Chemical Reviews

Volume 84, Number 3 June 1984

Catalysis of the Cope and Claisen Rearrangements

RAYMOND P. LUTZ

Department of Chemistry, Portland State University, Portland, Oregon 97207

Received November 8, 1983 (Revised Manuscript Received March 20, 1984)

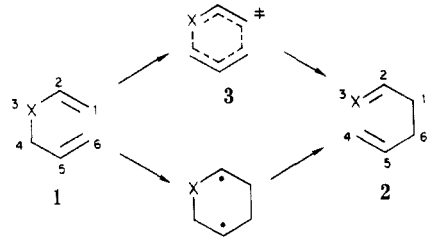
Contents

Raymond Lutz is Professor of Chemistry at Portland State University, Portland, OR. He has also held faculty positions at Harvard University and the University of Illinois (Chicago Circle). He was born in Cleveland, Ohio, and obtained his B.S. and M.S. in Chemistry at the University of Florida, Gainesville. After a period of employment with E. I. du Pont, he earned a Ph.D. (with J. D. Roberts) at the California Institute of Technology. His research is in the area of reaction mechanisms, particularly thermal rearrangements, and he has maintained a career-long interest in the Cope rearrangement.

0009-2665/84/0784-0205$06.50/0

I. Introduction

The Cope and Claisen rearrangements, like the perennial distinguished seminar speaker, scarcely need an introduction.[1,2] The reactions have held the interest of chemists for decades, both as the subjects of intensive theoretical investigations, and as increasingly utilized, stereochemically reliable reactions for organic synthesis. The rearrangements can be defined by the thermal isomerization, 1 → 2, with X = carbon for the Cope and X = oxygen for the Claisen rearrangement, or X = nitrogen or sulfur for the more familiar modifications of the latter.[3] Other positions in 1 may be occupied



by heteroatoms,[4] and the rearrangement substrate may possess a higher degree of unsaturation than shown in 1.

Both rearrangements fall under the classification [3,3]-sigmatropic shift and are loosely referred to as concerted. However, the Cope rearrangement depends on substituents in such a way as to suggest either the involvement of a biradical intermediate,[5] cyclohexane-1,4-diyl (4), or a spectrum of transition states ranging in structure from 3, representing interacting allyl radicals, to the biradical, 4.[6,7] Information about substituent effects in the Claisen rearrangement is limited, with recent work suggesting that a spectrum of mechanisms may also be operative in that reaction.[8] The question of stereochemistry in these reactions has been thoroughly addressed,[9] with the conclusion being that the rearranging substrate adopts a chairlike arrangement (5) in preference to a boatlike (6), unless the former is sterically precluded or in some way inhibited; the reaction can then occur partly or totally with boatlike topology.

Catalysis in these systems has been known almost as long as the reactions themselves, beginning with a 1912 report by Claisen of the apparent catalytic effect of ammonium chloride[10] on a Claisen rearrangement. Since then, numerous other substances, principally Brønsted and Lewis acids, bases, and transition-metal complexes, have been shown to demonstrate catalytic activity ranging from modest to dramatic. A comprehensive review of this subject has not appeared; limited aspects have been reviewed as noted in the appropriate sections below.

The concept of catalysis is considered broadly in this review, and examples include those in which the catalyst is used in stoichiometric or greater amounts (whether necessary for effective reaction or not). Specific reaction conditions are generally provided, as well as yield data[11] when available. In cases where a limited number of examples of catalysis are known, they are usually all reported here; if the examples are numerous, a broad enough selection is included to convey a feel for the characteristics of the catalyzed reaction and its utility as a preparative process. The literature was surveyed to mid-1983.

Catalyzed reactions exhibiting a regioselective structural change defined by 1 → 2 are referred to in this review as [3,3] processes, although the designation [*i,j*]-sigmatropic change was originally restricted to uncatalyzed intramolecular reactions.[12] The mechanisms that have been proposed for the catalyzed reactions are briefly reported, generally with minimal comment. This aspect of the field is in the process of development, and alternatives may not have been thoroughly evaluated in individual cases.[13] Most of the mechanisms fall into two broad categories, one of which is known as "charge-induced, or, better, charge-accelerated [3,3]-sigmatropic rearrangements",[14] and the other as cyclization-induced[15] rearrangements. Of note is the fact that the reported chair/boat selectivity of catalyzed reactions, irrespective of catalyst, nearly always parallels that of the corresponding thermal reaction, including situations in which chair, boat, or concurrent chair and boat topologies are observed.

The all-carbon Cope rearrangement is treated first in this review, followed by aromatic and aliphatic Claisen rearrangements, amino- and thio-Claisen rearrangements, and polyhetero-Cope and Claisen rearrangements. Propargyl and allenyl substrates are not separately categorized, but are included in the appropriate subsection. The ester enolate Claisen rearrangement and its modifications[2,153] are not discussed, as the reactions are not regarded as catalyzed [3,3]-sigmatropic shifts.

II. Cope Rearrangement

A. Thermal Reactions

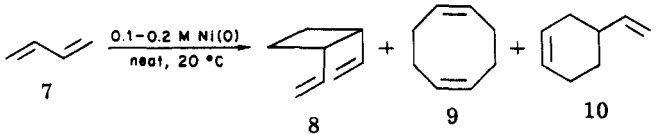
The most obvious manifestation of catalysis in a Cope rearrangement is a reduction in reaction temperature, so it is useful to have as a reference the temperature requirements of the purely thermal rearrangements. These vary widely depending on the structure and substitution pattern of the substrate, but a "typical" temperature range may be set at 150–200 °C, which is effective for acyclic substrates bearing an unsaturated, activating substituent such as phenyl, cyano, or carbalkoxy at the 3- or 4-position of the 1,5-hexadiene unit,[1a] or the 2- or 5-position.[5,6c,d] Additional activating groups

lead to a reduced reaction temperature. Unactivated acyclic dienes may require higher temperatures; rearrangement of the parent 1,5-diene itself (as 1,1-dideuteriohexa-1,5-diene) was studied at 210–260 °C.[16] Incorporating the 1,5-diene unit into a ring system can result in considerably lower temperatures; *cis*-1,2-divinylcyclopropane, for example, rearranges at 5 °C,[17] and semibullvalene (degenerate rearrangement) at −170 °C.[18]

The full analysis of possible transition-state geometries for thermally allowed [3,3]-sigmatropic shifts includes configurations other than the familiar chair and boat, **5** and **6**.[9] However, all evidence supports the assumption of a chairlike or boatlike transition state for most Cope rearrangements. The chair selectivity is high in unhindered cases (99.7% chair for *meso*-3,4-dimethylhexa-1,5-diene at 225 °C);[19] steric constraints can lead to rearrangements proceeding with concurrent chair and boat topologies (63% chair, 37% boat for *meso*-3,4-diphenylhexa-1,5-diene at 120 °C),[20] or with exclusive boat geometry, as for *cis*-1,2-divinylcyclopropane.[17]

