4q$	antara-supra	supra-supra
	supra-antara	antara-antara
$4q+2$	supra-supra	antara-supra
	antara-antara	supra-antara

The $[3,3]$ and $[2,3]$ sigmatropic rearrangements involve 6 electrons participating in transition state. The $[3,3]$ shifts

such as the Cope and the Claisen rearrangements⁵⁾ show characteristics typical of concerted processes. These have large negative entropies of activation and are highly stereoselective. The [2,3]changes are the anionic equivalent of the [3,3]shifts, are not confined to carbon systems,⁶⁾ but also involve many hetero systems.⁷⁾

1) [3,3]sigmatropic rearrangement

The transition state of [3,3]sigmatropic change can be considered as two interacting allylic systems. Various geometries are possible for the transition state, which can be classified according to whether each of the allylic systems interacts with lobes of the other system on the same side (suprafacially) or on the opposite side (antarafacially). Fig. 1 shows the transition state topologies. The modes of 1, 2, and 3 are *a priori* predicted to be thermally allowed and the mode of 4 to be thermally forbidden from the above selection rules for sigmatropic rearrangements. Of the three possible types of transition state, the antara-antara one 3 is much less likely to be found than the others, because it involves twisting of the allylic systems.

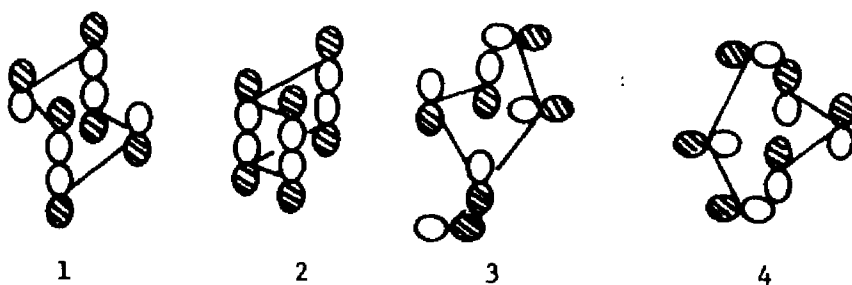
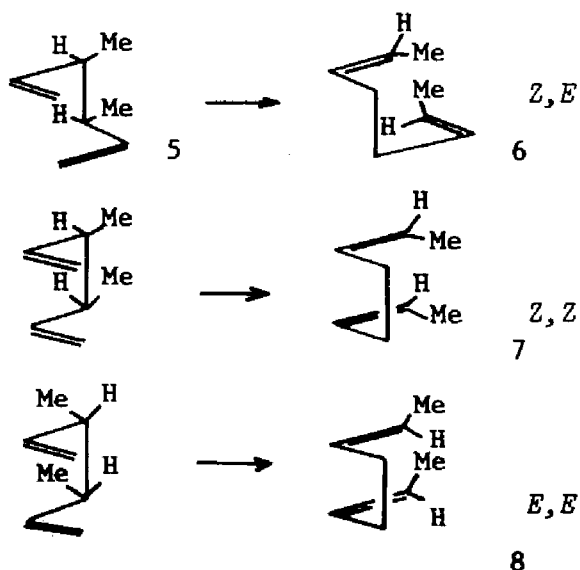


Fig. 1. Transition state topologies of [3,3]shifts.

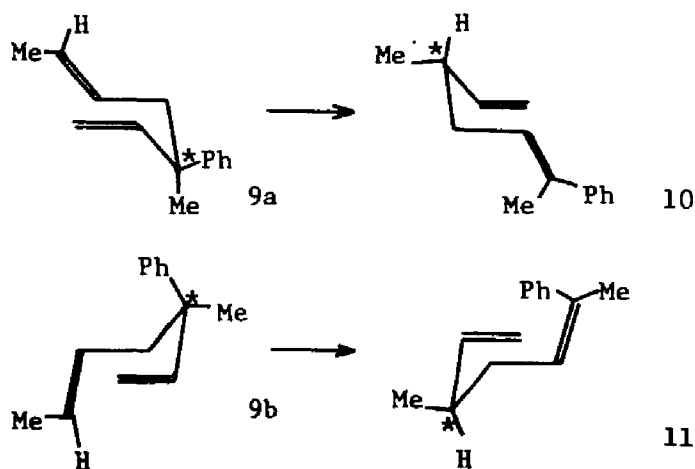
Yet the doubly antarafacial Cope rearrangements have been observed; the stereospecific rearrangement of [3,2,0]heptadiene derivatives have been reported.^{8a)} In these systems, both of the allylic parts are sterically fixed and in the correct position for a doubly antarafacial rearrangement. It is noteworthy, however, that alternative mechanisms for the rearrangements of the [3,2,0]systems have been advanced.^{8b)} Since the torsion of the allylic halves will strongly diminish the allylic resonance, the antara-antara mode can be safely excluded and the supra-supra modes are adopted in the flexible [3,3]rearrangement.

The chair and boat forms of the supra-supra transition state are both relatively strain-free. Of the two, the chair form 1 (4 center) might be expected to be more favored because the 6 *p*-lobes lie in a quasi-planar arrangement. The interaction of the central *p*-lobes of the two allylic systems in the boat form 2 (6 center) does appear to have a slight destabilizing effect. This has been shown with the aid of correlation diagrams by Woodward and Hoffmann,^{1a)} by means of molecular orbital calculations by Dewar,⁹⁾ and by other theoretical approaches.¹⁰⁾



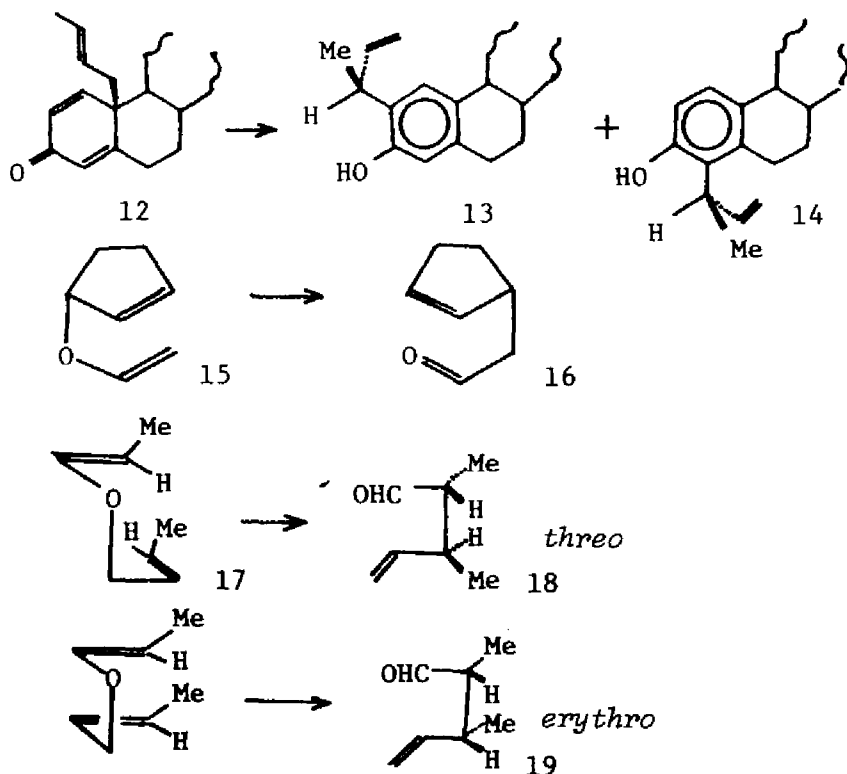
In the Cope rearrangement of **acyclic** 1,5-dienes, the evidence is that the transition state prefers a chair to a boat conformation. Doering and Roth showed this with the *meso*-diene (5) which rearranged almost exclusively (99.7%) to the *Z,E*-diene (6).^{5b,11} This stereochemistry is consistent only with a chair conformation for the transition state; a boat would give the *Z,Z*- (7) or *E,E*-diene (8).

Similarly, the stereochemistry of the Cope rearrangement was investigated from the viewpoint of self-immolative asymmetric synthesis.¹² The optically active hexadiene (9) rearranged to an 87:13 mixture of the new hexadienes (10) and (11), both of which were afforded with 94-96% optical yield. The geometry of double bonds and the absolute configurations of the products are consistent with the chair conformations shown for the reaction and place an upper limit of 2-3% on the contribution of boat conformations. The difference in energy of the two types of transition state is probably about 6 kcal/mol. Finally, the 87:13 preference for 10 corresponding to a free energy difference of about 2 kcal/mol between 9a (phenyl equatorial) and 9b (phenyl axial), lends confidence to the prediction of favored transition state conformation in 4 center thermal rearrangements on the basis of cyclohexane conformation analysis.



Another stereochemical study in the Cope rearrangement of a chiral dienone also shed light on the transition state topology.¹³⁾ The dienone (12) rearranged to 13 and 14, which is one step of the aromatic Claisen rearrangement. From the optical yield of the reaction, it follows that chair transition state accounts for at least 75-80% of the transformation of 12 to 13 and 14.

In some cyclic systems the chair transition state is sterically impossible to attain, and the Cope reaction still goes but by a boat transition state.

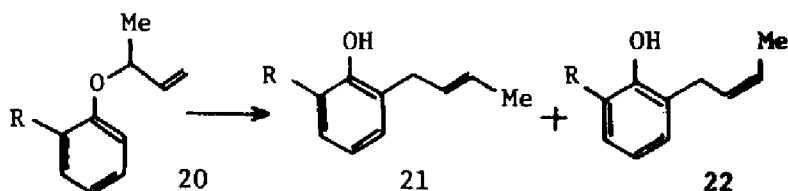


In the aliphatic Claisen rearrangement, the supra-supra transition state was proved by the study of a self-immolative asymmetric synthesis.¹⁴⁾ It appears that transfer of chirality from 15 to 16 is complete. The Claisen-type processes are ex-

cellent procedures for introducing various functionalized angular methyl groups in condensed-ring compounds.¹⁵⁾

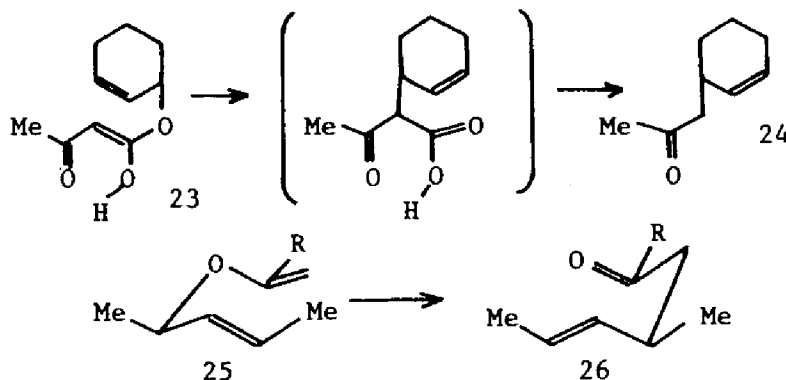
Like the Cope rearrangement, the Claisen seems to prefer the chair conformation. *E,E*-Ether (17) gave more than 97% of *threo*-aldehyde (18), indicating a preference for the chair transition state. Reaction in the boat conformation leads to the *erythro*-aldehyde (19). The same preference was supported by the use of *Z,Z*- and *Z,E*-crotyl propenyl ethers.¹⁶⁾

The supra-supra route in the aromatic Claisen rearrangement has been also established by the study of a self-immolative asymmetric synthesis.¹⁷⁾ The preference of chair transition state has been shown by various investigation. For example, in the rearrangement of α -methylallyl aryl ethers, the ratio of 21(*E*)/22(*Z*) is extremely sensitive to substituents in position 6. For R:H, Me, Et, *i*-Pr, and *t*-Bu this ratio is 14, 37.5, 39, 39, and 99 respectively. The steric influence is understandable if the rearrangement proceeds through chair transition state. Otherwise one would expect the reverse trend in the ratio 21(*E*)/22(*Z*).¹³⁾

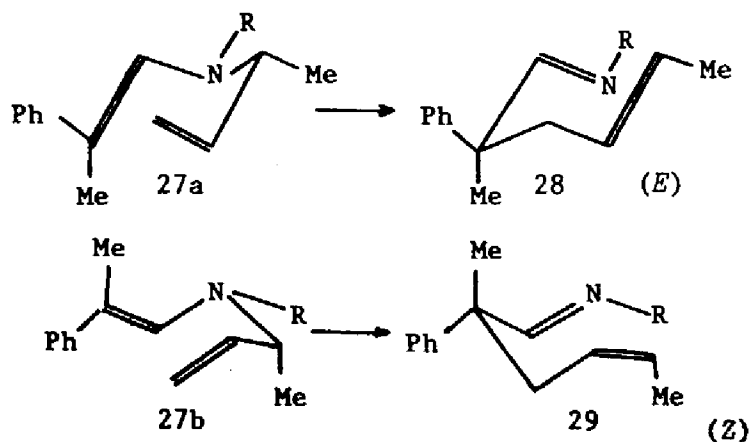


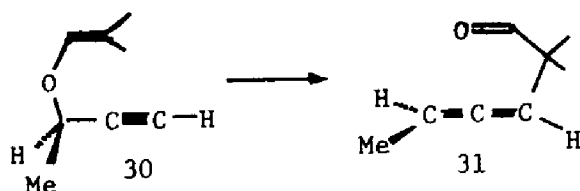
Other [3,3]shifts have been also investigated from the viewpoint of stereochemistry. The double Claisen-Cope rearrangement (Thomas method) has been confirmed to proceed *via* supra-supra fashion by the experiment using (-)-*cis*-carveol.¹⁸⁾ The Carroll reaction was shown in the conversion of 23 to 24. Although the extent of asymmetric synthesis was not known, the

stereochemical outcome supports the doubly suprafacial transition state.¹⁹⁾ The Claisen-type rearrangements of 25 to 26 have been proved to be highly stereoselective; the *E* isomer were obtained in more than 98% and the optical yields were about 90%.²⁰⁾

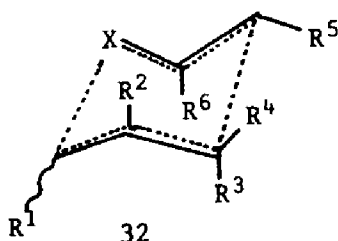


The study of a self-immolative asymmetric synthesis of 27 supports the chair transition state of the amino-Claisen rearrangement. The ratio of *Z* and *E* products (13:87) indicates that the transition state having the equatorial methyl group is preferred.²¹⁾ The rearrangement of an allylic phenylurethan to an aniline derivative was proved that the reaction proceeded *via* a supra-supra fashion.²²⁾ The conversion of centrodissymmetry to molecular dissymmetry was achieved in the Claisen rearrangement (30 → 31) involving a triple bond, which substantiates the concertedness of the reaction.²³⁾





The [3,3]rearrangements have been utilized for the stereoselective synthesis of natural products since the *E* isomer are usually produced much more than the *Z* counterparts.²⁴⁾ Faulkner has noted suprisingly close quantitative agreement between the observed *Z/E* ratios and the observed axial/equatorial ratios in cyclohexanes, notwithstanding the obvious fact that the transition state for these rearrangements are not identical with cyclohexanes. He suggested alternative approaches that will increase the stereospecificity; 1) the reaction should be carried out at lower temperature, 2) a trisubstituted double bond should be constructed in such a fashion that R^2 in 32 is not a hydrogen, and 3) suitable bulky substituents, possibly removable, should be placed at R^3 and perhaps R^6 .²⁵⁾



ii) [2,3]sigmatropic rearrangement

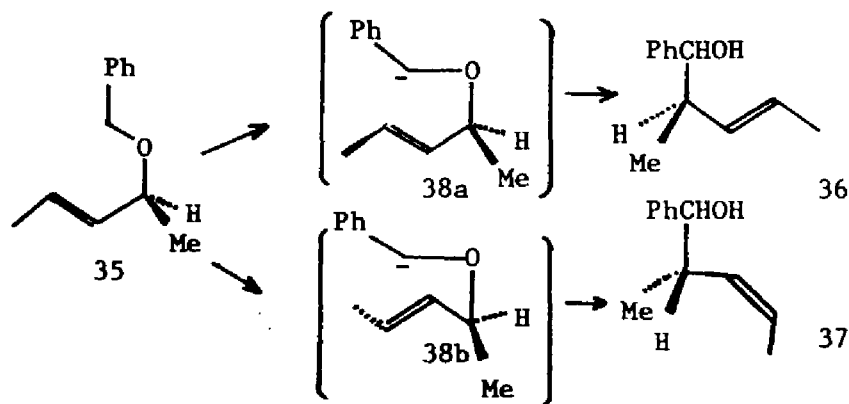
Based on the reaction systems, [2,3]sigmatropic rearrangements are formally classified in the following manner; anion, carbene, lone-pair, and ylide types. In all the systems, six electron participate and therefore the same selection rules for

[3,3]sigmatropic rearrangements can be applied. The supra-supra (33) and antarafantara (34) migrations are thermally allowed. Of the two, the doubly antarafacial fashion can be safely excluded because of the geometrical disadvantage.