B. Catalysis by Zerovalent Nickel Complexes[21]

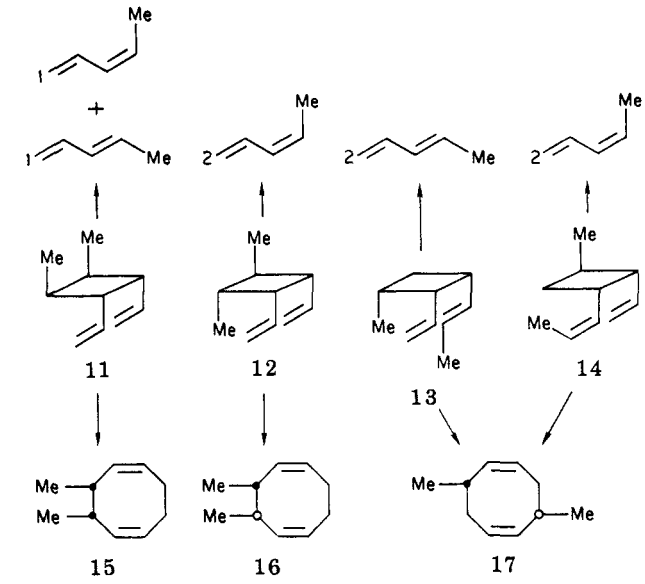
The first indication of catalysis of the Cope rearrangement by Ni(0) complexes was given by variations in product composition with degree of conversion during the catalyzed cyclodimerization of 1,3-butadiene, using complexes in which one of the four coordination sites of the metal was occupied by a phosphite or phosphine ligand. (Nickel complexes of this type promote cyclic dimer formation from butadienes at the expense of cyclic trimers.[22]) Butadiene (**7**) at 20 °C in the presence of a catalyst prepared from bis(*cis*,*cis*-cycloocta-1,5-diene)nickel(0) and tris(*o*-phenylphenyl) phosphite (Ni/P = 1/1 molar ratio) yielded *cis*-1,2-divinylcyclobutane (**8**) and *cis*,*cis*-cycloocta-1,5-diene (**9**), along with a small amount of 4-vinylcyclohexene (**10**).[23] The ratio

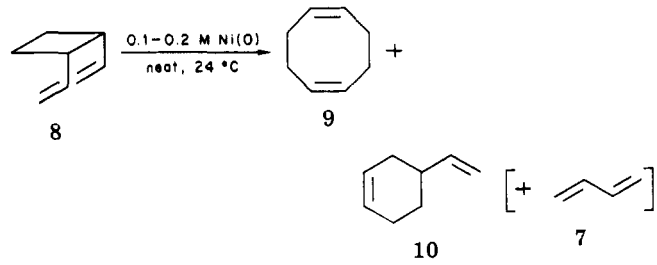


of **9** to **8** was 61/36 at both 30% and 85% conversion, increasing to 83/14 at 95% conversion and finally to 97/0 at 100% conversion, indicating that a catalyzed rearrangement of **8** to **9** was taking place under the conditions of the reaction.

This was confirmed by rearranging a sample of **8** directly.[24] Use of the catalyst shown above gave 99% of **9** along with 0.5% **10** at 24 °C; however, replacement of the phosphite ligand with a phosphine derivative led to substantial increases in the proportion of **10**, the [1,3]-shift product. Catalyst with a triphenylphosphine ligand gave 60% **9** and 31% **10**; with tricyclohexylphosphine the yields were 55% **9** and 33% **10**. Free butadiene (up to 30%) was also a product in reactions carried out at 80 torr,[22] showing that the dimerization is reversible and suggesting that part of the catalyzed rearrangement may actually be a dissociation–recombination process. The thermal Cope rearrangement of **8** to **9** (boat transition state) occurs at a convenient rate at about 80 °C.[25] Rate accelerations in the Ni(0)-catalyzed reactions were on the order of 10^3 (1 M **8**, 1 M Ni(0) with tris(*o*-phenylphenyl) phosphite, 24 °C).[26]

SCHEME I. Ni(0)-Catalyzed Rearrangement and Fragmentation

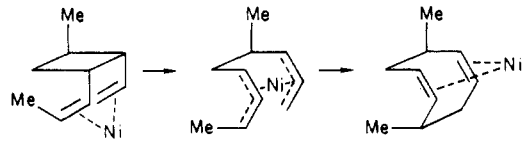




Catalyzed Cope rearrangement was also observed with a series of four dimethyl-substituted *cis*-divinylcyclobutanes (**11**–**14**, Scheme I).[27] Experimental details are sketchy; tris(*o*-phenylphenyl) phosphite ligand seemed to give the best results.[28,29] The reactions were highly stereoselective and were accompanied by stereoselective fragmentation to piperylenes, which were immediately removed from the reaction zone at 30 torr. Competing [1,3] shifts to vinylcyclohexenes were not reported. The rearrangement products were those expected from reaction via boat-type transition states related in configuration to the structures as depicted in Scheme I for the starting cyclobutanes, with vinyl groups oriented with respect to the ring in such a way as to lead to cis double bonds in the cyclooctadienes. This stereochemistry apparently parallels that of the thermal reactions (150 °C) in the case of **11** and **14**,[30] but reflects a more stereoselective process than the thermal rearrangements of **12** and **13**, where part of the reaction occurs through chair transition states to give cycloocta-1,5-dienes with one cis and one trans double bond. The thermal rearrangement (95 °C) of **12** gives 70% **16** and 30% of the corresponding *cis*,*trans*-1,5-diene, while **13** yields 93% of **17** and 7% *cis*,*trans*-diene.[28,31]

Dissociation to butadienes competes with rearrangement of the *cis*-divinylcyclobutanes, so that dissociation–recombination represents a potential rearrangement mode. However, the high stereo- and regioselectivity observed when dissociation products are removed as formed strongly supports the occurrence of a [3,3] process under these conditions.[32] The mechanism of

the Ni(0)-catalyzed Cope rearrangement is very likely intimately related to that of the reversible cyclodimerization of butadienes as well as associated catalyzed processes such as cis/trans isomerization of the butadienes.[33] These are all highly stereoselective and have been rationalized by an extensive interconnected system of π-allyl and σ-allyl nickel complexes.[34] On this basis, the catalyzed Cope rearrangement can be formulated in more than one way, the simplest being the conversion of a nickel(0)–diene complex, for example **14a**, into the bis(π-allyl)nickel(II) intermediate, **14b**, by oxidative addition, followed by reductive elimination in a new sense to **14c** and decomplexation (other ligands on Ni not shown).[35]

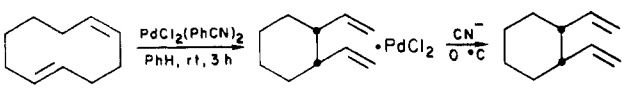


14a 14b 14c

Examples of Ni(0)-catalyzed Cope rearrangement appear to be restricted to the compounds mentioned above, and the general utility of these complexes as catalysts has yet to be explored. Nickel(0) catalysis with compounds like 11–14 would not be preparatively useful because competing dissociation–recombination as well as cis/trans isomerization of the dissociated 1,3-dienes would lead to loss of stereoselectivity. In some cases, compounds that have the potential for Cope rearrangement have been prepared in the presence of Ni(0) catalysts without complications due to catalyzed rearrangement.[36]

C. Catalysis by Palladium(II) Complexes[37]

Palladium dichloride complexes have been extensively studied as catalysts for the Cope rearrangement. The early work focused on stoichiometric reactions, beginning with the observation by Jonassen et al.[38] that *cis,trans*-cyclodeca-1,5-diene (**18**) reacted at room temperature with bis(benzonitrile)palladium dichloride to form a crystalline $PdCl_2$ complex, **19** (82%), which, when decomposed with aqueous KCN, yielded only *cis*-1,2-divinylcyclohexane (**20**), the product of the thermal Cope rearrangement of **18**. Complex **19** could



18 19 20

also be formed under similar conditions directly from **20**. The thermal reaction, **18** → **20**, takes place at 150 °C (5 h)[39] through a chair transition state, and it is obvious that a substantially accelerated rearrangement was taking place during the formation of **19**.