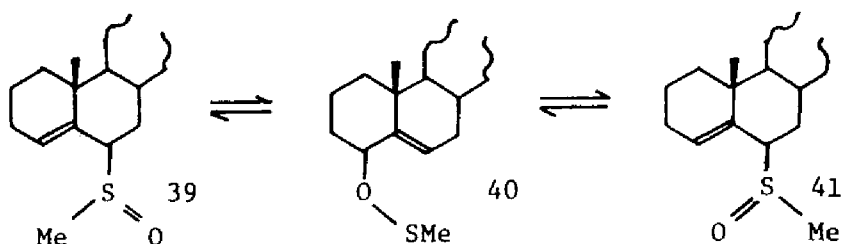
Fig. 2. Transition state topologies of [2,3]shifts.

The preference of the supra-supra transition state (33) has been supported clearly in the Wittig rearrangement.²⁶⁾ Chiral ether (35) rearranged to 36 (83%) and 37 (17%). The stereospecificity of the process was 72% for the *E* and 62% for the *Z* series. The extent of randomization derived from the classical Wittig [1,2]shift was established to be 28±5%. Then the [2,3]shift for the *E* isomer was proved to proceed with quantitative stereospecificity, and those processes were verified to be doubly suprafacial fashions. The preference for the *E* isomer formation can be rationalized by the favorable quasi-equatorial orientation of the methyl group in the envelope form (38).



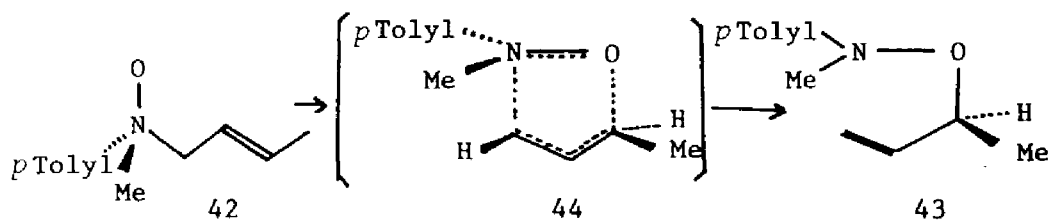
The [2,3]rearrangement of cyclic *N*-arylsulfimides was shown to proceed with a stereochemistry of 95% suprafacially with respect to the sulfoniumylide fragment.²⁷⁾

The allylic sufoxide-sulfenate rearrangements in the steroidal systems (39 $\rightleftharpoons$ 40 $\rightleftharpoons$ 41) have been shown to proceed suprafacially with respect to the allylic systems. The relation between chirality on sulfur and reaction rate was discussed in terms of the relative compressions in the model transition states.²⁸⁾

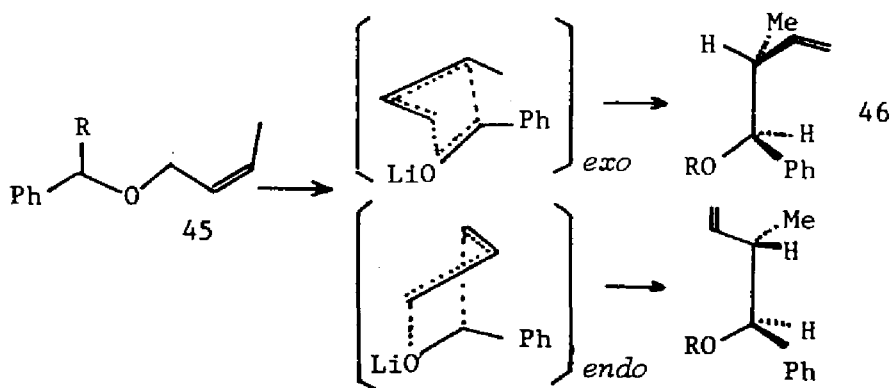


Self-immolative asymmetric syntheses were achieved with high stereospecificity in the rearrangements of an acyclic sulfenate to a sulfoxide,²⁹⁾ and of a sulfinate to a sulfone.³⁰⁾ The rearrangement of a sulfonium ylide to a sulfide was demonstrated to proceed with a minimum of 94% optical induction. The transition state topology is rather speculative since the absolute configuration of the starting material was not known.³¹⁾

The transition state topology of an allylic rearrangement of an amine oxide was unequivocally established with a self-immolative asymmetric synthesis. The chiral amine oxide (42) rearranged to give 43 with the retention of optical activity as high as 84%. The tolyl group and the methyl group were proved to orient *trans* to each other assuming the supra-supra mode (44).³²⁾

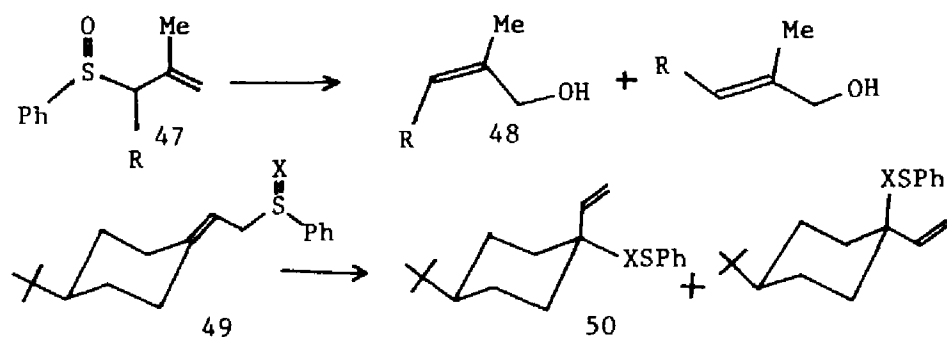


In the rearrangement of benzyl crotyl ethers, the configurations of products seem to be dominated by the steric hindrance in the transition state of envelope form.^{33a)} Lithiation of the *Z* ether (45) afforded only the *threo*-alcohol (46), which indicates that the *exo*-arrangement is more favorable than the *endo*-one. However, any selectivity did not appear in the *E*-ether. The ratio of the *erythro*-form to the *threo*-form from the *E*-ether was proposed to be 2 by another work.^{33b)} The same preference of the *exo*-arrangement to the *endo*-one has been proposed in the allylic rearrangement of sulfenates to sulfoxides.³⁴⁾



In the presence of sulfenate ester trapping agents (trimethyl phosphite and others), allylic sulfoxides (47) can be cleanly transformed into the rearranged alcohols (48), in which the *E* products are produced nearly exclusively.³⁵⁾ The [2,3]-sigmatropic rearrangement of sulfur ylides (49) in which a

cyclohexyl ring carbon is the migration terminus occurs highly regiospecifically; 97% equatorial attack (50).³⁶⁾ A similar selectivity in the Claisen rearrangement has also been reported but that was rather low; 75-77% equatorial attack.³⁷⁾



Now, [3,3] and [2,3]sigmatropic rearrangements are compared from the viewpoint of stereoselectivity. The energy level of the starting system of [2,3]rearrangements is usually higher than that of [3,3]rearrangements. Assuming that the energy difference between alternative steric courses, e.g. leading to *E* and *Z* products respectively, in [3,3]shift is equal to that of [2,3]-shift, higher selectivity should be expected for [2,3]shift which can be conducted at lower temperature. On the other hand, the radical by-path accompanying the concerted process often lowers the yield of the aimed product and the stereoselectivity.

1-2 Self-Immulative Asymmetric Synthesis

It is one of the most striking characteristics of the reaction in nature that it produces specifically one of the paired enantiomers. Thus, the mechanism of the phenomenon has been very mysterious and an attractive subject of a number of chemists' investigations. Chemical asymmetric synthesis is a point of contact between organic chemistry and biochemical process. Since organic chemistry originally means "chemistry of organism", the study of asymmetric synthesis should be an important area of organic chemistry.

In 1894, Fischer clearly outlined the concept of asymmetric synthesis based upon his experiments in the conversion of one sugar to its next higher homolog *via* the cyanohydrin reaction.³⁸⁾ The chemical definition of asymmetric synthesis was proposed by Marckward in 1904;³⁹⁾ "Asymmetric syntheses are those reactions which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical process." This classical definition is based on the observation of optical activity and experimental procedure.

The more general definition instead of the narrower one by Marckward has been proposed with accumulation of the knowledge about stereochemistry as well as development of the analytical technique. Now, the following definition is accepted in general; "An asymmetric synthesis is a reaction which converts a prochiral unit into a chiral unit under chiral environment so that unequal amounts of stereoisomeric products result." Chemical environment means not only chiral reagents but also chiral solvents, catalysts, and physical forces such as a circularly polarized light.

At first, the phenomenon of asymmetric synthesis was ex-

plained to be induced by "asymmetric molecular force" from the asymmetric center through chemical bonds, which was advocated by McKenzie.⁴⁰⁾ But the concept of the asymmetric synthesis mechanism was changed completely by the presentation of the now well-known rules of steric controls of asymmetric synthesis by Prelog⁴¹⁾ and Cram.⁴²⁾ These rules interpret the stereochemical correlation between a starting material and a product in terms of a model based on steric interactions in the transition state. Since then, these stereochemical models have been playing a role of leading principle in the area of the asymmetric synthesis investigation.

Since the organic reaction is controlled stereoelectronically, a steric model based solely on the interaction with steric bulkiness does not always represent the real transition state topology. Now one should attempt to analyze critically all such asymmetric syntheses on a rational thermodynamic and kinetic basis in terms of the steric and electronic interactions.

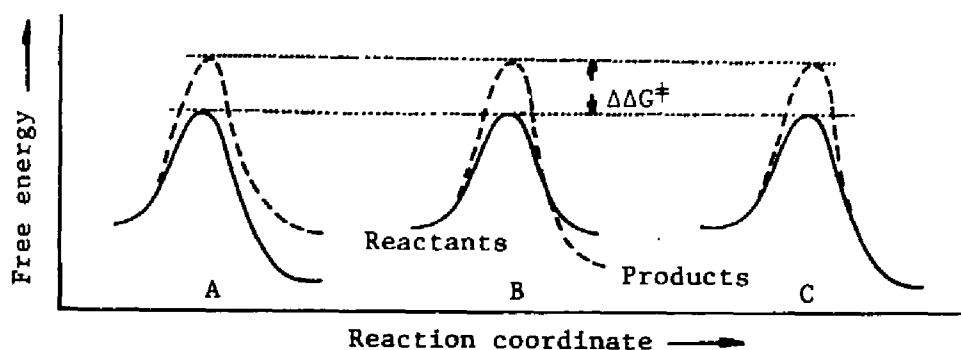
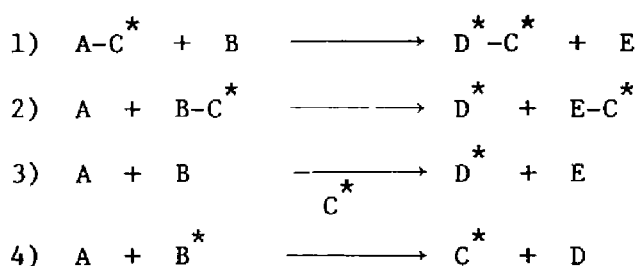


Fig. 3. Energy-reaction coordinate diagram.

Considering the energetics in the asymmetric synthesis, one recognizes three basic types of reactions which are under kinetical control. These reaction types, energy diagrams for which are given in Fig. 3, differ from each other as follow.

The ground state free energies of the reactants for the competing pathways are identical ($\Delta G^\circ=0$). Only the free energies of activation of the two pathways differ ($\Delta\Delta G^\ddagger\neq 0$); the extent of asymmetric transformation depends only upon the differences in the free energies of activation. A mixture of diastereomers is afforded in types A and B in which the ground state free energies of the products differ. The process of type C where G° is zero yields a mixture of enantiomers.

And, based on the reaction systems, asymmetric syntheses are formally classified in the following manner.

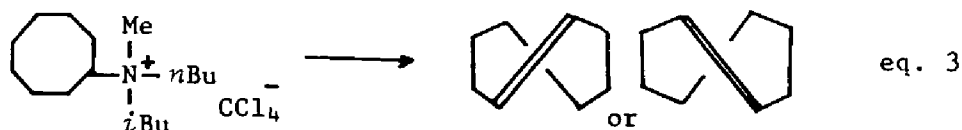
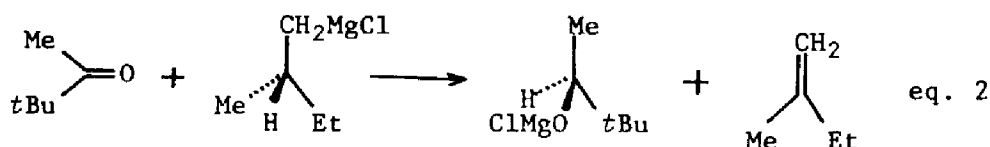
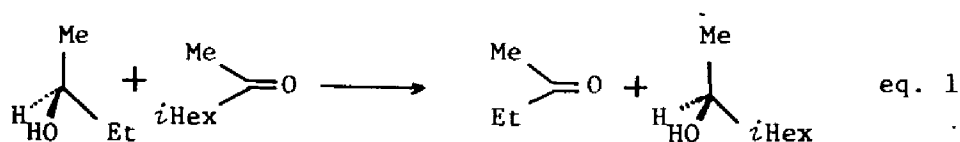


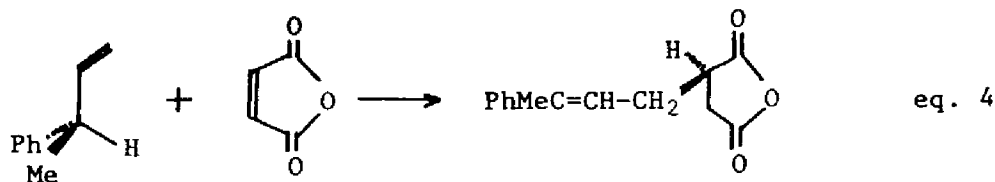
In system 1, the substrate holds a chiral center and the attacking species is achiral. On the other hand, the substrate is achiral and the attacking species is chiral in system 2, And in system 3, the substrate and the attacking species do not hold chiral center, but the reaction proceeds under chiral environment in the presence of chiral catalyst, solvent, and physical agent. The reaction of type 1 has the energy profile of A or B and is named diastereo differentiating reaction. And the reactions of type 2 and 3 are termed enantio differentiating reactions which have the energy profile of C.

In the above types of reactions, the chiral moiety employed is conserved whether or not it can be practically and quantitatively recovered, so that they are of common feature in this

point, hence being called "conservative asymmetric synthesis". On the other hand, the originally existing chiral center is being destroyed at the same time that the new chiral center is being formed in the reaction of type 4. It has been termed "self-immolative asymmetric synthesis" by Mislow⁴³⁾ and "asymmetric transfer" by Pracejus.⁴⁴⁾ The transfer of chirality includes the interconversion of centrodissymmetry and molecular dissymmetry. Self-immolative symmetric synthesis meets strictly the requirements of the energy profile of C that the ground state free energies of the reactants and products are identical respectively ($\Delta G^\circ=0$) and only the free energies of activation differ ($\Delta \Delta G^\ddagger \neq 0$).