Heimbach and Molin[40] extended this work to a series of mono- and disubstituted cyclodecadienes and trienes, some of which did not form crystalline complexes. Those complexes that did form possessed a Cope-rearranged carbon skeleton only. The experimental results were somewhat complicated by the fact that starting materials were used as mixtures, and the reactions were not investigated for any evidence of rearrangement occurring in addition to or in the absence of complex precipitation. Scheme II exemplifies a

SCHEME II

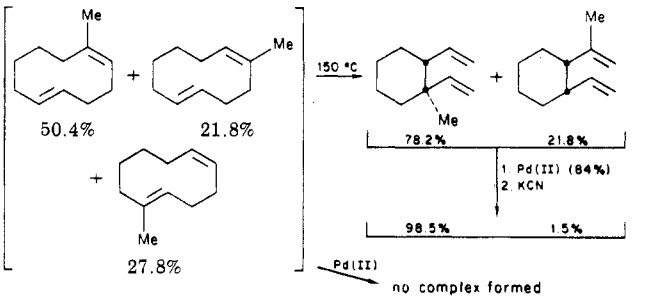
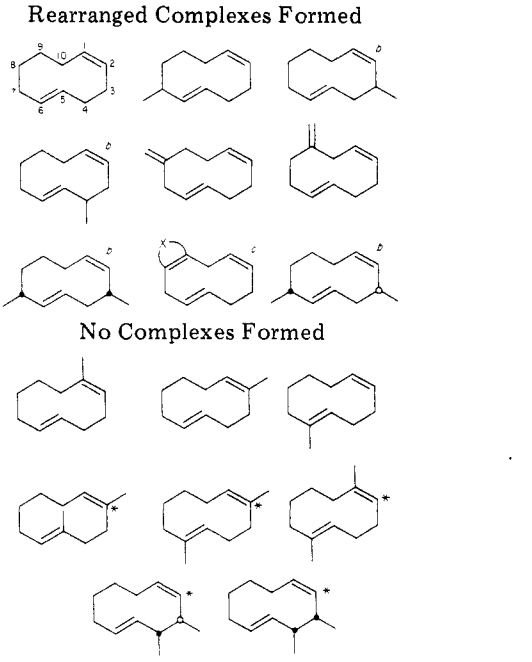


TABLE I. Reactions of Cyclodecadienes with Pd(II)[a]

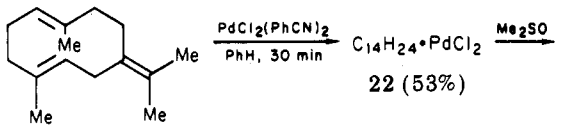


[a] $PdCl_2(PhCN)_2$ (1 equiv or less), PhH, 20 °C. [b] Low yield. [c] X = $(CH_2)_{10}$. * See text.

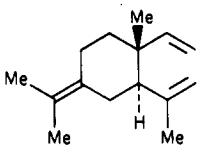
typical data set comparing thermal reactions with the formation of rearranged complexes. (Values under the formulas represent percent composition rather than yields.)

Table I subdivides the compounds examined into a group that did form complexes (some with low yields) and a group that did not. It can be seen that mono- or dimethyl substitution associated with the 1-, 2-, 3-, 4-, or 6-positions prevents or hinders complex formation. There is a certain ambiguity related to the dimethyl-substituted compounds marked with an asterisk in Table I. Control experiments showed that their Cope rearrangement products would not have formed crystalline complexes under the reaction conditions, so that undetected catalyzed rearrangements may have taken place. However, this is unlikely in view of the negative results with the monomethyl counterparts.

A substitution pattern that inhibited rearranged complex formation in the *cis,trans*-cyclodeca-1,5-dienes had no such effect in a case involving the trans,trans ring system. Germacratriene (**21**) reacted with $PdCl_2(PhCN)_2$ to form a complex (**22**) that yielded only δ-elemene (**23**) on decomposition with dimethyl sulfoxide.[41] The complex was also formed directly from **23**. The thermal rearrangement of **21** (<120 °C, 3 h, 91%) gave **23** as well, the trans geometry of the prod-



21

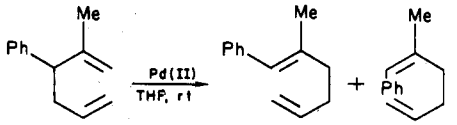


23

uct[42] requiring a chair transition state. Inspection of models suggests that both the chair and boat transition states are sterically accessible in this system, so that the catalyzed rearrangement here apparently exhibits the same selectivity regarding transition-state geometry as a typical thermal reaction.

Heimbach and Molin also observed rearranged products during complex formation (followed by complex decomposition), from *cis*-1,2-divinylcyclobutane and a number of mono- and dimethyl-substituted derivatives.[43] Results are summarized in Scheme III (1 equiv of $PdCl_2(PhCN)_2$, 20 °C, benzene, crude yields of $PdCl_2$ complexes). In contrast to the situation with Ni(0) catalysis in this system, no fragmentation to butadienes was observed. In all cases the regio and stereoselectivity was the same as that reported for the thermal rearrangements at 150 °C,[44] except for **24** and **25**, each of which yielded a mixture of cis–trans isomers, **26** and **27**. In the thermal reactions by way of sterically preferred boat transition states, **24** gives only the *cis*-dimethyl ring found in **26**, and **25** gives the *trans*-dimethyl ring of **27**. These two cases represent the only reported examples where the rearrangement involving Pd(II) does not parallel the stereochemistry of the corresponding thermal reaction.[45]

The use of Pd(II) in the Cope rearrangement was extended to acyclic dienes by Overman and Knoll,[46] who also established that the reactions could be carried out using catalytic amounts of Pd(II) without the isolation of $PdCl_2$/diene complexes. For example, 2-methyl-3-phenylhexa-1,5-diene (**28**) in tetrahydrofuran (THF) at room temperature (rt) in the presence of 0.06 equiv of bis(benzonitrile)palladium dichloride rearranged within 24 h (87%) to (*E*)- and (*Z*)-2-methyl-1-phenylhexa-1,5-diene (**29**, **30**; E/Z = 93/7). Control experiments



28 29 30

showed that the Pd(II) had established an equilibrium between **28**, **29**, and **30**, and that the observed E/Z ratio was the equilibrium value. The catalyzed reaction was considerably more stereoselective than the thermal rearrangement, which yielded **29**/**30** in a kinetically controlled ratio of 3/1 (177 °C, C_6D_6, half-life = 13 h). The catalyzed rearrangement was substantially faster in benzene than in THF or CH_2Cl_2. A catalytic rate acceleration of 10^{10} (1 M catalyst) was estimated for the former solvent.[47] A different Pd(II) salt, $Pd(OAc)_2$, was ineffective as a catalyst, as were a Pd(0) complex, $Pd(PPh_3)_4$, and $Hg(CF_3CO_2)_2$.

SCHEME III. Formation of Rearranged $PdCl_2$ Complexes at 20 °C

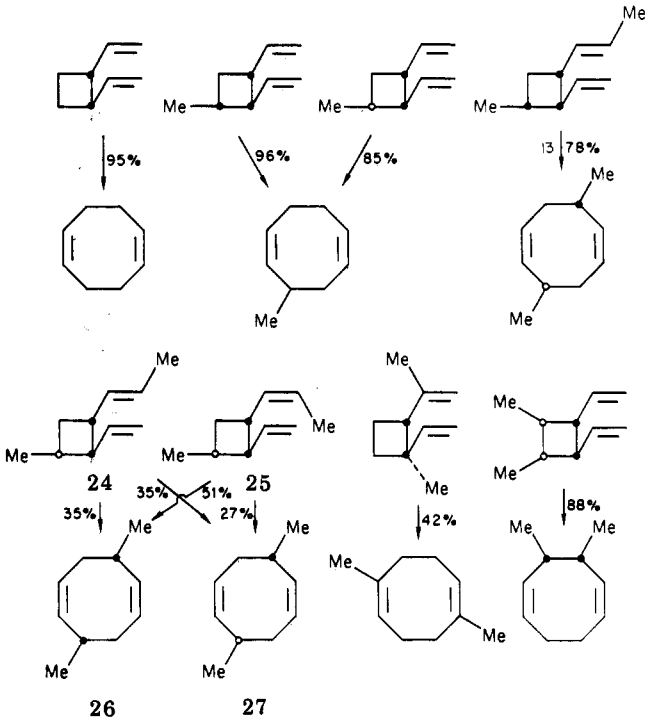
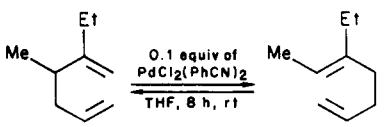


TABLE II. Pd(II)-Catalyzed[a] Rearrangement of Acyclic Hydrocarbon Hexa-1,5-dienes

substituents	% [3,3] yield
5-methyl-3-phenyl	96 (97% *E*)
1,2-dimethyl-3-phenyl	72 (>90% *E*)
(*E*)-2,6-dimethyl-3-phenyl	54 (>90% *E*)
(*E*)-2,3,6-trimethyl-3-phenyl	88 (71% *Z*)[b]
3-phenyl	no rearrangement
1-methyl-3-phenyl	no rearrangement
6-methyl-3-phenyl	no rearrangement
(*E*)-3,6-dimethyl-3-phenyl	no rearrangement
2,5-dimethyl-3-phenyl	no rearrangement

[a] 0.10 equiv of $PdCl_2(PhCN)_2$ in THF, room temperature, 5–48 h. [b] Originally reported as 71% *E*; see ref 48.

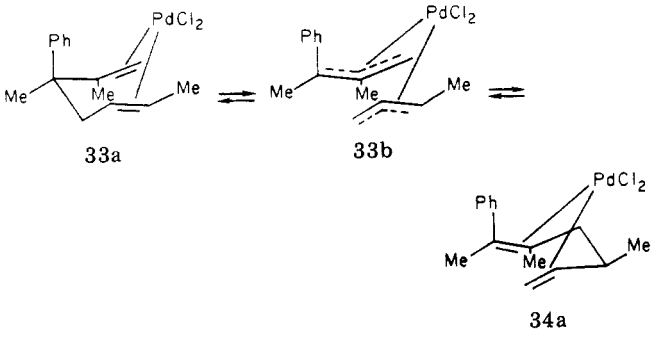
Table II summarizes results with other acyclic hydrocarbon substrates, including those for which no catalyzed rearrangement was observed; all possessed a 3-phenyl substituent. The rearrangement occurred here only with those compounds bearing a substituent at C-2 or C-5 (but not both). (In the case of the *cis,trans*-cyclodeca-1,5-dienes, substitution at C-2 was seen to hinder formation of rearranged $PdCl_2$ complexes; see above.) The catalyzed rearrangements showed a uniformly high selectivity for the *E* configuration in newly formed disubstituted double bonds; as expected, selectivity was low for a trisubstituted double bond. The catalyzed equilibration of **31** and **32** demonstrated that a phenyl group was not essential for the reaction.



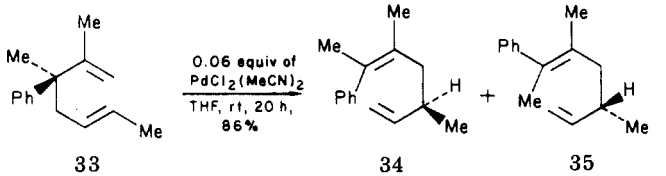
31 (34%) 32 (66%)

Catalyzed rearrangement of (3*R*,5*E*)-2,3-dimethyl-2-phenylhepta-1,5-diene (**33**) (99% enantiomeric excess) yielded optically active **34** (97 ± 5% enantiomeric ex-

SCHEME IV

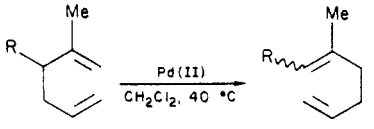


cess) and **35** (96 ± 6% enantiomeric excess) in a 7/3 ratio.[48] The transfer of chirality was in the same sense



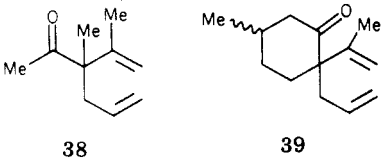
as that of the thermal reaction of **33** (240 °C, 16 h, 50%), which furnished equal parts of **34** and **35**, each with 90% enantiomeric excess. The stereochemistry of **34** and **35** requires a chair topology for the catalyzed and thermal reactions.[49] Reaction of **33** provides an unambiguous example in which the Pd(II)-catalyzed rearrangement in the absence of steric constraints exhibits the same chair/boat selectivity as the thermal reaction (cf. **21** → **23**).

Catalysis by $PdCl_2$ was also effective with substrates possessing a typical unsaturated, electron-withdrawing, activating group such as ester, cyano, etc., at C-3 along with an alkyl substituent at C-2.[50] For example, **36** (R = CO_2Et) rearranged in 5 h at 40 °C with 0.1 equiv of $PdCl_2(MeCN)_2$ in CH_2Cl_2 to a mixture (83%) of *E*-**37** and *Z*-**37** (*E*/*Z* = 65/35). Analogous reactions occurred

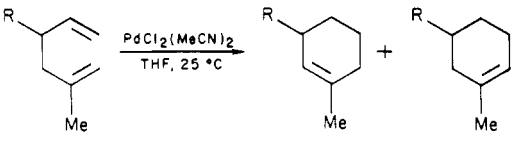


with R = COMe (5.5 h, 94%, *E*/*Z* = 68/31), R = CN (36 h, 0.3 equiv of Pd(II), 77%, *E*/*Z* = 75/25), and R = CO_2H (24 h, 64%, *E*/*Z* = 65/35). There was no reaction when R = tertiary amide. The reported *E*/*Z* ratios do not necessarily reflect kinetic control, as *E*- and *Z*-**37** (R = CO_2Et) were found to interconvert under the reaction conditions.