Self-immolative asymmetric syntheses are achieved both in intermolecular and intramolecular fashions. The examples of the former are the asymmetric Meerwein-Ponndorf-Verley reaction⁴⁵⁾ (eq. 1) and the reduction with the chiral Grignard reagent⁴⁶⁾ (eq. 2). Asymmetric eliminations can be looked upon as a form of self-immolative asymmetric synthesis (eq. 3).⁴⁷⁾ A thermal reaction of olefines with maleic anhydride yielded optically active adducts (eq. 4), which is a concerted process termed "ene reaction".⁴⁸⁾



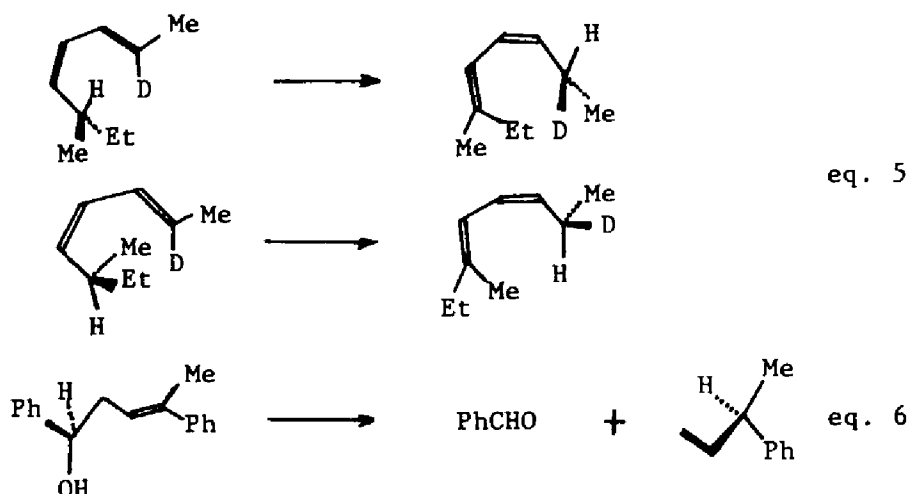


The self-immolative asymmetric synthesis in intramolecular mode is achieved *via* a molecular rearrangement. It is the phenomenon that the chirality originally residing on a moiety of a molecule is transferred to another part in the same molecule during simultaneous fission and formation of chemical bonds. Consequently, the study of the intramolecular self-immolative asymmetric synthesis can be regarded as the study of the stereochemistry of molecular rearrangement. The change of stereochemistry at the same atom during a reaction is excluded from self-immolative asymmetric synthesis but is the object of stereochemical study of rearrangement.

Interest in the asymmetric synthesis of this category has often been focused on the reactions which occur through [3,3] and [2,3]sigmatropic rearrangements. As was referred to in the preceding section, these investigations have shed light on the stereochemical course of the sigmatropic rearrangements. The development of the stereochemical theory of the sigmatropic rearrangement has a close relation to the accumulation of experimental results of these self-immolative asymmetric syntheses.

In other than [3,3] and [2,3]changes, a self-immolative asymmetric synthesis was also carried out through the [1,5]-sigmatropic rearrangement. The optically active diene gave the two isomers expected from thermally allowed suprafacial fashions (eq. 5).⁴⁹⁾ Recently, an asymmetric induction in the pyrolysis

of β -hydroxy olefines was reported (eq. 6),⁵⁰⁾ which is classified in "retro-ene reaction".

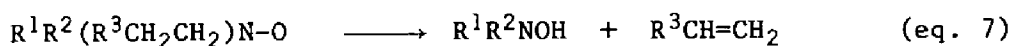


Contrary to the concerted process, the radical dissociation-recombination mechanism makes one recall a loose stereochemical course resulting in a low asymmetric yield. Although the Stevens rearrangement proceeds *via* a radical path, the extent of asymmetric synthesis was presumed to be substantial.⁵¹⁾ A self-immolative asymmetric synthesis with nearly quantitative stereoselectivity was effected in the base-catalyzed 1,3-tautomerism of 3-methyl-1-alkylindenes to 3-alkyl-1-methylindenes.⁵²⁾ Stereoselective intramolecular hydrogen transfer has been observed in the acid catalyzed isomerization of an alcohol to a ketone.⁵³⁾

2 STEREOCHEMISTRY OF THE REARRANGEMENT OF AN ALLYLIC AMINE OXIDE

2-1 Objective

The reactions upon heating of tertiary amine oxides fall in the following categories.



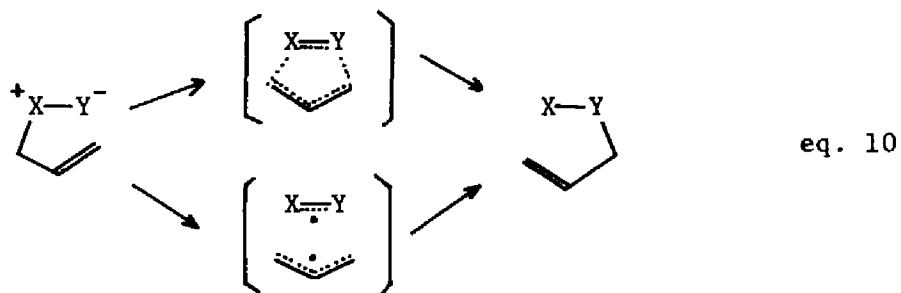
Elimination (eq. 7); The tertiary amine oxides decompose, when heated, to yield olefines plus hydroxylamines,⁵⁴⁾ which proceeds by *cis*-elimination mechanism.⁵⁵⁾ Oxidation (eq. 8); Pyridine oxide can oxidize halides to yield aldehydes or ketones in the presence of epoxides.⁵⁶⁾ Rearrangement (eq. 9); In the case that a benzyl group is attached to nitrogen atom of amine oxides, this group may migrate from nitrogen atom to oxygen atom to yield *O*-substituted hydroxylamines. Similar reaction can proceed when an allyl group is attached to nitrogen atom. These rearrangement reactions are designated as the Meisenheimer rearrangement.⁵⁷⁾

Reactions belonging to the last category are of interest from the mechanistic point of view. The reaction mechanism of the amine oxides carrying a benzyl group is believed to differ from that of the allylic amine oxides. In the rearrangement of benzylamine oxide, the reaction proved to proceed through the radical dissociation-recombination by esr⁵⁸⁾ and CIDNP⁵⁹⁾ studies. Besides, this route through which racemization should

be expected to occur was confirmed by the investigation employing optically active *N,N*-dimethylbenzyl-(α -*d*)-amine oxide.⁵⁸⁾

In the case of allylic amine oxides, the concerted mechanism *via* a 5 membered cyclic transition state was suggested from the observation that *N*-crotyl-*N*-methylaniline oxide rearranged with inversion of the crotyl group.⁶⁰⁾ Recently the concertedness of this reaction was more clearly confirmed with the study of a self-immolative asymmetric synthesis of a chiral amine oxide.³²⁾

This process is classified in the [2,3]sigmatropic rearrangement. It is also known that this process is accompanied by a second pathway shown to be a radical-pair mechanism. The dual pathway (eq. 10) have been observed actually in the Wittig rearrangement²⁶⁾ and the rearrangements of *N*-ammonio-amidates⁶¹⁾ and carbenes derived from imidates.⁶²⁾ The mechanistic difference depends on molecular environment and reaction condition.⁶³⁾ In the case of the rearrangement of triallylamine oxide and the analogs, radical mechanism was proposed from the kinetic study.⁶⁴⁾ The concerted process usually has lower activation energy, as revealed by the fact that the proportion of the product which is formed by the concerted pathway to that afforded by the radical pathway increases at lower temperature.



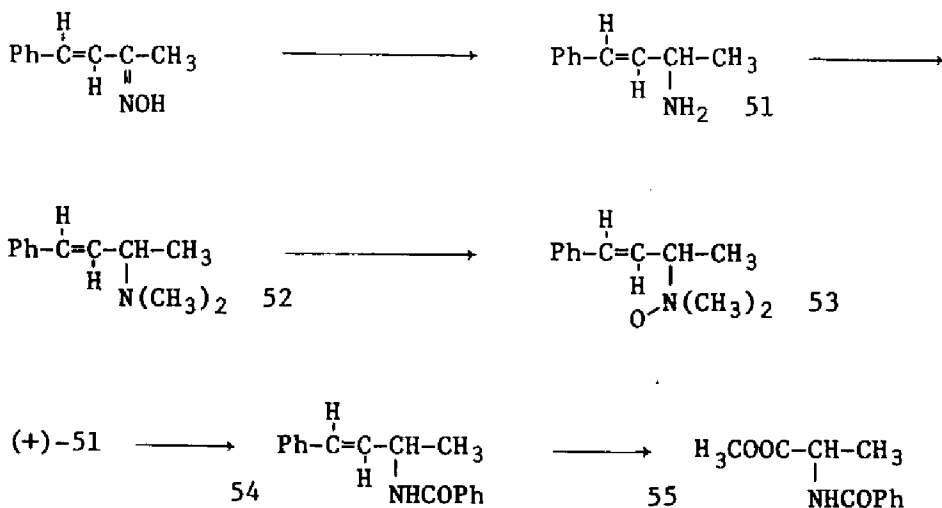
In order to clarify the stereochemistry of the rearrangement of the allylic amine oxide and to discuss the reaction mechanism, the present author undertook to effect the thermal rearrangement of an optically active allylic amine oxide, *N,N*-dimethyl-(2*E*)-1-methyl-3-phenyl-2-propenyl amine oxide (53), which was expected to rearrange into *O*-1-phenyl-2-butenyl-*N,N*-dimethylhydroxylamine (56) through the concerted mechanism. The result of the present self-immolative asymmetric synthesis will enable one to elucidate the steric course and the transition state topology of the [2,3]shift and add to the knowledge of the reaction mechanism. Furthermore the influence of temperature on the variation of the rearrangement products and the stereochemistry might also shed light on the reaction mechanism.

2-2 Result and Discussion

Preparation of the chiral amine oxide, N,N-dimethyl-(2E)-(1S)-1-methyl-3-phenyl-2-propenylamine oxide (53).

Benzalacetone oxime⁶⁵⁾ from benzalacetone⁶⁶⁾ was reduced with zinc dust in acetic acid to yield $(\pm)$ -(1E)-1-phenyl-3-amino-1-butene $[(\pm)$ -51].⁶⁷⁾ The levorotatory enantiomer having $[\alpha]_D -7.8^\circ$ was obtained by optical resolution with (+)-tartaric acid. The Eschweiler-Clarke methylation⁶⁸⁾ of (-)-51 gave the N-methylated amine $[(-)$ -52, $[\alpha]_D -34.0^\circ$]. The amine oxide (53) was obtained by the action of peracetic acid and directly subjected to the rearrangement reaction because of the lability of 53. The amine oxide (53) was characterized by the picrate, $[\alpha]_D -54.4^\circ$, in a parallel run starting from (-)-52 having a rotation $[\alpha]_D -36.4^\circ$.

Scheme 1



The *S* configuration of (-)-51 was established by chemical correlation of the enantiomeric (+)-51 to (-)-*N*-benzoylalanine methyl ester⁶⁹⁾ of the well defined *R* configuration, through the consecutive *N*-benzoylation, barium permanganate cleavage, and esterification with diazomethane. In the earlier stage of this investigation, the author deduced the *R* configuration to (-)-51 based on the catalytic hydrogenation of (-)-51 ($[\alpha]_D -8.9^\circ$) to give (+)-1-phenyl-3-aminobutane ($[\alpha]_D 10.1^\circ$), to which the *R* configuration was inferred by Červinka.⁷⁰⁾ In contrast, the opposite *S* configuration was claimed for the same (+) enantiomer by Terent'ev.⁷¹⁾ The author was inextricably confused by this situation and so he worked out the absolute assignment of configuration by independent and unambiguous means. Recently, the *S* configuration of (+)-1-phenyl-3-aminobutane was supported by Nagai⁷²⁾ based on chiroptical data; the CD spectrum of the *N*-DNP derivative of the (+)-saturated amine shows the positive Cotton effect around 400nm which indicates the positive chirality of the two transition moment (phenyl and DNP groups) and consequently the *S* configuration.

The optical purity of (-)-51 was determined to be 81% on the basis of the maximum rotation, $[\alpha]_D 9.6^\circ$, found by the optical resolution *via* the (-)-malic acid salt.

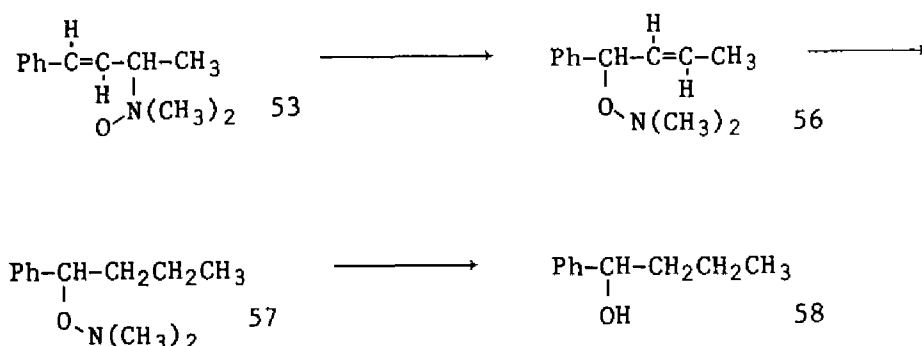
Rearrangement and correlation of products

After testing several rearrangement conditions, it was found to be most appropriate to stand the amine oxide (53) at -20°C for 24 days. Under these conditions, 53 rearranged to *O*-(2*E*)-1-phenyl-2-butenyl-*N,N*-dimethylhydroxylamine (56) in 44% yield based on (-)-52. The *E* geometry of the double bond in 56 was established by ir and pmr spectra in comparison with

(2*E*)-1-phenyl-2-buten-1-ol.

Since the rearrangement product 56 was not so stable as to permit one to observe constant rotation at room temperature, it was at once hydrogenated over platinum oxide to give the saturated hydroxylamine [(-)-57], $[\alpha]_D -83.4^\circ$. Reductive N-O bond fission of (-)-57 with zinc dust in acetic acid afforded (-)-1-phenyl-1-butanol [(-)-58], $[\alpha]_D -31.6^\circ$.

Scheme 2



Successful transfer of the chirality originally residing on the tetrahedral carbon to the trigonal carbon was thus achieved in the present system. Since the *S* configuration of the end product (-)-58 has been unambiguously established,⁷³⁾ the same configuration can be assigned to the parent (-)-57 and 56. Consequently, the *S* configuration of the [2,3]rearrangement product 56 was newly created at the expense of the *S* chirality of the substrate amine oxide (53). The optical purity of (-)-58 proved to be 69% based on the reported maximum rotation $[\alpha]_D -45.9^\circ$,⁷⁴⁾ so that 85% optical activity was retained during the present process. It was reported that ca. 16% racemization occurred when the hydroxylamine derivative of (-)-benzyl alcohol- α -*d* was treated with zinc dust in acetic

acid.⁷⁵⁾ To assess the extent of racemization inherent to the method for N-O bond cleavage, (-)-1-phenyl-1-butanol (58) having a rotation $[\alpha]_D -41.2^\circ$ was subjected to exactly the same treatment and the recovered alcohol had a rotation $[\alpha]_D -35.4^\circ$ which corresponded to ca. 86% retention of optical activity. It then follows that the optical yield in the present self-immolative asymmetric synthesis can be looked upon as being nearly quantitative.

The complete transfer of chirality during the [2,3]shift supports the concerted mechanism and excludes the radical dissociation-recombination. There are two conceivable transition states expected for thermally allowed [2,3]sigmatropic rearrangement from the viewpoint of the conservation of orbital symmetry; doubly suprafacial and doubly antarafacial (cf. p.10).

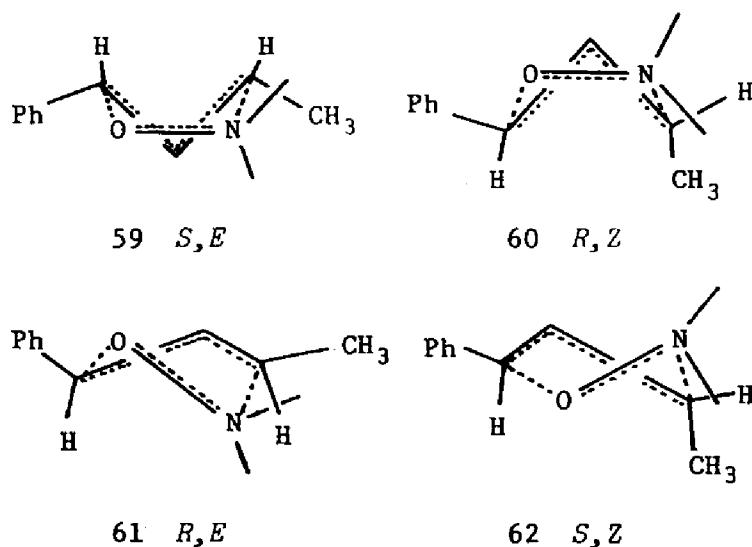


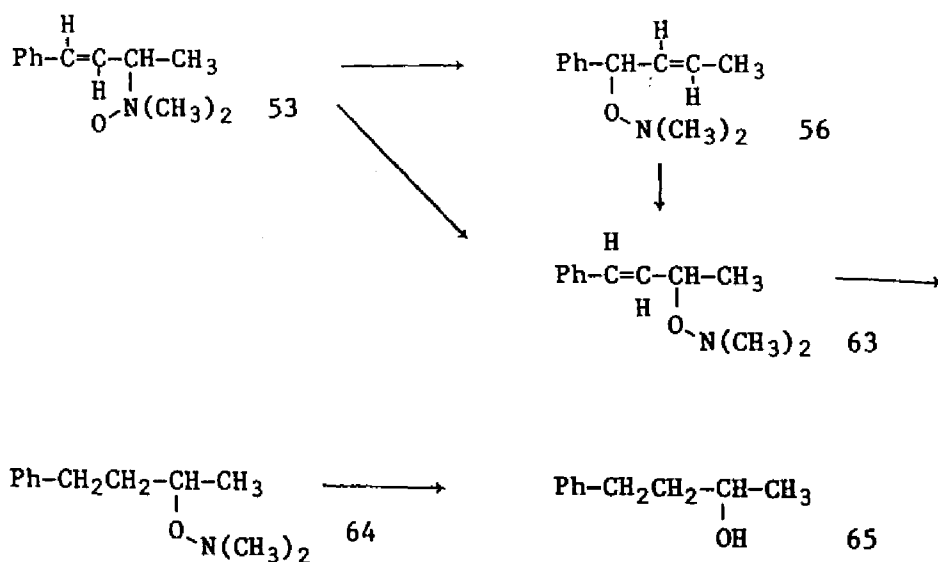
Fig. 4. Transition state topologies of [2,3]shift of 53

Depicted in Fig. 4 are the conceivable transition state topologies which may not only meet the orbital symmetry require-

ments, but also may account for the newly created chirality and double bond geometry of the product in the present [2,3]sigmatropic rearrangement. The finding that (*S*)-(*E*)-amine oxide (53) rearranged to give (*S*)-(*E*)-hydroxylamine (56) cogently supports the fashion 59. In this fashion, both fragments orient doubly suprafacial, which is geometrically preferred to the antarafacial modes (61 & 62) (cf. p.11). The preference of the mode 59 to an alternative suprafacial 60 could be rationalized by the unfavorable nonbonded interaction between methyl group and hydrogen atom which orient syn-quasi-axial in an envelope form of the latter.