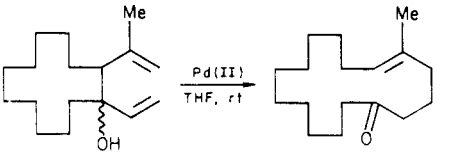
Good yields were also obtained in the catalyzed rearrangement of more complex substrates, including **38** (77%, *E*/*Z* = 50/50) and **39** (81%, *E*/*Z* = 50/50).[50]



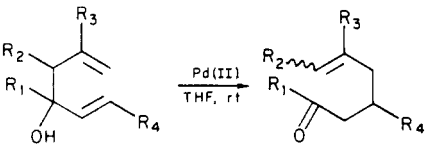
The Pd(II)-catalyzed process was preparatively superior in these cases to the purely thermal reactions (220–240 °C), which were complicated by double-bond isomerization of the products.[51] Palladium(II) catalysis was not effective with substrates such as **40**, with the alkyl group at C-5 and the activating substituent, R, at C-3. In such cases, cyclization products were obtained in low yield.[52]



The oxy-Cope rearrangement (see below, base catalysis) was also subject to Pd(II) catalysis,[53] as illustrated by the conversion of **41** in 65% yield to **42** (pure *E*) in 6 h at room temperature, using 0.1 equiv of $PdCl_2(PhCN)_2$ in THF. Analogous reactions took place with



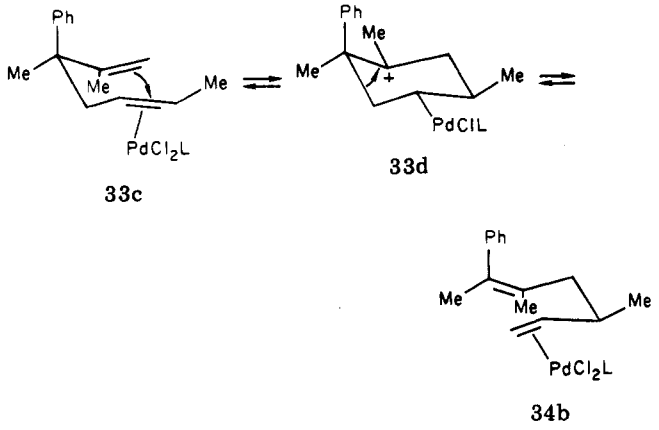
other substrates, **43** → **44**; 100% in 3 h for $R_1 = R_3$ = Me, $R_2 = R_4$ = H; 76% (pure *E*) in 3 h for $R_1 = R_3$ = Me, $R_2 = CH_2CH{=}CMe_2$, R_4 = H; 85% in 3 h for $R_1 = R_3$ = Me, $R_2 = CH_2CH{=}CMeCH_2CH_2CH{=}CMe_2$, R_4 = H; 55% (*E*/*Z* = 9) in 24 h for $R_1,R_2 = -(CH_2)_4-$, R_3 = Me, R_4 = H. No catalyzed reaction occurred with



secondary alcohols (R_1 = H) or substrates which lacked an alkyl group at C-5 (R_3 = H). (The necessity for an alkyl group at C-2 (or C-5) is characteristic of the Pd(II)-catalyzed rearrangement of open-chain 1,5-dienes.) Reflux temperatures (THF) were required if the catalyst were $PdCl_2$·2LiCl or $PdCl_2(COD)_2$ (COD = cyclooctadiene), whereas $PdCl_2(MeCN)_2$ caused unspecified isomerization, and no reaction was observed with $PdCl_2(PPh_3)_2$, $Pd(CH_3CO_2)_2$, or $Pd(PhCO_2)_2$. Benzene, ether, and CH_2Cl_2 were also suitable solvents. Palladium(II) catalysis of the oxy-Cope rearrangement complements Hg(II) catalysis and the anionic oxy-Cope rearrangement (see below).

There are two prime candidates among a number of proposed mechanisms for the Pd(II)-catalyzed reactions,[54] but a definitive choice can't be made on the basis of available data. One of these (Scheme IV, illustrated for **33** → **34**) essentially involves breaking the original diene unit into two allylic fragments attached to palladium, followed by recombination in the [3,3] sense. Accordingly, the original Pd(II)/diene complex, **33a**, generates a bis(η^3-allyl)palladium(IV) intermediate (**33b**) by oxidative addition of the metal, followed by reductive elimination to the rearranged complex, **34a**. The observed chair topology for the reactions requires that the allylic units in **33b** maintain the geometry shown.[55] Support for intermediates such as **33b** in the catalyzed Cope rearrangement has been claimed[56] on the basis that the same type of intermediate can account for the formation of acetone from 1,5-hexadiene under Wacker oxidation conditions ($PdCl_2$, CuCl, $CuCl_2$,

SCHEME V

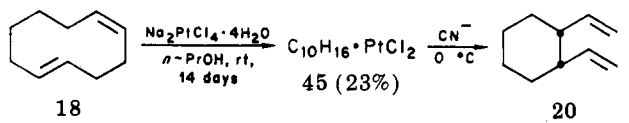


O_2, 60 °C), but the connection is somewhat tenuous.

A second potential mechanism (Scheme V) is analogous to those previously invoked by Overman[57] as well as others,[58,59] to account for various catalyzed [3,3]-sigmatropic shifts. In this process, referred to as a cyclization-induced rearrangement, the Pd(II) functions as a Lewis acid to give a cyclic cationic intermediate, which fragments to the Cope-rearranged produce (cf. **33c** → **33d** → **34b**, L = ligand). This type of intermediate may also be involved in those cases where the 1,5-diene actually cyclized in the presence of Pd(II) rather than rearranged.[60] Overman[46] tentatively recommends the cyclization-induced process as the more compatible with available data, including the apparent requirement in acyclic cases for an alkyl substituent at the 2-position. A substituent here would stabilize the cationic center of the cyclic intermediate (cf. **33d**). However, 2-methyl-*cis,trans*-cyclodeca-1,5-diene does not rearrange catalytically, whereas the parent diene does so readily, as do *cis*-divinylcyclobutanes lacking an alkyl group in the analogous position (see Scheme III). Another characteristic of this and other Pd(II)-catalyzed sigmatropic shifts (see below) is the lack of reactivity in cases where a substituent would lead to a tertiary Pd–C bond in an assumed cyclic intermediate. The lack of stereospecificity in the rearrangements of **24** and **25** is not accounted for by either Scheme IV or Scheme V; these compounds merit further scrutiny.

D. Catalysis by Platinum Complexes

The use of platinum complexes to accelerate Cope rearrangement appears to be confined to the stoichiometric reaction of *cis,trans*-cyclodeca-1,5-diene (**18**) with sodium tetrachloroplatinate.[38] The resultant

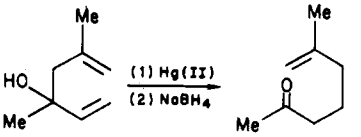


18 20

$PtCl_2$(diene) complex, **45**, yielded only *cis*-1,2-divinylcyclohexane (**20**) on decomposition with KCN, and could be formed directly from **20**. Complex **45** was also obtained using the corresponding Pt(IV) salt, Na_2PtCl_6.

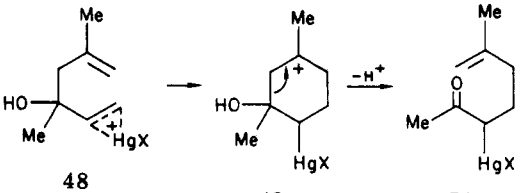
E. Catalysis by Hg(II) Salts[37b]

Catalysis of the Cope rearrangement by Hg(II) is limited to a few examples involving the oxy-Cope rearrangement (see below), including the conversion of **46** to **47** (75%) using stoichiometric amounts of mercuric trifluoroacetate in CH_2Cl_2 at 20 °C for a few minutes, followed by treatment with $NaBH_4$ in Na_2CO_3 solution.[61] The reaction was assumed to proceed by



46 47

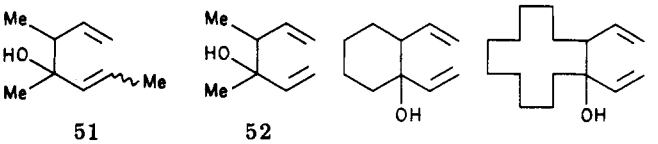
a cyclization-induced mechanism in which an Hg(II)–olefin complex, **48**, cyclized to **49**, which then opened with loss of a proton to **50**. Demercuration with $NaBH_4$ then gave **47**. Compound **47** was formed at longer



48 49 50

reaction times without $NaBH_4$ treatment, apparently by demercuration of **50** with the trifluoroacetic acid generated in the reaction, but the yield was only about 40%. Under these conditions metallic mercury formed, so that Hg(II) was not regenerated for another reaction cycle. A 30% yield of **47** was also obtained using $Hg(CH_3CO_2)_2$ or $HgCl_2$ in THF/H_2O without $NaBH_4$ treatment, but no reaction occurred with these two salts in THF or diglyme.

The conditions shown above for **46** → **47** were also effective for the rearrangements of **51** (50%, E/Z = 80/20), **52** (62%, E/Z = 80/20), **53** (35%), and **54** (70%, E/Z = 70/30); successful reaction did not depend on the presence of an alkyl group at C-5, as was the case with Pd(II) catalysis of similar alcohols (see above). In both cases, no catalyzed reaction occurred with secondary alcohols.

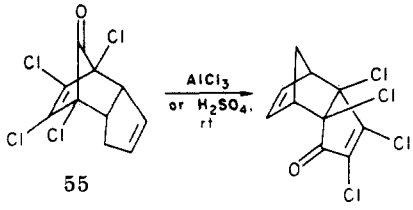


51 52 53 54

F. Catalysis by Brønsted Acids and Lewis Acids

Brønsted and Lewis acids will be considered together because individual substrates are often observed to be susceptible to catalysis by both types of acids, and the number of different acids employed is limited. The range of substrates examined is also limited; aside from a case involving phenyl substitution (see below), examples of Brønsted/Lewis acid catalyzed Cope rearrangement are confined to 1-, 2-, or 3-acyl-1,5-dienes and some nitrogen derivatives. This includes the allylcyclohexadienones, which are treated as a separate category.

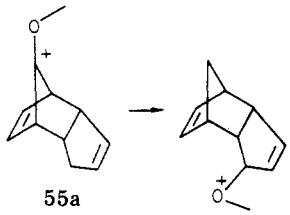
The chlorinated dicyclopentadienone **55**, a 3-acyl-1,5-diene, rearranged to **56** within 3 min at room temperature in the presence of a large excess of $AlCl_3$ in CCl_4, compared to a thermal reaction occurring in 1 h at 135 °C.[62] The rearrangement was also catalyzed by H_2SO_4. The nonchlorinated analogue of **55** rearranged rapidly at 20 °C with a trace of BF_3 in cyclohexane, and at room temperature with HCl in dioxane.[63] The non-



55 56

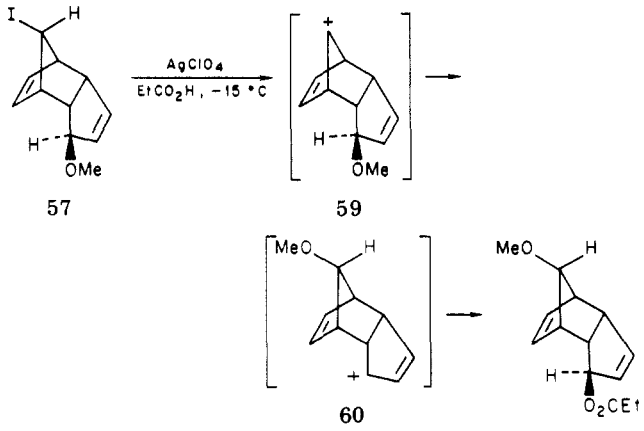
chlorinated substrate was stable at room temperature in cyclohexane, but it rearranged upon melting (63–64 °C) and even slowly at room temperature in neutral ethanol. Although specific tests for [3,3]-sigmatropic processes were not carried out in these systems, the rearrangements are consistent with analogous Cope rearrangements of dicyclopentadienes[64] and would be sterically constrained to a boatlike geometry for the transition state.

The acid catalyst very likely functions by attachment to oxygen, so that the species actually undergoing rearrangement possesses some cationic character at the carbonyl carbon (cf. **55a** → **56a**). That a cationic



55a 56a

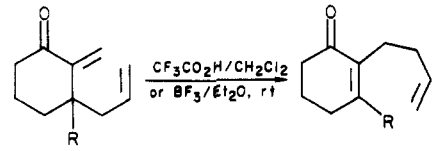
species such as **55a** would rearrange rapidly is supported by the observation that iodide **57** yields the rearranged propionate **58** upon silver-assisted solvolysis at −15 °C, presumably by way of cations **59** and **60**.[65]



57 59 60 58

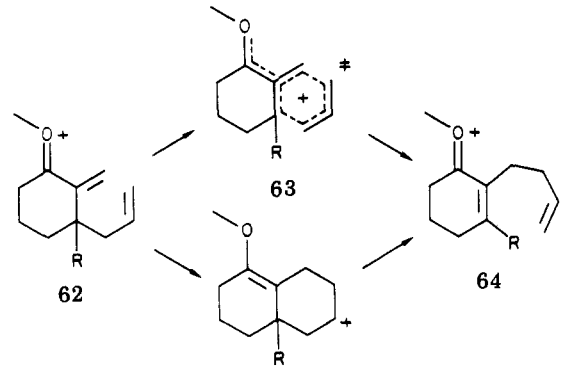
Processes of this sort have been termed charge-accelerated [3,3]-sigmatropic rearrangements,[66] and are invoked in a number of systems examined in this review. Rate acceleration is attributed principally to mutal delocalization of the charge and the six electrons of the Cope transition state.[65–68]

1,5-Dienes with acyl groups at C-2 also undergo a strongly acid-catalyzed Cope rearrangement, exemplified by the rearrangement of **61a,b** catalyzed by 1.0 equiv of CF_3CO_2H or BF_3.[69] Conditions and results are given in Table III. The thermal reactions of both **61a** and **61b** occur with a half-life of 2 h in refluxing benzene. A [3,3]-sigmatropic process was assumed for the thermal and catalyzed reactions, although inversion of both allylic moieties was not demonstrated; the results provide no information about transition-state geometries.



61a, R = Me
61b, R = H

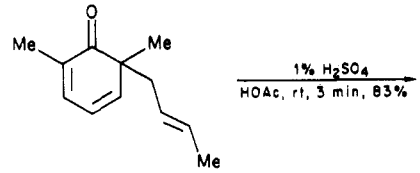
Rate acceleration in the catalyzed systems was attributed either to a charge-accelerated rearrangement (cf. **62** → **63** → **64**), or a cyclization-induced process (**62** → **65** → **64**). (According to Carpenter's approach to



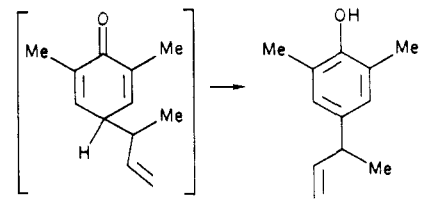
62 63 64 65

substituent effects on [3,3]-sigmatropic rearrangements,[67] a conjugating positive center at C-2 of the 1,5-diene should actually inhibit Cope rearrangement.)