When the amine oxide (53) derived from (*R*)-(+)-52, $[\alpha]_D^{25}$ 36.6° (87% optical purity), was heated in chloroform under reflux for 1 hr, the [1,2]shift product, (+)-*O*-(2*E*)-1-methyl-3-phenyl-2-propenyl-*N,N*-dimethylhydroxylamine [(+)-63], $[\alpha]_D^{25}$ 6.9°, was obtained in an overall yield of 56% from 52 through 63. There was no detectable contamination of the [2,3]shift product 56.

Scheme 3



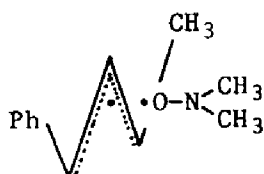
Hydrogenation of (+)-63 over platinum oxide gave the saturated hydroxylamine [(-)-64], $[\alpha]_D -6.6^\circ$. Subsequent treatment of (-)-64 with zinc dust in acetic acid afforded (-)-4-phenyl-2-butanol (65), $[\alpha]_D -3.2^\circ$. The *R* configuration can be safely assigned to (-)-64 and (+)-63, and the optical purity was assessed to be 17% by transformation to (-)-65 whose *R* configuration⁷⁰⁾ and maximum rotation, $[\alpha]_D^{20} -19.41^\circ$,⁷⁶⁾ have been known.

The chirality at the carbon atom originally bonded to the nitrogen atom was conserved to the extent of 20% (corrected for the optical purity of the amine oxide used) at the same chiral center during the present thermal process.

An aliquot of chloroform solution of the chiral amine oxide (53) was subjected to [2,3]rearrangement under the same condition described above and the resultant product 56 was then heated in chloroform under reflux for 1 hr. Along with a small amount of 56, the compound (+)-63 was obtained, which upon hydrogenation was converted into (-)-64 having a rotation $[\alpha]_D -6.5^\circ$. Consequently, the conservation of chirality in the course of the present consecutive [2,3] and [1,3]rearrangements compared well with that of the direct thermal [1,2]shift.

These facts show that the [1,2]shift upon heating takes place *via* the classical Meisenheimer mechanism.⁵⁹⁾ The higher the temperature, the more radical path seems to prevail in competition with the [2,3] concerted rearrangement, which is often observed in similar thermal processes (cf. p.11). The radical dissociation-recombination is supported by the fact that the conservation of chirality at the carbon atom was of the extent of 20%, which might be a little bit larger because of the method employed for N-O bond fission. The value is in accordance with the observation that the rearrangement of

(+)-*N,N*-dimethyl-benzyl- α -*d*-amine oxide preceeded with 22-39% retention of configuration *via* a radical intermediate.⁵⁸⁾ The radical pair intermediate of the present [1,2]shift can be formulated as explicit in 66. *N,N*-Dimethylnitroxide radical is in juxtaposition to the allylic radical. The orientation seems to permit access of no less than 20% of retention at the chiral center concerned during the thermal process which has inevitable randomness.



66

It seems likely that the [1,3]shift from 56 to 63 involves a process of dissociation into two halves, since the magnitude of racemization is comparable with that of direct [1,2]shift. The same solvent-caged radical pair was assumed in the [1,3]-rearrangement of *O*-linalyl-*N,N*-dimethylhydroxylamine.⁷⁷⁾

Concerted processes have large negative entropies of activation, $\Delta S^\ddagger$ and relative small enthalpies of activation, $\Delta H^\ddagger$. On the other hand, radical dissociation-recombination processes have smaller $\Delta S^\ddagger$ and larger $\Delta H^\ddagger$ (cf. p.1). Since activation free energy is defined as $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$, it is rational that the radical mechanism becomes to prevail over the concerted process with increasing temperature. This is the case for the present thermal processes and the energy profile of the reaction can be roughly depicted as in Fig. 5. It can be explained by product stability that the [1,2]shift product was finally obtained on heating. The higher stability of 63 than 56 is rationalized

by the conjugation of double bond with phenyl.

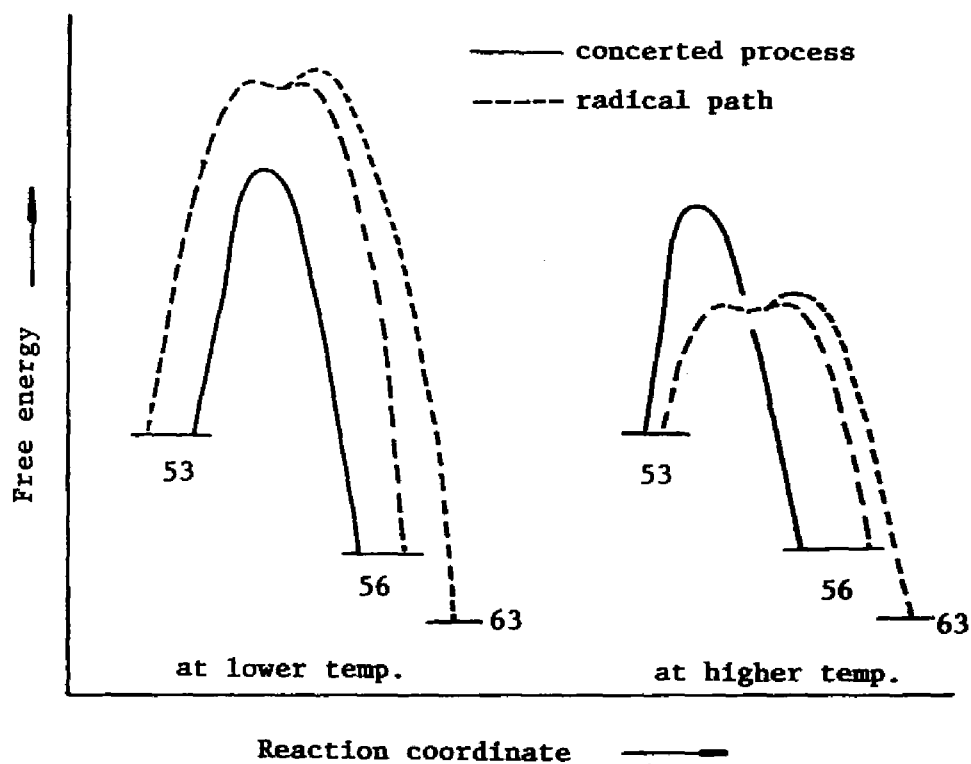


Fig. 5. Energy-reaction coordinate diagram.

2-3 Experimental

All melting and boiling points were uncorrected. Ir spectra were recorded with a Hitachi EPS-2 and a Model 215. Pmr spectra were measured on a Vairian Associates Model A-60 and a Model EM-360. Elementary analyses were done by a Yanagimoto CHN-corder TM-1. Optical rotations were observed with a Yanagimoto OR-50 or a Perkin Elmer R-241.

In pmr spectra, chemical shifts are reported in δ -values relative to TMS as an internal standard, and the data are given in the order of multiplicity (s; singlet, d; doublet, t; triplet, m; multiplet), integration and assignment.

A Varian aerograph Model A-700 was used for preparative vpc (column; length 3m, diameter 3/8inch).

Preparation of the chiral amine oxide

Benzalacetone oxime

Benzalacetone⁶⁶⁾ (200g, 1.37 mol), hydroxylamine hydrochloride (114g, 1.64 mol) and sodium acetate (135g) were heated under reflux in ethanol (960ml) for 4 hr, and allowed to stand overnight at room temperature. The mixture was filtered and evaporated to a reduced volume. Addition of water gave the crystalline oxime. Recrystallization from ethanol-water yielded 196g (89%) of benzalacetone oxime; mp 117°C (lit.⁶⁵⁾ mp 89°C).

($\pm$)-(1E)-1-Phenyl-3-amino-1-butene [($\pm$)-51]

Benzalacetone oxime (63g, 0.39 mol) was dissolved in a mixture of ethanol (500ml) and acetic acid (500ml). Zinc dust (284g, 3.7 g atom) was added to the mixture in small portions at 10°C with mechanical stirring. The mixture was allowed to stand over-

night at room temperature and heated under reflux for 1 hr, then filtered and distilled in steam. The remaining solution was made alkaline with 30% sodium hydroxide and the amine was distilled off with steam. The steam distillate was saturated with potassium carbonate and extracted with ether. The ether extract was dried over anhydrous potassium carbonate and evaporated. Distillation gave 20g (29%) of ($\pm$)-51; bp 120-122°C (20mm), n_D^{21} 1.5614, ir (liquid): ν_{NH_2} 3400 & 3320, $\delta=CH(E)$ 966cm⁻¹, pmr (CDCl₃): δ 1.23(d, 3H, CH₃), 1.41(s, 2H, NH₂), 3.65(m, 1H, CH), 5.96-6.64(m, 2H, CH=CH), 7.14-7.43(m, 5H, phenyl). Benzamide; mp 137°C (lit.⁶⁷) mp 136-137°C).

(-)-(1E)-1-Phenyl-3-amino-1-butene [(-)-51]

The racemic amine (30g, 0.2 mol) was added to (+)-tartaric acid (31g, 0.2 mol) in ethanol (1200ml) and the salt formed was recrystallized twice from ethanol to yield colorless plates (11g); mp 165-166°C, $[\alpha]_D^{21}$ 0.0° (c 0.20, ethanol). The amine liberated from the salt had $[\alpha]_D^{20}$ -7.8° (c 10.0, benzene).

Benzamide; mp 145-146°C

Elementary analysis C₁₇H₁₇NO

Calcd C: 81.24 H: 6.82 N: 5.57

Found C: 81.23 H: 6.86 N: 5.55

(+)-(1E)-1-Phenyl-3-amino-1-butene [(+)-51]

The racemic amine (31g, 0.21 mol) was added to (-)-malic acid (28g, 0.21 mol) in ethanol (230ml). The salt obtained was recrystallized 6 times from ethanol to yield 2.8g of crystals; mp 157-158°C, $[\alpha]_D^{26}$ 35.1°C (c 1.0, ethanol). The physical constants did not alter on further recrystallizations. From the crystals the optically pure enantiomer was obtained; $[\alpha]_D^{27}$ 9.6° (c 9.8, benzene).

Configurational correlation of (+)-51

(-)-N-Benzoylalanine methyl ester [(-)-55] from (+)-51

The *N*-benzoylation of (+)-51 (4.0g, 27 mmol, $[\alpha]_D^{20}$ 7.2°) was effected in the usual manner to give (+)-(1*E*)-1-phenyl-3-benzoylamino-1-butene (6.5g, 95%); mp 132°C, $[\alpha]_D^{20}$ 34.2° (*c* 1.0, methanol). To the benzoylamine [(+)-54, 2.5g, 10 mmol] dissolved in pyridine (20ml) were added, alternately and stirring barium permanganate (5.0g, 13 mmol) in water (40ml) and barium hydroxide (5.0g) in warm water (50ml). The temperature was kept at 40°C. Manganese dioxide was filtered off, washed well with hot water, and the filtrate and washings were combined. The solution was warmed with a small amount of methanol to destroy excess of permanganate, carbon dioxide was passed to precipitate barium and the solid was filtered off. The filtrate was evaporated to dryness and the residue was dissolved in 50% ethanol. Barium was removed with 4*N* sulfuric acid with rhodizonic indicator. The filtrate was evaporated to a reduced volume and extracted with ethyl acetate. After drying over anhydrous sodium sulfate, ethyl acetate was evaporated to dryness and benzoic acid was removed with hot ligroin. The residue was dissolved in ethanol (5ml) and ethereal solution of diazomethane was added to the solution until a faint yellow color persisted. After standing overnight, the mixture was evaporated. The product was purified by the silica gel column chromatography (eluent; benzen:ethyl acetate=8:1). Crystallization from ligroin yielded (-)-55; mp 53-54°C (lit.^{69a} mp 58°C), $[\alpha]_D^{19}$ -29° (*c* 2.0, acetylene tetrachloride), ir (KBr): ν_{NH} 3300, $\nu_{\text{C=O}}$ 1745, $\nu_{\text{N=C}}$ 1630 cm^{-1} , pmr (CDCl_3): δ 1.52(d, 3H, CH₃), 3.82(s, 3H, OCH₃), 4.62-5.13(m, 1H, CH), 6.65-7.08(broad, 1H, NH), 7.40-8.08(m, 5H, phenyl).

Elementary analysis $\text{C}_{11}\text{H}_{13}\text{NO}_3$

Calcd C: 63.75 H: 6.32 N: 6.76

Found C: 63.75 H: 6.49 N: 6.94

The ir and pmr spectra were identical in every respect with those of the authentic (+)-55 which was derived from (+)-alanine.

(+)-N-Benzoylalanine methyl ester [(+)-55] from (+)-alanine

(+)-Alanine (3.0g, 35 mmol) was dissolved in water (30ml), then sodium bicarbonate (22g) and benzoyl chloride (14.5g, 103 mmol) in small portions were added. The mixture was shaken at room temperature for 1 hr and filtered. The crude product was deposited by the addition of conc. hydrochloric acid. Benzoic acid was extracted off with hot ligroin. Recrystallization from water yielded (+)-benzoylalanine (3.5g, 54%); mp 140-155°C, $[\alpha]_D^{20}$ 19.1° (c 9.3, water containing equivalent of potassium hydroxide) (lit.^{69b}) mp 150-151°C, $[\alpha]_D^{20}$ 37.13°. By the addition of diazomethane, (+)-55 was obtained (56%); $[\alpha]_D^{19}$ 33°.

(-)-(1E)-1-Phenyl-3-N,N-dimethylamino-1-butene [(-)-52]

To (-)-51 (4.0g, 27 mmol) formic acid (98%, 25g, 530 mmol) was added with ice cooling, then formaldehyde (36%, 20g, 240 mmol) was added. The mixture was heated at 55-60°C for 13 hr and under reflux for 4 hr. The mixture was treated with conc. hydrochloric acid (12ml) and distilled in steam. Then the remaining mixture was made alkaline with 30% sodium hydroxide and the amine was distilled in steam. The steam distillate was saturated with potassium carbonate and extracted with ether. The ether extract was dried over anhydrous potassium carbonate and evaporated. Distillation gave (-)-52 (2.3g, 47%); bp 133-134°C (21mm), n_D^{22} 1.5351 [lit.⁷⁸] bp 139-140°C (25mm), n_D^{25} 1.5350 for the racemate], $[\alpha]_D^{20}$ -34.0° (c 10.0, benzene), ir (liquid): δ =CH(E) 969cm⁻¹, pmr (CDCl₃): δ 1.23(d, 3H, CH₃), 2.27

[s,6H,N(CH₃)₂], 3.04(m,1H,CH), 5.94-6.63(m,2H,CH=CH), 7.14-7.46(m,5H,phenyl).