Brønsted/Lewis acid catalyzed [3,3]-sigmatropic shifts often represent the predominant reaction mode among a number of other possibilities in the catalyzed rearrangements and cleavage of allylcyclohexadienones. Much of the work in this area has been reviewed.[71] Catalysts include H_2SO_4 in aqueous[72,73] or acetic acid[74] solution, HCl in methanol[75] or chlorobenzene,[76] BCl_3 or BCl_3/HCl in chlorobenzene,[76] BF_3[77] or *p*-toluenesulfonic acid[78] in diethyl ether, and CF_3CO_2H in hexane.[77] The catalyzed reactions are observed at 0 °C to room temperature, whereas the thermal rearrangements occur for the most part at about 70–110 °C.[71] An early example involved inversion of both allylic moieties of the starting material, ortho dienone **66** → **67**, and demonstrated the [3,3]-sigmatropic nature of the reaction.[74] The thermal



66



66a 67

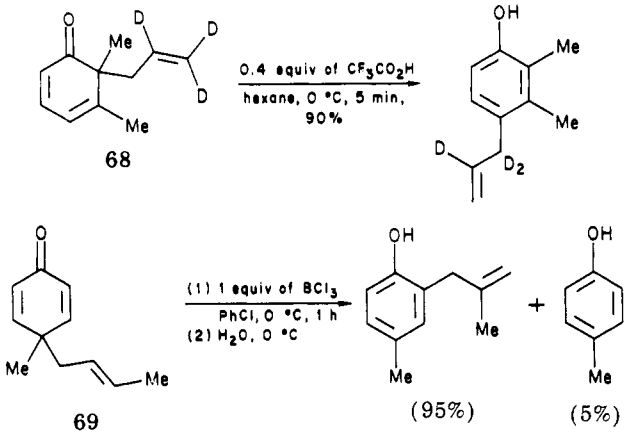
reaction (105 °C, 1 h, 83%) as well as the catalyzed reaction are assumed to proceed through an intermediate para dienone, **66a**, which rapidly enolizes to the

TABLE III. Catalyzed Rearrangements of 61

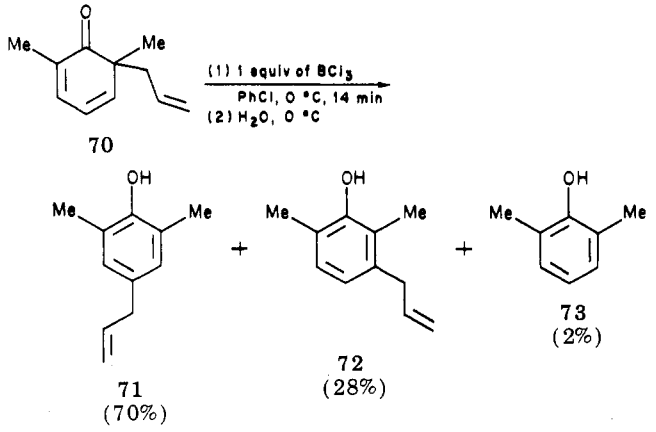
substrate (61)	conditions	yield, %
a, R = Me	CF_3CO_2H (1 equiv), CH_2Cl_2, rt, 15 min	74
a, R = Me	BF_3 (1 equiv), Et_2O, rt, 10 min	73
b, R = H	CF_3CO_2H (1 equiv), CH_2Cl_2, rt, 90 min	34
b, R = H	BF_3 (1 equiv), Et_2O, rt, 20 min	*a*

[a] The crude reaction mixture contained 50% product and at least 5 minor components.

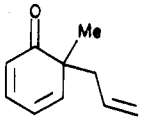
observed phenolic product. (This represents overall a type of dienone–phenol rearrangement. In cases where there is no enolizable hydrogen at the ring migration terminus, the reaction usually stops at a stage comparable to **66a**.) A [3,3] process was also seen in the rearrangement of deuterated substrate **68**[78] as well as a representative para dienone, **69**.[76] Ortho and para cyclohexadienones of this type are formally analogous to 3-acyl- and 1-acyl-1,5-dienes, respectively.



Numerous other examples of acid-catalyzed Cope rearrangements in these systems have been summarized and tabulated by Miller.[71] Several general trends emerge, including the tendency for BCl_3 to lead to more side reactions than the Brønsted acids.[77] Treatment of **70** with BCl_3, for example, gave the [3,3] product, **71**, accompanied by significant amounts of the 1,2-shift product, **72**, as well as a small amount of cleavage phenol, **73**.[76] In contrast, catalysis by HCl (satd) in

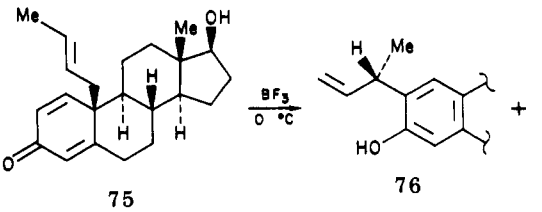


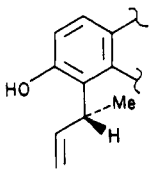
chlorobenzene (0 °C, 2 h) lead to 95% **71** and 5% **72**. Substrates with more highly substituted rings often yield higher proportions of side reactions, as evidenced by the fact that **74** gave exclusively the [3,3] product even with BCl_3.[76,79] The crotyl group often leads to higher proportions of [3,3] product than the allyl group,[71] and rearranges much faster than allyl.[74]



74

In the cases examined, the stereochemistry of the acid-catalyzed cyclohexadienone Cope rearrangements closely paralleled that of the thermal reactions, for which chair as well as boat topologies were observed. The optically active steroidal para dienone, **75**, rearranged with BF_3 in ether (0.7 equiv, 0 °C, 0.5 h, then H_2O) to a mixture of **76** (29%) and **77** (19%), both of which are products of rearrangement with chair geometry.[77] The optical purities of the products showed that

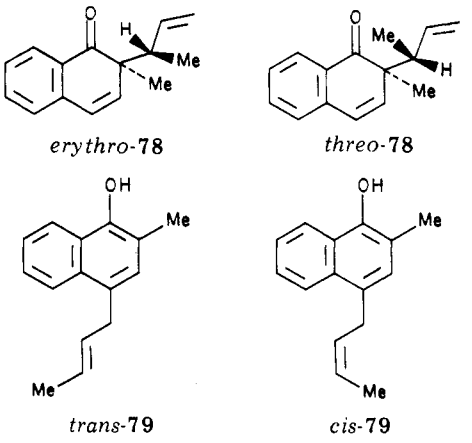




77

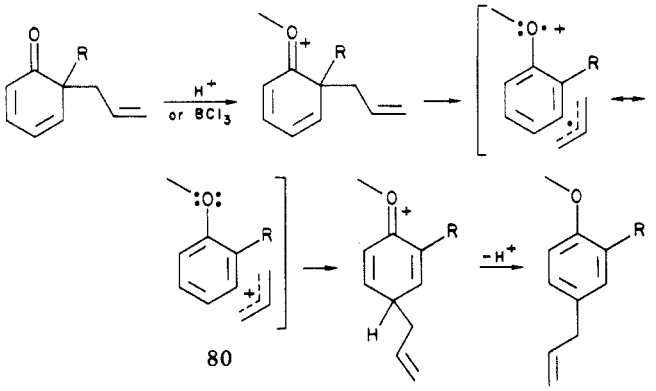
the preference for the chair transition state was >94.5% in the case of **76** and >99% for **77**. The thermal reaction (120 °C, 2.5 h, *N,N*-diethylaniline) yielded about 52% **76** and 48% **77**, whose optical purities indicated that 94% of the reaction in each case occurred with chair geometry.