Picrate of *N,N*-dimethyl-(2*E*)-1-methyl-3-phenyl-2-propenyl-amine oxide (53)

Peracetic acid (40%, 1.3g, 7 mmol) was added dropwise at -40°C to (-)-52 (0.81g, 4.7 mmol, $[\alpha]_D^{18} -36.4^\circ$) in chloroform (20ml). The reaction mixture was allowed to stand at -20°C overnight and then made alkaline with 10% sodium hydroxide and the aqueous layer was extracted with chloroform (15ml $\times$ 3). The combined extract was dried over anhydrous potassium carbonate and filtered. Picric acid (0.85g, 3.7 mmol) in ethanol (20ml) was added to the filtrate, and the mixture was stored in a refrigerator. The picrate salt deposited (0.75g, 38%); mp 141-142°C. Recrystallization from ethanol yielded the analytical sample; 144-145°C, $[\alpha]_D^{21} -54.4^\circ$ (c 0.50, methanol), ir (KBr): ν_{N-O} & $\delta=CH(E)$ 968 & 962cm⁻¹, pmr (DMSO-*d*₆): δ 1.57(d,3H,CH₃), 3.30(broad,1H,OH), 3.39 & 3.42[s,6H,N(CH₃)₂], 4.50(m,1H,CH), 6.15-7.08(m,2H,CH=CH), 7.22-7.68(m,5H,phenyl), 8.58(s,2H,picrate).

Elementary analysis	C ₁₈ H ₂₀ N ₄ O ₈		
Calcd	C: 51.43	H: 4.80	N: 13.33
Found	C: 51.14	H: 4.98	N: 13.10

Rearrangement and correlation of products

[2,3]Rearrangement of 53 to give *O*-(2*E*)-1-phenyl-2-butenyl-*N,N*-dimethylhydroxylamine (56)

The amine oxide (53) was obtained by the oxidation of (-)-52 (2.3g, 13 mmol, $[\alpha]_D^{20} -34.0^\circ$) with peracetic acid (40%, 3.8g, 20 mmol) in chloroform (60ml) in exactly the same way as de-

scribed above. The amine oxide in chloroform was allowed to stand still at -20°C for 24 days. The chloroform solution was filtered through activated alumina (50g) and evaporated in vacuo at 0°C . The hydroxylamine (56) [1.1g, overall yield of 44% from (-)-52]; ir (liquid) $\delta=\text{CH(E)}$ 962cm^{-1} , pmr (CCl_4): δ 1.70(m, 3H, CH_3), 2.47[s, 6H, $\text{N}(\text{CH}_3)_2$], 4.74-5.72(m, 3H, CH & $\text{CH}=\text{CH}$), 7.27(s, 5H, phenyl).

(-)-O-1-Phenylbutyl-N,N-dimethylhydroxylamine [(-)-57]

Over platinum oxide (40mg) in ethanol (80ml), 56 (1.1g, 5.2 mmol) was hydrogenated with ice cooling in a shaking apparatus, 122ml of hydrogen having been absorbed (91% of the theoretical amount). After filtration, the ethanol solution was evaporated to give the saturated hydroxylamine [(-)-57] (1.0g, 90%). The analytical sample was obtained by preparative vpc (5% DEGS on Neosorb, 150°C , He 80ml/min); n_{D}^{25} 1.4842, $[\alpha]_{\text{D}}^{26}$ -83.4° (c 6, benzene), pmr (CCl_4): δ 0.93(m, 3H, CH_3), 1.15-1.85(m, 4H, CH_2CH_2), 2.37[s, 6H, $\text{N}(\text{CH}_3)_2$], 4.43(t, 1H, CH), 7.19(s, 5H, phenyl).

(-)-1-Phenyl-1-butanol [(-)-58]

Zinc dust (2.0g, 26 mg atom) and 30% acetic acid (20ml) were added to (-)-57 (1.0g, 5.2 mmol, $[\alpha]_{\text{D}}^{26}$ -83.4°). The mixture was heated under reflux for 5 hr and extracted with ether. The ether extract was washed with saturated sodium carbonate and water, dried over anhydrous sodium sulfate, and evaporated to give the levorotatory alcohol [(-)-58], (0.58g, 75%). The analytical sample was obtained by preparative vpc (5% PEG 20M on Neosorb, 200°C , He 70ml/min); mp $36-37^{\circ}\text{C}$ (lit.⁷⁴) $49-50^{\circ}\text{C}$ for pure enantiomer), $[\alpha]_{\text{D}}^{22}$ -31.6° (c 10.0, benzene), ir (KBr): ν_{OH} 3260cm^{-1} , pmr (CDCl_3): δ 0.98(m, 3H, CH_3), 1.14-1.95(m, 4H,

CH₂CH₂), 2.03(s, 1H, OH), 4.73(t, 1H, CH), 7.42(s, 5H, phenyl).

Elementary analysis C₁₀H₁₄O

Calcd C: 79.95 H: 9.39

Found C: 79.77 H: 9.53

Control reaction

Zinc dust (4.0g) and 30% acetic acid (40ml) were added to (-)-58 (1.55g, $[\alpha]_D^{19} -41.2^\circ$) and the mixture was treated in exactly the same way as described above. The recovered alcohol (-)-58 (1.3g) had $[\alpha]_D^{20} -35.4^\circ$.

[1,2]Rearrangement of 53 to give (+)-O-(2E)-1-methyl-3-phenyl-2-propenyl-N,N-dimethylhydroxylamine [(+)-63]

The amine oxide (53), obtained from (+)-52 (5.0g, $[\alpha]_D^{25} 36.6^\circ$) and peracetic acid (40%, 8.2g) in chloroform (120ml), was divided into two portions, (i) 200ml and (ii) 160ml.

The portion (i) was heated under reflux for 1 hr and evaporated, then the product was purified by the alumina column chromatography (eluent; hexane) to give the hydroxylamine [(+)-63] [1.7g, 56% from (+)-2]; $n_D^{26} 1.5178$, $[\alpha]_D^{25} 6.9^\circ$ (c 5.8, benzene), ir (liquid): $\delta = \text{CH}(E) 955\text{cm}^{-1}$, pmr (CCl₄): δ 1.27(d, 3H, CH₃), 2.55[s, 6H, N(CH₃)₂], 4.35(m, 1H, CH), 6.00-6.78(m, 2H, CH=CH), 7.20-7.62(m, 5H, phenyl).

(-)-O-1-Methyl-3-phenylpropyl-N,N-dimethylhydroxylamine [(-)-64]

Over platinum oxide (100mg) in ethanol (50ml), (+)-63 (1.7g, 8.2 mmol, $[\alpha]_D^{25} 6.9^\circ$) was hydrogenated in a shaking apparatus, 193ml of hydrogen (89% of the theoretical amount) having been absorbed. After filtration, the ethanol solution was evaporated to afford the saturated hydroxylamine [(-)-64] (1.3g, 76%). The

analytical sample was obtained by preparative vpc (5% PEG 20M on Neosorb, 180°C, He 80ml/min); n_D^{26} 1.4823, $[\alpha]_D^{25}$ -6.6° (c 10.3, benzene), pmr (CCl₄): δ 1.15(d, 3H, CH₃), 1.34-2.17 & 2.58-2.99 (m, 4H, CH₂CH₂), 2.53[s, 6H, N(CH₃)₂], 3.71(m, 1H, CH), 7.27(s, 5H, phenyl).

(-)-4-Phenyl-2-butanol [(-)-65]

Zinc dust (1.6g) and 30% acetic acid (16ml) were added to (-)-64 (0.8g, $[\alpha]_D^{25}$ -6.6°) and the subsequent work up in exactly the same manner as described for (-)-58 yielded the levorotatory alcohol [(-)-65] (0.64g, 96%). The analytical sample was obtained by preparative vpc (5% DEGS on Neosorb, 170°C, He 50 ml/min); n_D^{28} 1.5090, $[\alpha]_D^{26}$ -3.2 (c 6.2, benzene), ir (liquid) ν_{OH} 3350cm⁻¹, pmr (CCl₄) δ 1.17(d, 3H, CH₃), 1.49-1.92 & 2.53-2.90(m, 4H, CH₂CH₂), 2.13(s, 1H, OH), 3.75(m, 1H, CH), 7.19(s, 5H, phenyl).

Phenylurethane; mp 113-114°C (lit.⁷⁹) mp 113°C for racemate).

Elementary analysis C₁₇H₁₉NO₂

Calcd C: 75.81 H: 7.11 N: 5.20

Found C: 76.03 H: 7.27 N: 5.25

Consecutive [2,3] and [1,3]rearrangements of 53

The portion (ii) containing the amine oxide (53) was first allowed to stand at -20°C and worked up in the same way as described for 56 to afford the same product 56 (1.2g, 48%), which was then heated in chloroform (160ml) under reflux for 1 hr to yield crude (+)-63 (1.1g, 92%). The contamination by 56 was detected to an extent of ca. 17% as estimated by pmr spectroscopy. The product 63 was hydrogenated to give (-)-64, which on purification by preparative vpc afforded the analytical sample,

$[\alpha]_D^{27} -6.5^\circ$.

(±)-1-Phenyl-1-butanol [(±)-58]

Butyraldehyde (36g, 0.5 mol) in ether (100ml) was added dropwise to phenylmagnesium bromide [from bromobenzene (86g, 0.55 mol) and magnesium (12g, 0.5 g atom)] in ether (500ml). The reaction mixture was stirred overnight at room temperature. The Grignard adduct was worked up in the usual manner and distillation gave (±)-58 (50g, 67%); bp 119-122°C (21mm) [lit.⁷⁴ bp 116-118°C (20mm)].

Acid phthalate of (±)-58

Phthalic anhydride (74g, 0.5 mol) and anhydrous pyridine (26g) were added to (±)-58 (50g, 0.33 mol). The mixture was heated at 100°C for 4 hr and poured into 6N hydrochloric acid with ice cooling. The product was extracted with ether and the ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated. The residue was crystallized from a mixture of carbon disulfide and petroleum ether to afford the acid phthalate (74g, 74%); mp 89-90°C (lit.⁷⁴ mp 88°C).

(-)-1-Phenyl-1-butanol [(-)-58]

To the acid phthalate (70g, 0.23 mol) in benzene (300ml) (-)-α-phenylethylamine⁸⁰ [28.4g, 0.23 mol, $[\alpha]_D^{20} -39.9^\circ$ (neat) (lit. $[\alpha]_D^{25} -39.2- -39.7^\circ$)] was added. The salt obtained was recrystallized twice from benzene to yield slender needles (24.4g); mp 114-115°C, $[\alpha]_D^{20} -1.8^\circ$ (c 5.0, methanol). The salt was treated with 6N hydrochloric acid the liberated acid phthalate was extracted with ether. The ether extract was dried and evaporated. The levorotatory acid phthalate (17g); mp 61-65°C, $[\alpha]_D^{19} -10.9^\circ$ (c 5.6, ether) (lit.⁷⁴ mp 53°C, $[\alpha]_D -10.2^\circ$). It

was hydrolyzed in 10% sodium hydroxide (180ml) by heating at 80°C for 1.5 hr. The resulting carbinol was extracted with ether. Distillation gave (-)-1-phenyl-1-butanol [(-)-58] (7.0g, 87% from the levorotatory acid phthalate); mp 38-40°C, $[\alpha]_D^{19}$ -41.2° (c 10.0, benzene) (lit.⁷⁴) mp 49°C, $[\alpha]_D$ -45.9° resolved with strychnine).

(2E)-1-Phenyl-2-buten-1-ol

E-Crotonaldehyde (7.0g, 0.1 mol) in dry tetrahydrofuran (10ml) was added dropwise with ice cooling to phenylmagnesium bromide [from bromobenzene (15.7g, 0.1 mol) and magnesium (2.4g, 0.1 g atom)] in tetrahydrofuran (50ml). The reaction mixture was stirred overnight at room temperature. The Grignard adduct was hydrolyzed with ice cold water and was worked up in the usual manner. Distillation gave (2E)-1-phenyl-2-buten-1-ol (8.1g, 55%); bp 74-75°C (3mm) [lit.⁸¹) 90-92°C (2mm)], n_D^{25} 1.5321, ir (liquid): δ =CH(*E*) 958cm⁻¹, pmr (CCl₄): δ 1.72(m, 3H, CH₃), 2.56(s, 1H, OH), 4.94-5.84(m, 3H, CH & CH=CH), 7.34(m, 5H, phenyl).

Hydrogenation of (-)-51 to yield (+)-1-phenyl-3-aminobutane

Over palladium carbon (5%, 250mg) in ethanol (80ml), (-)-51 (5.0g, 34 mmol, $[\alpha]_D^{25}$ -8.9°) was hydrogenated in a shaking apparatus, 830ml of hydrogen (the theoretical amount) having been absorbed. Distillation gave the saturated amine; bp 108-109°C (18mm) n_D^{27} 1.5081, $[\alpha]_D^{27}$ 10.1° (neat), [lit.⁶⁷) bp 101-102°C (14mm), n_D^{20} 1.5152 for the racemate).

Acetamide; bp 149°C (2mm), mp 68-69°C, $[\alpha]_D^{26}$ -35.2° (c 0.7, ethanol), [lit.⁷⁰) bp 142-150°C (3mm), mp 55°C].

Elementary analysis C₁₂H₁₇NO

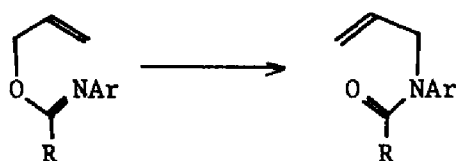
Calcd C: 75.35 H: 8.96 N: 7.32

Found C: 75.33 H: 9.11 N: 7.38

3 STEREOCHEMISTRY OF THE REARRANGEMENT OF TRICHLOROACETIMIDATES

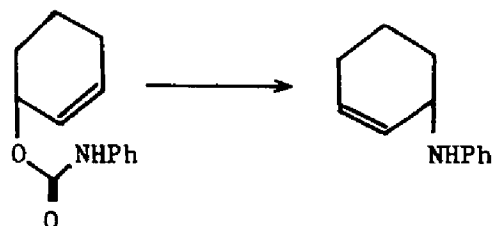
3-1 Objective

In the preceding section, the author described transfer of chirality from tetrahedral carbon to trigonal carbon with nearly quantitative conservation of chirality. The finding not only indicates that the reaction proceeds *via* [2,3]sigmatropic rearrangement but also offers a novel method for stereospecific synthesis of alcohols from amine oxides with allylic inversion. The reverse transformation, allylic alcohols to amines with allylic inversion, can be achieved by the Chapman-type rearrangements (eq. 11),⁸²⁾ which are classified as [3,3]sigmatropic rearrangement according to the Woodward-Hoffmann rule. The conversion of an allylic phenylurethan into an *N*-phenylallylamine by Hill was the sole precedent in which the stereochemistry was thoroughly elucidated (eq. 12).²²⁾ In spite of the reasonable stereochemical outcome in favor of a doubly suprafacial mode, the optical yield obtained (65%) was rather moderate in view of the general observations in this type of rearrangements (cf. p.6 & 9). This may presumably be due to the radical by-path.



eq. 11

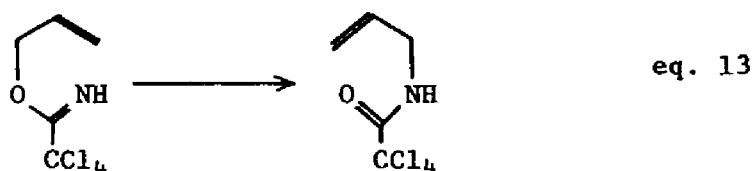
The Chapman Rearrangement



eq. 12

O.Y. 65%

Recently, the rearrangement of allylic trichloroacetimidates to trichloroacetamides was reported by Overman (eq. 13).⁸³⁾ This process would be advantageous in enabling one to ensure high yields of primary amines over those which are limited by substituents on nitrogen.



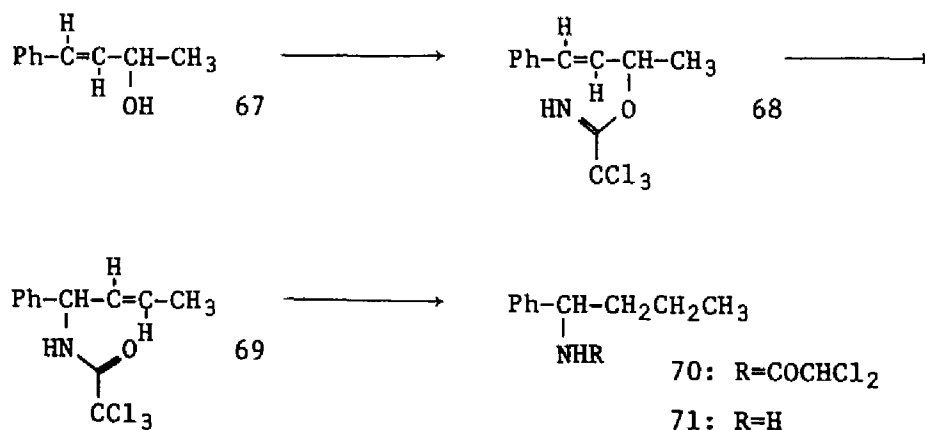
The author now presents another self-immolative asymmetric synthesis of amines from chiral allylic alcohols by the use of trichloroacetimidic ester as an intermediary. The substrate used in the present study was the chiral trichloroacetimidate, (+)-(2*E*)-1-methyl-3-phenyl-2-propenyl trichloroacetimidate [(+)-68].

3-2 Result and Discussion

[3,3]Rearrangement of (2E)-(1R)-1-methyl-3-phenyl-2-propenyl trichloroacetimidate (68).

By the treatment with sodium hydride and trichloroacetonitrile, (+)-(3E)-4-phenyl-3-buten-2-ol [(+)-67, $[\alpha]_D^{25} 17.3^\circ$]⁸⁴ was converted to the trichloroacetimidic ester [(+)-68] having $[\alpha]_D^{25} 34.7^\circ$ in 94% yield, whose purity proved to be 85% as assessed by pmr spectrum. The trichloroacetimidate [(+)-68] was heated in toluene under reflux to give the [3,3]shift product, (+)-N-[(2E)-1-phenyl-2-butenyl]trichloroacetamide [(+)-69, $[\alpha]_D^{25} 15.1^\circ$] in 74% yield. The E geometry of double bond in resulting (+)-69 was established by ir and pmr spectra. Neither Z-isomer nor [1,3]shift product was detected in the reaction mixture. Hydrogenation of (+)-69 over palladium charcoal resulted in the formation of the saturated dichloroacetamide [(+)-70, $[\alpha]_D^{25} 32.7^\circ$], one of the three chlorine atoms having been simultaneously replaced by hydrogen during the reaction process.

Scheme 4



The absolute configuration as well as enantiomeric purity of 70, crucial to the mechanistic picture of the present rearrangement, were obtained by the conversion of optically pure (-)-1-phenyl-1-aminobutane [(-)-71, $[\alpha]_D -22.2^\circ$] of the well-defined *S* configuration⁸⁵⁾ into (-)-70, $[\alpha]_D -71.7^\circ$. Consequently, the end product (+)-70 and the parent rearrangement product (+)-69 can be safely assigned the *R* configuration and should be of 45.6% optical purity.

Since the *R* configuration^{84a,c)} of the starting (+)-67 has been unambiguously established by the correlation to (*R*)-(-)-4-phenyl-2-butanol,⁷⁰⁾ and the pmr spectroscopy with the use of a chiral shift reagent showed the chiral alcohol [(+)-67] to be of 45±2% enantiomeric purity, the present thermal rearrangement proceeded with complete retention of chirality.



Fig. 6.
Chemical shift non-equivalence
of methyl doublets of 67.

The finding that the complete transfer of chirality was achieved during the [3,3]shift and that the [1,3]shift product was not detected at all corroborates the concertedness of the process and excludes radical dissociation-recombination. Two transition states would be conceivable for doubly suprafacial

fashion in thermally allowed [3,3]sigmatropic rearrangement; 4-centered chair form and 6-centered boat form (cf. p.5). In view of the Cope and the Claisen rearrangements attained so far, the author can reasonably formulate the transition state topology of choice for the allylic rearrangement of trichloroacetimidate as the former in agreement with Overman. Furthermore, the finding that the (*R*)-(*E*)-trichloroacetimidate [(+)-68] rearranged to give the (*R*)-(*E*)-trichloroacetamide [(+)-69] cogently supports the fashion 72. The (*S*)-(*Z*) product, which would be expected from the alternative 4-centered mode 73, was not detected at all in the present rearrangement. The preference of fashion 72 to 73 could be rationalized by the unfavorable non-bonded interaction in the latter between methyl group and hydrogen atom which orient syn-axial, while both methyl and phenyl groups orient equatorial in the former, therefore thermodynamically more favorable.

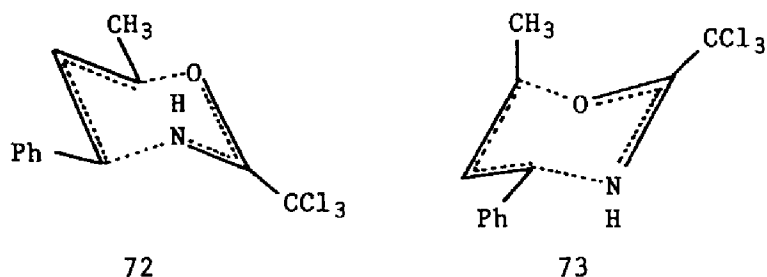


Fig. 7. Transition state topologies of [3,3]shift of 68.

Now the author examines the energetics of the present system according to the Faulkner treatment (cf. p.10). It is assumed that the presence of a nitrogen atom in the ring does not make significant change on the energetics although Faulkner treated only the Cope and the Claisen rearrangements. Since the present

system has no *gem*-substitution, this method is expected to be efficient for the examination of *E/Z* selectivity. The equatorial and the axial orientation of methyl group in the transition state lead to the *E* and *Z* products respectively. The found ratio of *E/Z* (no detectable amount of the *Z* product) indicates the activation energy difference ($\Delta\Delta G^\ddagger$) of >3.5 kcal/mol. In this system, substitutions occur at R^1 , R^4 , and R^6 which correspond to methyl, phenyl, and trichloromethyl groups respectively (Fig. 8). Since it was pointed out that the product ratio seems to be insensitive to the nature of substituent R^4 , the discussion can be focused only on R^1 and R^6 . The value for G°_{methyl} is reported to be 1.7 kcal/mol⁸⁶⁾; the free energy change for the conversion of methyl group from the equatorial to the axial position of a cyclohexane. This value can be adopted at the reaction temperature (toluene reflux: 111°C). It is clear that the found $\Delta\Delta G^\ddagger$ is not explained alone by the term of $\Delta G^\circ_{\text{methyl}}$, but that an additional interaction exists. Faulkner suggested that a bulky substituent at R^6 leads high *E/Z* selectivity. In the present system, R^6 is trichloromethyl group which is extremely bulky. It can be considered that the interaction between axial methyl group and trichloromethyl group is appreciably large. The high *E/Z* selectivity was also observed in some di- and trisubstituted trichloroacetimidates by Overman.⁸³⁾

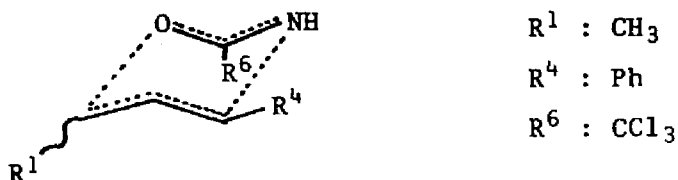
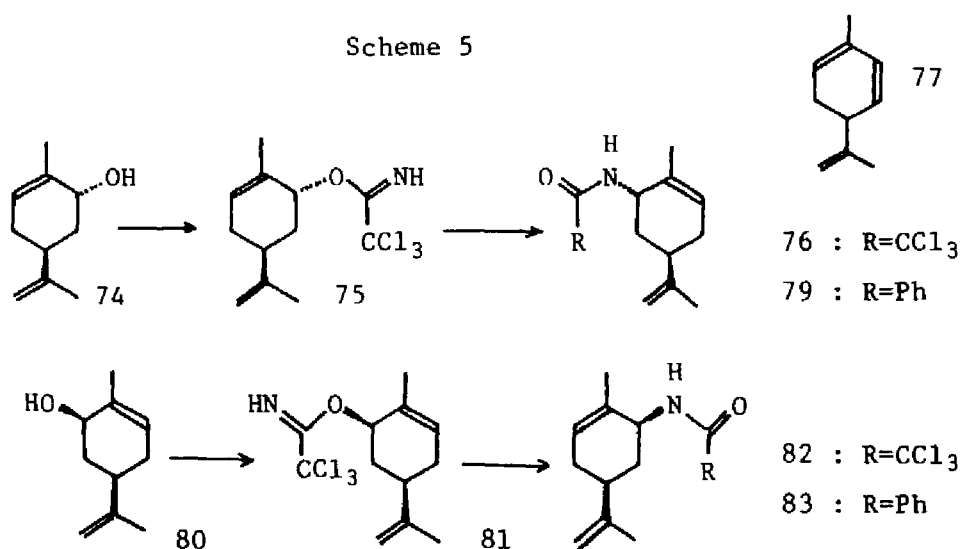


Fig. 8. The Faulkner treatment.

[3,3]Rearrangements of carveol derivatives

As a probe of synthetic utility, the present rearrangement was successfully applied to the naturally derived allylic alcohols whose configurations have been known.

According to scheme 5, (+)-*trans*-carveol [(+)-74 α_D^{20} 172°]⁸⁷⁾ was converted into the corresponding trichloroacetimidate [(+)-75 $[\alpha]_D^{20}$ 72°] in 85% yield. In this case, potassium hydride was used in place of sodium hydride which provided an unsatisfactory yield for carveols. It is noted in this system that the allylic group is tied back in a 6 membered ring, which *a priori* compels the transition state topology to assume nothing but a doubly suprafacial mode.



Upon heating, (+)-75 gave (-)-*N*-carveyltrichloroacetamide [(-)-76 $[\alpha]_D^{20}$ -117°] in 44% yield. The observed lowering in the yield of rearrangement product may be attributed to the elimination side process, as actually indicated by the formation of the triene (77 18%) and trichloroacetamide (78 41%). The yield

of 77 lower than that of 78 can be ascribed to the loss during the purification work-up because of the high volatility of 77. The transformation of (-)-76 by the consecutive alkaline hydrolysis and benzylation gave (-)-*N-trans*-carveylbenzamide [(-)-79]. The absolute configuration of (-)-79 can be safely assigned as depicted in scheme 5 by the comparison of physical constants in agreement with those in the literature (Table 2).

In the case of the (-)-*cis* counterpart [(-)-81, $[\alpha]_D -48^\circ$, from (-)-80 ($\alpha_D -22^\circ$)⁸⁹⁾], (-)-*N*-carveyltrichloroacetamide [(-)-82, $[\alpha]_D -43.6^\circ$] was obtained in 42% yield along with 78 (35%). By exactly the same work-up as for (-)-*trans* isomer, (-)-82 was transformed into (-)-*N-cis*-carveylbenzamide [(-)-83].

Table 2. Physical constants of *N*-carveylbenzamides

Compound	Found	Literature
79	mp 112-113°C $[\alpha]_D -245^\circ$	mp 103°C (lit. 88a)
		$[\alpha]_D -175.4^\circ$
		mp 114°C (lit. 88b)
		$[\alpha]_D -250^\circ$
83	mp 169°C $[\alpha]_D -95.2^\circ$	mp 169°C (lit. 88a)
		$[\alpha]_D -91.9^\circ$
		mp 169°C (lit. 88b)
		$[\alpha]_D -96^\circ$

In both cases, the absolute configurations of the rearrangement products coincided with those predicted from the doubly suprafacial transition state. The stereospecific 1,3-

transposition of alcohol and amine functions was thus achieved by the present self-immolative asymmetric synthesis.

3-3 Experimental

(±)-(3E)-4-Phenyl-3-buten-2-ol [(±)-67]

To benzalacetone (224g, 1.5 mol) in methanol (1000ml), sodium borohydride (22g, 0.58 mol) was added portionwise with ice cooling. The mixture was allowed to stand overnight at room temperature. After addition of water (50ml), the mixture was evaporated and extracted with ether. The ether extract was washed with 2N hydrochloric acid, saturated sodium bicarbonate, and water. Distillation gave (±)-67 (177g, 78%); bp 141-143°C (22mm) [lit.^{84a} bp 129-131°C (11mm)].

Acid phthalate of (±)-67

Phthalic anhydride (250g, 1.7 mol) and pyridine (750ml) were added to (±)-67 (250g, 1.7 mol). The mixture was heated at 100°C for 5 hr and poured into a mixture of ice and conc. hydrochloric acid. The resulting oil was dissolved in ether and extracted with saturated sodium carbonate. After acidification, the aqueous layer was extracted with ether. The product was crystallized from a mixture of ether and pentane to give the acid phthalate (140g, 28%); mp 92-93.5°C (lit.^{84a} mp 92-93.5°C, lit.^{84b} mp 95.0-96.8°C).

(+)-(3E)-4-Phenyl-3-buten-2-ol [(+)-67]

To the acid phthalate (140g, 0.47 mol) in hot ethyl acetate (420ml), cinchonidine (140g, 0.47 mol) was added. The salt obtained was systematically recrystallized from methanol to yield slender needles (20g); mp 167-169°C. The salt was treated with 2N hydrochloric acid and the liberated acid phthalate was extracted with ether. The ether layer was extracted with saturated sodium carbonate, and the aqueous layer was acidified and extracted with ether to afford the levorotatory acid phthalate (5.0g); $[\alpha]_D^{20} -11.2^\circ$ (*c* 5, ethyl acetate) (lit.^{84a}) $[\alpha]_D -19.0^\circ$. It was hydrolyzed in a mixture of ethanol (17ml) and 5N sodium hydroxide (13ml) by heating under reflux. Distillation gave (+)-67 (2.1g, 84% from the levorotatory acid phthalate); $[\alpha]_D^{20} 17.3^\circ$ (*c* 5.1, chloroform) (lit.^{84a}) $[\alpha]_D 24.7^\circ$, lit.^{84b}) $[\alpha]_D^{30} 34.7^\circ$.

Assessment of the enantiomeric purity of (+)-67

Chemical shift non-equivalence of the enantiomer was observed on the following conditions; carbon tetrachloride solution of (+)-67 (0.45M, $[\alpha]_D^{20} 17.3^\circ$) and tris-[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium (III) (84, 0.06M) using JEOL MH-100 (100 MHz). Methyl doublets of enantiomers appeared at (δ 2.31 & 2.37) and (δ 2.34 & 2.40) respectively. The enantiomeric purity of (+)-67 proved to be 45 $\pm$ 2% by the calculation from peak heights and areas. The maximum rotation was calculated to be 38 $\pm$ 2° (reported maximum rotation: lit.^{84a}) $[\alpha]_D 24.7^\circ$, lit.^{84b}) $[\alpha]_D^{30} 78\pm 6^\circ$.

(+)-(2*E*)-1-Methyl-3-phenyl-2-propenyl trichloroacetimidate [(+)-68]

A solution of (+)-67 (1.8g, 12 mmol, $[\alpha]_D^{20} 17.3^\circ$) in dry ether (20ml) was treated with sodium hydride (110mg, 47% in

mineral oil, 2.1 mmol) which had been previously washed 3 times with dry hexane. The resulting mixture was added to trichloroacetonitrile (1.8g, 12 mmol) in dry ether (10ml) at -15°C in nitrogen atmosphere. After stirring at 0°C for 1.5 hr, the solution was concentrated under reduced pressure. Pentane (40ml) containing methanol (0.8ml, 2.1 mmol) was added and the mixture was shaken for 1 min. Successive filtration and evaporation gave (+)-68 (3.3g, 94%) whose purity proved to be 85% as assessed by pmr [Methyl doublet of unreacted (+)-67 appeared at δ 1.33]. The trichloroacetimidate [(+)-68]; $[\alpha]_{\text{D}}^{20}$ 34.7° (c 5.0, chloroform), ir (liquid): ν_{NH} 3350, $\nu_{\text{C=N}}$ 1650, $\delta=\text{CH(E)}$ 960 cm^{-1} , pmr (CCl_4): δ 1.63(d, 3H, CH_3), 5.77-6.28(m, 1H, CH), 6.39-7.33(m, 2H, CH=CH), 7.57-8.00(m, 5H, phenyl), 8.70-9.00(broad, 1H, NH).

[3,3]Rearrangement of (+)-68 to give (+)-N-[(2E)-1-phenyl-2-butenyl]trichloroacetamide [(+)-69]

The trichloroacetimidate [(+)-68] (3.2g, purity 85%, $[\alpha]_{\text{D}}^{20}$ 34.7°) in toluene (35ml) was heated under reflux for 4 hr. Distillation gave (+)-69 (2.0g, 74%); bp $121-124^{\circ}\text{C}$ (0.06mm), mp $62-64^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{20}$ 15.1° (c 2.7, chloroform), ir (KBr): ν_{NH} 3400, $\nu_{\text{C=O}}$ 1680, $\delta=\text{CH(E)}$ 962 cm^{-1} , pmr (CCl_4): δ 1.70-1.91(m, 3H, CH_3), 5.28-5.87(m, 3H, CH & CH=CH), 6.44-7.00(broad, 1H, NH), 7.31(s, 5H, phenyl).

Elementary analysis	$\text{C}_{12}\text{H}_{12}\text{NOCl}_3$		
Calcd	C: 49.26	H: 4.13	N: 4.79
Found	C: 49.30	H: 4.18	N: 4.76

(+)-N-(1-Phenylbutyl)dichloroacetamide [(+)-70]

Over palladium carbon (5%, 200mg) in ethanol (100ml), (+)-69 (1.0g, 3.4 mmol) was hydrogenated in a shaking apparatus, 170ml of hydrogen having been absorbed at room temperature

(2 equivalent amount). The reaction mixture was neutralized with aqueous potassium carbonate. Distillation gave (+)-70 (0.74g, 83%); bp 116°C (0.03mm), mp 92-93.5°C, $[\alpha]_D^{20}$ 32.7° (c 3.0, chloroform), ir (KBr): ν_{NH} 3280, $\nu_{\text{C=O}}$ 1660 cm^{-1} , pmr (CDCl_3): δ 0.78-1.12(m, 3H, CH_3), 1.13-2.08(m, 4H, CH_2CH_2), 4.78-5.20(m, 1H, CH), 5.98(s, 1H, CHCl_2), 7.41(s, 5H, phenyl).

Elementary analysis $\text{C}_{12}\text{H}_{15}\text{NOCl}_2$

Calcd C: 55.40 H: 5.81 N: 5.38

Found C: 55.34 H: 6.07 N: 5.39

(±)-1-Phenyl-1-aminobutane [(±)-71]

Butyrophenone (220g, 1.5 mol) was reacted with ammonium formate (300g, 4.7 mol) in exactly the same manner as for synthesis of α -phenylethylamine.⁹⁰ The racemic amine [(±)-71] (129g, 59%); bp 109-111°C (21mm) [lit.⁹¹ bp 107-109°C (16mm)].

(-)-1-Phenyl-1-aminobutane [(-)-71]

The racemic amine (136g, 0.91 mol) was added to (-)-*N*-acetylleucine (158g, 0.91 mol) in methanol (1200ml) and the salt formed was recrystallized 4 times from methanol to yield fine needles (4.6g); mp 196-198°C, $[\alpha]_D^{25}$ -1.8° (c 5.0, methanol). The physical constants did not alter on further recrystallizations. The amine liberated from the salt had $[\alpha]_D^{25}$ -22.2° (c 3.1, chloroform). The racemic 71 exhibited an apparent chemical shift non-equivalence for the methine proton in carbon tetrachloride solution of (±)-71 (0.4M) and the shift reagent (84, 0.02M), whereas no separation of the same signal was observed with the resolved amine under the same conditions.

(-)-*N*-(1-Phenylbutyl)dichloroacetamide [(-)-70]

To the solution of dichloroacetyl chloride (1.5g, 10 mmol)

in benzene (10ml), the mixture of (-)-71 (1.5g, 10 mmol) and anhydrous pyridine (1.6g, 20 mmol) in benzene (10ml) was added dropwise at 0°C. After stirring at room temperature overnight, the resulting dichloroacetamide was extracted with benzene. Distillation gave (-)-70 (1.7g, 56%); $[\alpha]_D^{25} -71.7^\circ$ (c 3.1, chloroform).

(+)-trans-Carveol [(+)-74]

To the mixture of (-)-carvone [60g, 0.4 mol, $[\alpha]_D^{29} -58^\circ$ (neat)] and hydrogen peroxide (30%, 115g, 1.0 mol) in methanol (400ml), 6N sodium hydroxide (33ml) was added dropwise under vigorous stirring at -15°C. After stirring at 60°C for 2 hr, the mixture was allowed to stand overnight at room temperature. After evaporation, the resulting epoxide was extracted with ether. Distillation gave the epoxide (38g, 58%); bp 93-98°C (8mm), $n_D^{29} 1.4781$, $\alpha_D^{29} 80^\circ$ (neat) (lit.⁸⁷) $n_D^{20} 1.4825$, $\alpha_D^{24} 87.58^\circ$. To the solution of the epoxide (42g, 0.25 mol) in anhydrous methanol (250ml) and acetic acid (3g), hydrazine hydrate (38g, 0.75 mol) was added dropwise with stirring at 0°C. After the evolution of nitrogen gas ceased, the mixture was evaporated and extracted with ether. Distillation gave (+)-74 (16.5g, 43%); bp 73-75°C (3mm), $n_D^{26} 1.4916$, $\alpha_D^{20} 172^\circ$ (neat) (lit.⁸⁷) $n_D^{20} 1.4962$, $\alpha_D^{20} 185.8^\circ$. 3,5-Dinitrobenzoate; mp 110-111°C, $[\alpha]_D^{29} 220^\circ$ (c 2, chloroform) (lit.^{89a}) mp 111.5°C, $[\alpha]_D^{16} 232.0^\circ$.

(+)-trans-Carveyltrichloroacetimidate [(+)-75]

The reaction of (+)-74 (1.5g, 10 mmol, $\alpha_D^{20} 172^\circ$) and trichloroacetonitrile (1.4g, 10 mmol) was conducted with potassium hydride (500mg, 23.8% in mineral oil, 2 mmol) in place of sodium hydride. The subsequent work-up in exactly the same manner

as described for (+)-68 yielded (+)-75 (2.5g, 85%). In this case, the unreacted (+)-74 was not detected in pmr spectrum; n_D^{20} 1.5089, $[\alpha]_D^{22}$ 72° (c 3.0, chloroform), ir (liquid): ν_{NH} 3350, $\nu_{C=N}$ 1650 cm^{-1} , pmr (CCl_4): δ 0.68-2.75(m, 5H, ring protons), 1.78(s, 3H, CH_3), 1.82(s, 3H, CH_3), 4.78-4.99(m, 2H, $=CH_2$), 5.41-5.66(m, 1H, $CH-O$), 5.77-6.07(m, 1H, $=CH-$), 8.33-8.63(broad, 1H, NH).

[3,3]Rearrangement of (+)-75 to give (-)-N-carveyltrichloroacetamide [(-)-76]

The trichloroacetimidate (+)-75 (2.5g, $[\alpha]_D^{22}$ 72°) in toluene (25ml) was heated under reflux for 10 hr. The reaction mixture was concentrated and treated with warm hexane. After removal of the insoluble material, trichloroacetamide (78, 560mg, 41%, mp 138-139°C), the solution was evaporated. After 1,5,8(9)-*p*-menthatriene (77, 200mg, 18%) was removed, (-)-76 (1.1g, 44%) distilled at 114-115°C (0.15mm). The analytical sample was obtained by recrystallization from hexane; mp 91-93°C, $[\alpha]_D^{23}$ -117° (c 3.0, chloroform), ir (KBr): ν_{NH} 3310, $\nu_{C=O}$ 1690 cm^{-1} , pmr (CCl_4): δ 1.20-2.58(m, 5H, ring protons), 1.80(s, 6H, $2CH_3$), 4.28-4.66(m, 1H, $CH-N$), 4.85-5.00(m, 2H, $=CH_2$), 5.79-6.01(m, 1H, $=CH-$), 6.40-6.83(broad, 1H, NH).

Elementary analysis $C_{12}H_{16}NOCl_3$

Calcd	C: 48.59	H: 5.44	N: 4.72
Found	C: 48.55	H: 5.58	N: 4.69

(-)-N-trans-Carveylbenzamide [(-)-79]

Sodium hydroxide (1.6g, 40 mmol) in water (8ml) was added to (-)-76 (400mg, 1.4 mmol, $[\alpha]_D^{23}$ -117°) in ethanol (13ml). The reaction mixture was stirred in nitrogen atmosphere at room temperature for 40 hr. The amine extracted with ether was treat-

ed with benzoyl chloride (420 mg, 3 mmol) in pyridine (3ml). The resulting benzamide was extracted with chloroform and recrystallized from methanol-water, (-)-79 (40mg, 11%); mp 112-113°C, $[\alpha]_D^{18} -245^\circ$ (c 3.0, chloroform) (lit.^{88a}) mp 103°C, $[\alpha]_D^{21} -175.4^\circ$, lit.^{88b}) mp 114°, $[\alpha]_D -250^\circ$.

Elementary analysis $C_{17}H_{21}NO$

Calcd C: 79.96 H: 8.29 N: 5.49

Found C: 79.76 H: 8.36 N: 5.41

(-)-cis-Carveol [(-)-80]

To lithium aluminum hydride (1.1g, 0.029 mol) in anhydrous ether (25ml), (-)-carvone (15g, 0.1 mol, $[\alpha]_D^{29} -58^\circ$) in ether (25ml) was added dropwise. After heating under reflux for 1 hr, water (5ml) was added with ice cooling, followed by 10% hydrochloric acid (70ml). The product was extracted with ether. Distillation gave crude (-)-80 (10.5g, 69%, containing a little amount of the *trans* isomer); bp 85-87°C (5mm), $n_D^{30} 1.4900$, $[\alpha]_D^{30} -35.7^\circ$ (neat) [lit.^{89b}] bp 109-111°C (12mm), $n_D^{20} 1.4955$, $[\alpha]_D -36.2^\circ$. To the crude product (26g, 0.17 mol) in anhydrous pyridine (70ml), 3,5-dinitrobenzoyl chloride (40g, 0.17 mol) was added with ice cooling. The reaction mixture was stirred overnight and heated at 80°C for 3 hr. The resulting 3,5-dinitrobenzoate was extracted with dichloromethane and recrystallized 3 times from acetone-ethanol to yield pale yellow needles (25g, 42%); mp 92-92.5°C, $[\alpha]_D^{25} 48^\circ$ (c 2.0, chloroform) (lit.^{89a}) mp 92-92.5°C, $[\alpha]_D 44.2^\circ$, lit.^{89b}) mp 91-92.5°C, $[\alpha]_D 45.0^\circ$. The 3,5-dinitrobenzoate (24g, 0.07 mol) was heated under reflux for 20 min with 5% methanolic potassium hydroxide (94ml, 0.08 mol). The free alcohol was extracted with ether and washed with saturated sodium bicarbonate. Distillation gave (-)-80 (9.6g, 91%); bp 86-87°C (7mm), $n_D^{26} 1.4941$, $\alpha_D^{24} -22^\circ$ (neat)

(lit.^{89a}) bp 101.2-101.4°C (10mm), n_D^{25} 1.4959, α_D^{25} -22.8°).

(-)-cis-Carveyltrichloroacetimidate [(-)-81]

By the same procedure as described for the (+)-*trans* counterpart [(+)-75], (-)-80 (1.5g, 10 mmol, α_D^{24} -22°) was converted to (-)-81 (2.9g, 99%); n_D^{23} 1.5163, $[\alpha]_D^{23}$ -48° (*c* 3.0, chloroform), ir (liquid): ν_{NH} 3350, $\nu_{C=N}$ 1660 cm^{-1} , pmr (CCl₄): δ 0.87-2.80(m, 5H, ring protons), 1.85(s, 6H, 2CH₃), 4.97-5.18(m, 2H, =CH₂), 5.71-6.19(m, 2H, CH-O & =CH-), 8.71-8.95(broad, 1H, NH).

[3,3]Rearrangement of (-)-81 to give (-)-N-carveyltrichloroacetimidate [(-)-82]

The trichloroacetimidate (-)-81 (2.6g, $[\alpha]_D^{23}$ -48°) in xylene (26ml) was heated under reflux for 8 hr. The reaction mixture was worked up in exactly the same manner as described for (-)-76. Along with 78 (500mg, 35%), (-)-82 was obtained (1.1g, 42%); bp 109-110°C (0.1mm), mp 87-89°C, $[\alpha]_D^{23}$ -43.6° (*c* 3.0, chloroform), ir (KBr): ν_{NH} 3270, $\nu_{C=O}$ 1680 cm^{-1} , pmr (CCl₄): δ 1.05-2.63(m, 5H, ring protons), 1.73(s, 3H, CH₃), 1.77(s, 3H, CH₃), 4.26-4.75(m, 1H, CH-N), 4.73-4.93(m, 2H, =CH₂), 5.52-5.87(m, 1H, =CH-), 6.35-6.93(broad, 1H, NH).

Elementary analysis C₁₂H₁₆NOCl₃

Calcd C: 48.59 H: 5.44 N: 4.72

Found C: 48.82 H: 5.54 N: 4.77

(-)-N-cis-Carveylbenzamide [(-)-83]

By the same procedure as described for (-)-79, (-)-82 (600mg, 2 mmol, $[\alpha]_D^{23}$ -43.6°) was converted to (-)-83 (100mg, 19%); mp 169°C, $[\alpha]_D^{20}$ -95.2° (*c* 4.7, chloroform) (lit.^{88a}) mp 169°C, $[\alpha]_D^{19}$ -91.9°, lit.^{88b} mp 169°C, $[\alpha]_D$ -96°).

Elementary analysis		$C_{17}H_{21}NO$		
Calcd	C: 79.96	H: 8.29	N: 5.49	
Found	C: 79.97	H: 8.24	N: 5.66	

(-)-N-Acetylleucine

To the suspension of (+)-leucine (50g, 0.38 mol) in water (133ml), acetic anhydride (117g, 1.1 mol) and sodium hydroxide (107g, 2.7 mol) in water (133ml) were added simultaneously during 2 hr with ice-salt-cooling at 5-15°C. After 20 min the cold mixture was gradually acidified with conc. hydrochloric acid (244ml). The product deposited on ice cooling overnight. Recrystallization from methanol-water (1:2) yielded translucent prisms (48g, 73%); mp 173.5-174°C, $[\alpha]_D^{25} -24.2^\circ$ (c 4, methanol) (lit.⁹²) mp 185-186°C, $[\alpha]_D^{25} -24.1^\circ$.

1.5,8(9)-p-Menthatriene (77) was identified by ir and pmr spectroscopy; ir (liquid): $\nu_{C=CH_2}$ 1640, $\delta_{=CH_2}$ 890, $\delta_{=CH-}$ 790, $CH=CH$ (Z) 730 cm^{-1} , pmr (CCl_4): δ 1.51-1.87(m, 3H, CH_3), 1.70(s, 3H, CH_3), 1.87-3.20(m, 3H, ring protons), 4.59-4.89(m, 2H, $=CH_2$), 5.25-6.00(m, 3H, $=CH-$ & $CH=CH$).

4 SUMMARY

The stereochemistry of the rearrangement of the allylic amine oxide and the allylic trichloroacetimidate was established from the viewpoint of self-immolative asymmetric synthesis.

The rearrangement of *N,N*-dimethyl-(2*E*)-(1*S*)-1-methyl-3-phenyl-2-propenylamine oxide (53) to give *O*-(2*E*)-(1*S*)-1-phenyl-2-butenyl-*N,N*-dimethylhydroxylamine (56) was effected at -20°C with nearly complete transfer of chirality from tetrahedral carbon to trigonal carbon. The finding indicates that the reaction proceeds *via* the concerted mechanism; doubly suprafacial [2,3]sigmatropic rearrangement. The transition state topology was proved to be a 5 membered ring orientation of an envelope form in which both phenyl and methyl groups orient quasi-equatorial positions.

At higher temperature, the [1,2]shift product, *O*-(2*E*)-1-methyl-3-phenyl-2-propenyl-*N,N*-dimethylhydroxylamine (63), was exclusively yielded with conservation of chirality to the extent of 20%. This fact reveals that this process progressed through a radical pair intermediate; *N,N*-dimethylnitroxide radical being in juxtaposition to the allylic radical.

The steric course of the allylic rearrangement of the trichloroacetimidate was clarified using (2*E*)-(1*R*)-1-methyl-3-phenyl-2-propenyl trichloroacetimidate (68), which thermally rearranged to give *N*-[(2*E*)-(1*R*)-1-phenyl-2-butenyl]trichloroacetamide (69) with nearly complete transfer of chirality. The finding indicates the reaction to proceed *via* [3,3]sigmatropic rearrangement of a doubly suprafacial mode; a chair form orientation in which both phenyl and methyl groups orient equatorial positions. As a probe of synthetic utility, the

present reaction was successfully applied to the conversion of chiral carveols to chiral carveyl amines.

The doubly suprafacial [2,3] and [3,3]sigmatropic rearrangements enable the stereospecific transformation of amines to alcohols and alcohols to amines with allylic inversion (asymmetric 1,3-transposition).

- a) Y.Yamamoto, J.Oda, and Y.Inouye, *Chem.Comm.*, 848 (1973)
'Asymmetric Induction in the Allylic Rearrangement of Chiral amine Oxide'
- b) Y.Yamamoto, J.Oda, and Y.Inouye, *J.Org.Chem.*, 41, 303 (1976)
'Self-Immolative Asymmetric Synthesis. II. Transfer of Chirality from Tetrahedral Carbon to Trigonal Carbon in Chiral Amine Oxide Rearrangement'
- c) Y.Yamamoto, H.Shimoda, J.Oda, and Y.Inouye, *Bull.Chem.Soc.Jpn.*, 49, 3247 (1976)
'Self-Immolative Asymmetric Synthesis. III. Allylic Rearrangement of Optically Active Trichloroacetimidate'
- d) Y.Yamamoto, J.Oda, and Y.Inouye, *ibid.*, 48, 3744 (1975)
'Absolute Configuration of 3-Amino-1-phenylbutane'

5 REFERENCES

- 1) a) R.B.Woodward and R.Hoffmann, 'The Conservation of Orbital Symmetry', Verlag Chemie, Weinheim, 1970.
b) R.Hoffmann and R.B.Woodward, *J.Am.Chem.Soc.*, 87, 4389 (1965)
- 2) a) K.Fukui and H.Fujimoto, *Tetrahedron Lett.*, 251 (1966)
b) K.Fukui and H.Fujimoto, *Bull.Chem.Soc.Jpn.*, 40, 2018 (1967)
- 3) M.J.S.Dewar, 'Aromaticity', Chem.Soc., London, 1969, p.177.
- 4) a) J.J.C.Mulder and L.J.Oosterhoff, *Chem.Commun.*, 305 (1970)
b) P.Beltrame, A.Gambe, and M.Simonetta, *ibid.*, 1660 (1970)
- 5) a) S.J.Rhoads in 'Molecular Rearrangements' Part I, P.de Mayo Ed., Interscience, New York, 1963, p.655.
b) W.von E. Doering and W.R.Roth, *Angew.Chem.Int.Ed.*, 2, 115 (1963)
c) A.Jefferson and F.Scheinmann, *Quart.Review*, 22, 391 (1968)
d) S.J.Rhoads and N.R.Raulins, *Org.React.*, 22, 1 (1975)
- 6) J.E.Baldwin and F.J.Urban, *Chem.Commun.*, 165 (1970)
- 7) a) J.E.Baldwin, J.DeBernardis, and J.E.Patrick, *Tetrahedron Lett.*, 353 (1970)
b) H.E.Zimmerman in 'Molecular Rearrangements' Part I, P.de Mayo Ed., Interscience, New York, 1963, p.345.
c) B.M.Trost, 'Sulfur Ylides', Academic Press, New York, 1975, p.108.
- 8) a) T.Miyashi, M.Nitta, and T.Mukai, *Tetrahedron Lett.*, 3433 (1967)
b) J.E.Baldwin and M.S.Kaplan, *J.Am.Chem.Soc.*, 93, 3969 (1971)
- 9) A.Brown, M.J.S.Dewar, and W.Schoeller, *ibid.*, 92, 5516 (1970)
- 10) M.Simonetta, G.Favini, C.Mariani, and P.Gramaccioni, *ibid.*,

- 90, 1280 (1968)
- 11) W.E.Doering and W.R.Roth, *Tetrahedron*, 18, 67 (1962)
 - 12) R.K.Hill and N.W.Gilman, *Chem.Comm.*, 619 (1967)
 - 13) a) H.-J.Hansen and H.Schmid, *Chem.Brit.*, 5, 111 (1969)
b) H.-J.Hansen and H.Schmid, *Tetrahedron*, 30, 1959 (1974)
c) Gy.Fráter, A.Habich, H.-J.Hansen, and H.Schmid, *Helv.Chim. Acta*, 52, 335 (1969)
 - 14) R.K.Hill and A.G.Edwards, *Tetrahedron Lett.*, 3239 (1964)
 - 15) a) A.W.Burgstahler and J.C.Nordin, *J.Am.Chem.Soc.*, 83, 198 (1961)
b) W.S.Dauben and T.J.Dietsch, *J.Org.Chem.*, 37, 1212 (1972)
c) R.F.Church, R.E.Ireland, and J.A.Marshall, *ibid.*, 31, 2526 (1966)
 - 16) P.Vittorelli, T.Winkler, H.-J.Hansen, and H.Schmid, *Helv.Chim. Acta*, 51, 1457 (1968)
 - 17) a) H.L.Goering and W.I.Kimoto, *J.Am.Chem.Soc.*, 87, 1748 (1965)
b) E.N.Marvell, J.L.Stephenson, and J.Ong, *ibid.*, 87, 1267 (1965)
 - 18) A.F.Thomas and G.Ohloff, *Helv.Chim.Acta*, 53, 1145 (1970)
 - 19) R.K.Hill and M.E.Synerholm, *J.Org.Chem.*, 33, 925 (1968)
 - 20) a) R.K.Hill, R.Soman, and S.Sawada, *ibid.*, 37, 3737 (1972)
b) W.Sucrow, B.Schubert, W.Richter, and M.Slopianka, *Ber.*, 103, 750 (1970), *ibid.*, 104, 3679, 3689 (1971), *ibid.*, 106, 2236 (1973), *Tetrahedron Lett.*, 1833 (1971)
 - 21) R.K.Hill and N.W.Gilman, *ibid.*, 1421 (1967)
 - 22) M.E.Synerholm, N.W.Gilman, J.W.Morgan, and R.K.Hill, *J.Org. Chem.*, 33, 1111 (1968)
 - 23) a) E.R.H.Jones, J.D.Loder, and M.C.Whiting, *Proc.Chem.Soc.*, 180 (1960)
b) R.J.D.Evans, S.R.Landor, and J.P.Regen, *Chem.Comm.*, 397 (1965)

- c) S.R.Landor, B.J.Miller, J.P.Regan, and A.R.Tatchell, *ibid.*, 585 (1966)
- 24) a) P.Loew, J.B.Siddal, V.L.Spain, and L.Werthemann, *Proc. Nat.Acad.Sci., U.S.A.*, 67, 1465 (1970)
b) L.Werthemann and W.S.Johnson, *ibid.*, 67, 1810 (1970)
c) F.E.Ziegler, *Account Chem.Res.*, 10, 227 (1977)
- 25) C.L.Perrin and D.J.Faulkner, *Tetrahedron Lett.*, 2783 (1969)
- 26) J.E.Baldwin and J.E.Patrick, *J.Am.Chem.Soc.*, 93, 3556 (1971)
- 27) P.K.Claus, W.Rieder, and F.W.Vierhapper, *Tetrahedron Lett.*, 1335 (1976)
- 28) D.N.Jones, J.Blenkinsopp, A.C.F.Edmonds, E.Helmy, and R.J.K. Taylor, *J.Chem.Soc., Perkin I*, 2602 (1973)
- 29) P.Bickart, F.W.Carson, J.Jacobus, E.G.Miller, and K.Mislow, *J.Am.Chem.Soc.*, 90, 4869 (1968)
- 30) S.Braverman, *Int.J.Sulfur Chem., C*, 6, 149 (1971)
- 31) B.M.Trost and R.F.Hammen, *J.Am.Chem.Soc.*, 95, 962 (1973)
- 32) a) M.Moriwaki, S.Sawada, and Y.Inouye, *Chem.Comm.*, 419 (1970)
b) M.Moriwaki, Y.Yamamoto, J.Oda, and Y.Inouye, *J.Org.Chem.*, 41, 300 (1976)
- 33) a) V.Rautenstrauch, *Chem.Comm.*, 4 (1970)
b) U.Schöllkopf, K.Fellenberger, and M.Rizk, *Liebigs Ann. Chem.*, 734, 106 (1970)
- 34) V.Rautenstrauch, *Chem.Comm.*, 526 (1970)
- 35) a) D.A.Evans and G.C.Andrews, *J.Am.Chem.Soc.*, 94, 3672 (1972)
b) D.A.Evans and G.C.Andrews, *Account Chem.Res.*, 7, 147 (1974)
- 36) a) G.C.Andrews and D.A.Evans, *Tetrahedron Lett.*, 5121 (1972)
b) D.A.Evans and C.L.Sims, *ibid.*, 4691 (1973)
c) D.A.Evans, C.L.Sims, and G.C.Andrews, *J.Am.Chem.Soc.*, 99, 5453 (1977)
d) L.N.Mander and J.V.Turner, *J.Org.Chem.*, 38, 2915 (1973)

- 37) H.O.House, J.Lubinkowski, and J.J.Good, *J.Org.Chem.*, 40, 86 (1975)
- 38) E.Fischer, *Ber.*, 27, 3231 (1894)
- 39) W.Marckwald, *ibid.*, 37, 1368 (1904)
- 40) A.McKenzie and P.D.Ritchie, *Biochem.Z.*, 237, 1 (1931)
- 41) a) V.Prelog, *Helv.Chem.Acta*, 36, 308 (1953)
b) V.Prelog, *Bull.Soc.Chim.Fr.*, 987 (1956)
- 42) D.J.Cram and F.A.Abd Elhafez, *J.Am.Chem.Soc.*, 74, 5828, 5851 (1952)
- 43) K.Mislow, 'Introduction to Stereochemistry', W.A.Benjamin, New York, 1966, p.122.
- 44) H.Pracejus, *Fortsch.Chem.Forsch.*, 8, 493 (1967)
- 45) a) W.Doering and R.W.Young, *J.Am.Chem.Soc.*, 72, 631 (1950)
b) L.M.Jackman, J.A.Mills, and J.S.Shannon, *ibid.*, 72, 4814 (1950)
- 46) H.S.Mosher and E.La Combe, *ibid.*, 72, 3994, 4991 (1950)
- 47) A.C.Cope, W.R.Funke, and F.N.Jones, *ibid.*, 88, 4693 (1966)
- 48) R.K.Hill and M.Rabinovitz, *ibid.*, 86, 965 (1964)
- 49) W.R.Roth, J.König, and K.Stein, *Ber.*, 103, 426 (1970)
- 50) H.K.Spencer and R.K.Hill, *J.Org.Chem.*, 41, 2485 (1976)
- 51) R.K.Hill and T.H.Chan, *J.Am.Chem.Soc.*, 88, 866 (1966)
- 52) a) A.-M.Weidler and G.Bergson, *Acta Chem.Scand.*, 18, 1487 (1964)
b) J.Almy and D.J.Cram, *J.Am.Chem.Soc.*, 91, 4459 (1969)
- 53) R.K.Hill and R.M.Carlson, *ibid.*, 87, 2772 (1965)
- 54) A.C.Cope, T.T.Foster, and P.H.Towle, *ibid.*, 71, 3929 (1949)
- 55) a) D.J.Cram and J.E.McCarty, *ibid.*, 76, 5740 (1954)
b) A.C.Cope and O.L.Bumgardner, *ibid.*, 79, 960 (1957)
- 56) R.Oda, Y.Hayashi, and T.Yoshida, *Nippon Kagaku Zasshi*, 87, 978 (1966)
- 57) a) J.Meisenheimer, *Ber.*, 52, 1667 (1919)

- b) J.Meisenheimer, H.Greske, and A.Willmersdorf, *ibid.*, 55, 513 (1922)
- 58) U.Schöllkopf, M.Patsch, and H.Schäfer, *Tetrahedron Lett.*, 2515 (1964)
- 59) A.P.Lepley, P.M.Cook, and G.F.Willard, *J.Am.Chem.Soc.*, 92, 1101 (1970)
- 60) a) R.F.Kleinschmidt and A.C.Cope, *ibid.*, 66, 1929 (1944)
b) A.H.Wragg, T.S.Stevens, and D.M.Ostle, *J.Chem.Soc.*, 4057 (1958)
- 61) J.E.Baldwin, J.E.Brown, and R.W.Cordell, *Chem.Commun.*, 31 (1970)
- 62) G.Büchi, M.Cushman, and H.Wüest, *J.Am.Chem.Soc.*, 96, 5563 (1974)
- 63) a) J.E.Baldwin and R.E.Hackler, *ibid.*, 91, 3646 (1969)
b) U.Schöllkopf, *Angew.Chem.Int.Ed.*, 9, 763 (1970)
c) J.E.Baldwin, W.F.Erickson, R.E.Hackler, and R.M.Scott, *Chem.Commun.*, 576 (1970)
- 64) I.Tabushi, J.Hamuro, and R.Oda, *Nippon Kagaku Zasshi*, 90 197 (1969)
- 65) J.Baddiley, G.Ehrensward, and H.Nilsson, *J.Biol.Chem.*, 178, 399 (1949)
- 66) *Org.Syn.*, coll.vol.1, 77
- 67) C.Harries and A.S.de Osa, *Ber.*, 36, 2997 (1903)
- 68) M.L.Moore, *Org.React.*, 5, 301 (1960)
- 69) a) K.Freudenberg and F.Rhino, *Ber.*, 57, 1547 (1924)
b) E.Fischer, *ibid.*, 32, 2451 (1899)
- 70) O.Červinka, E.Kroupová, and O.Bélovský, *Collect.Czech.Chem. Commun.*, 33, 3551 (1968)
- 71) V.M.Potapov, V.M.Dem'yanovich, and A.P.Terent'ev, *Zh.Obshch. Khim.*, 35, 1538 (1965); *Chem.Abstr.*, 63, 17854h (1965)
- 72) U.Nagai, private communication.

- 73) R. MacLeod, F. J. Welch, and H. S. Mosher, *J. Am. Chem. Soc.*, **82**, 876 (1960)
- 74) a) J. Kenyon and S. M. Partridge, *J. Chem. Soc.*, 128 (1936)
 b) K. Mislow and C. L. Hamermesh, *J. Am. Chem. Soc.*, **77**, 1590 (1955)
- 75) U. Schölkopf and I. Hoppe, *Liebigs Ann. Chem.*, **765**, 153 (1972)
- 76) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 1115 (1914)
- 77) V. Rautenstrauch, *Helv. Chem. Acta*, **56**, 2492 (1973)
- 78) J. F. Bunnett, J. L. Marks, and H. Moe, *J. Am. Chem. Soc.*, **75**, 985 (1953)
- 79) A. Klages, *Ber.*, **37**, 2301 (1904)
- 80) *Org. Syn.*, coll. vol. 2, 506
- 81) Y. Pocker and M. J. Hill, *J. Am. Chem. Soc.*, **91**, 3243 (1969)
- 82) a) R. M. Roberts and F. A. Hussein, *ibid.*, **82**, 1950 (1960)
 b) J. W. Schulenberg and S. Archer, *Org. React.*, **14**, 28 (1965)
 c) O. Mumm and F. Möller, *Ber.*, **70**, 2214 (1937)
 d) W. M. Lauer and C. S. Benton, *J. Org. Chem.*, **24**, 804 (1959)
- 83) a) L. E. Overman, *J. Am. Chem. Soc.*, **96**, 597 (1974)
 b) L. E. Overman, *Tetrahedron Lett.*, 1149 (1975)
 c) L. E. Overman, *J. Am. Chem. Soc.*, **98**, 2901 (1976)
- 84) a) J. Kenyon, S. M. Partridge, and H. Phillips, *J. Chem. Soc.*, 85 (1936)
 b) H. L. Goering, G. S. Koerner, and E. C. Lindsay, *J. Am. Chem. Soc.*, **93**, 1230 (1971)
 c) J. B. M. Coppock and S. M. Partridge, *Nature*, **137**, 907 (1936)
- 85) a) P. A. Levene, A. Rothen, and M. Kuna, *J. Biol. Chem.*, **120**, 777 (1937)
 b) O. Červinka, V. Suchan, O. Kotýnek, and V. Dudek, *Collect. Czech. Chem. Commun.*, **30**, 2484 (1965)
- 86) J. A. Hirsh in 'Topics in Stereochemistry' vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, 1967, p. 199.
- 87) S. Schroeter, *Liebigs Ann. Chem.*, **674**, 118 (1964)

- 88) a) H.Goldschmidt and A.Fischer, *Ber.*, 30, 2069 (1897)
b) S.Schroeter and E.L.Eliel, *J.Am.Chem.Soc.*, 86, 2066 (1964)
- 89) a) R.G.Johnston and J.Read, *J.Chem.Soc.*, 233 (1934)
b) R.H.Reitsema, *J.Am.Chem.Soc.*, 75, 1996 (1953)
- 90) *Org.Syn.*, coll.vol.2, 503
- 91) M.Busch and L.Leefhelm, *J.Prakt.Chem.*, 77, 1 (1908)
- 92) H.D.DeWitt and A.W.Ingersoll, *J.Am.Chem.Soc.*, 73, 3359 (1951)