Rearrangements of the optically active diastereomeric ortho dienones, *erythro*- and *threo*-**78**, were not as straightforward.[80] The thermal reactions yielded predominantly the naphthols, *cis*- and *trans*-**79**. The



product composition showed that thermal rearrangement of *erythro*-**78** (60 °C, half-life = 75 min) occurred with a >90% preference for chair geometry (giving *trans*-**79**), whereas *threo*-**78** rearranged (85 °C, half-life = 71 min) to the extent of 74% with chair geometry

SCHEME VI

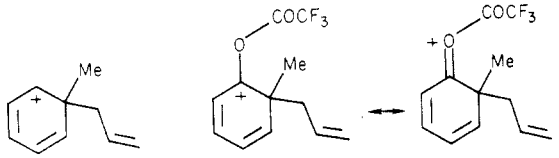


80

(giving *cis*-**79**) and 26% with boat geometry (giving *trans*-**79**). The contrasting behavior of the diastereomers of this and other ortho dienones is not readily rationalized.[81] Of interest here is the fact that acid-catalyzed rearrangements of **78** (CF_3CO_2H or methanolic H_2SO_4, 0–20 °C) gave similar product compositions as the thermal reactions,[82] implicating the same transition-state geometries for reactions under both conditions.

These catalyzed rearrangements of cyclohexadienones have been taken as examples of charge-accelerated Cope rearrangements (see above).[66] Because of the special structural features involved, the transition state may possess to some degree the character of a complex between a phenol and an allyl cation (cf. **80**, Scheme VI).

There is evidence to suggest that in these systems excessive cationic character at what was originally the carbonyl carbon atom promotes side reactions characteristic of carbonium-ion rearrangements.[71] In the full cyclohexadienyl carbonium ion, **81** (obtained by acid treatment of the corresponding alcohol), the [3,3] process is a minor (10%) rearrangement mode.[83] Likewise,

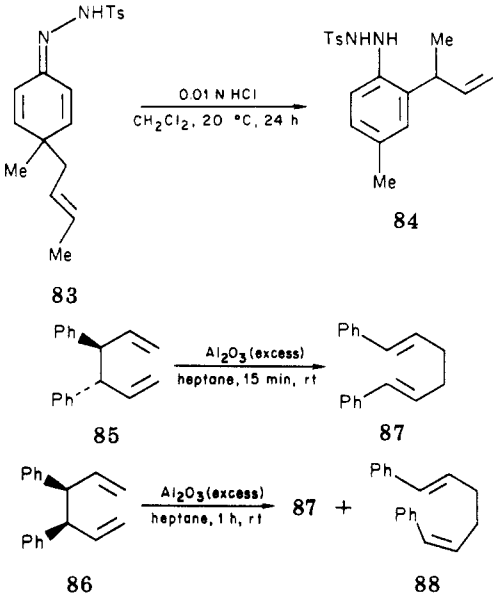


81 82

competing cationic rearrangements lead to a diminished yield of [3,3] product in species such as **82**, obtained by treatment of the corresponding dienone with $(CF_3CO)_2O$.[84] The polar effect of the acyl group in **82** would lead to greater cationic character of the ring than would be the case in a protonated dienone or in a dienone/BCl_3 adduct.[85]

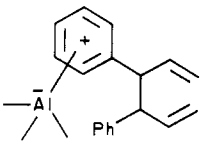
Nitrogen analogues of allylcyclohexadienone have also been shown to undergo acid-catalyzed Cope rearrangement ("dienimine–aniline" rearrangement). Tosylhydrazone **83**, for example, rearranged in 88% yield at room temperature in the presence of HCl to **84**.[86] Inversion of both allyl moieties supports the conclusion that a [3,3] process operates here. A thermal rearrangement was not reported, but no reaction occurred in the absence of acid. A charge-accelerated process analogous to those occurring in the parent dienones was proposed.

The final examples of acid catalysis are the alumina-catalyzed Cope rearrangements of *dl*- and *meso*-3,4-diphenylhexa-1,5-diene (**85**, **86**).[59] Rearrangement



83 84 85 86 87 88

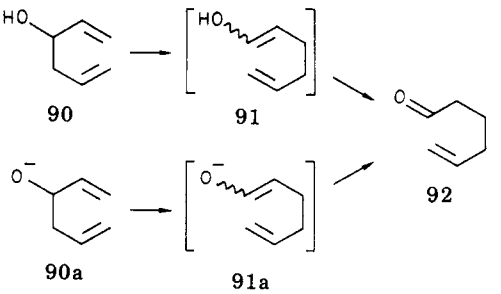
of **85** yielded only the *E*,*E* diene, **87** (84%), the same product as the thermal reaction (80 °C, half-life = 8 h), and one requiring reaction through a chair transition state. The slower-reacting meso diene, **86**, (20% conversion in 1 h over alumina) gave a diene mixture containing 32% **87** and 68% of the *E*,*Z* isomer, **88**, the same product composition as observed in the thermal reaction at 120 °C (half-life = 15 h). The meso diene under both conditions reacted with boat (**86** → **87**) as well as chair (**86** → **88**) topology. A cyclization-induced rearrangement analogous to Scheme V was suggested for these rearrangements, with alumina functioning as the Lewis acid. A charge-accelerated rearrangement involving a species such as **89** is also a reasonable possibility in this system.



89

G. Catalysis by Base (Anionic Oxy-Cope Rearrangement)

The presence of a hydroxy substituent at the 3-position of a 1,5-diene leads to a rearrangement known as the oxy-Cope,[87] characterized by initial formation of an enol which rapidly equilibrates with the corresponding carbonyl derivative (cf. **90** → **91** → **92**). Relatively high



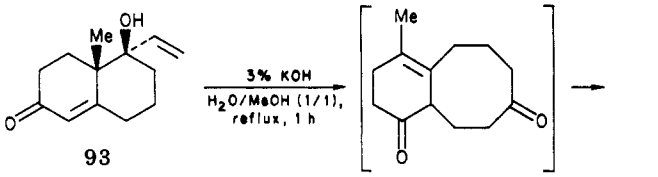
90 91 92

90a 91a

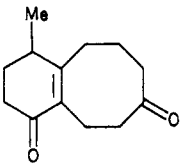
temperatures (>200 °C) are usually required; yields can be high, but β-hydroxy olefin cleavage is often a significant side reaction, particularly in acyclic systems. A variation of this process in basic media would involve

the corresponding anion, **90a**, whose rearrangement would yield the enolate, **91a**, which, depending on conditions, would be converted to the carbonyl compound in situ or upon workup. This variation is now a well-characterized process known as the anionic oxy-Cope, in which extraordinary rate enhancement can be observed in the anion compared to the parent alcohol. (See above for Pd(II) and Hg(II) catalysis of the oxy-Cope rearrangement.)

The anionic oxy-Cope process was apparently first invoked by Swaminathan and co-workers[88] as a possible mechanism for the base-catalyzed rearrangement of dienol **93** to **94**,[89,90] the same product as obtained in the thermal reaction of **93** in refluxing diethylene glycol (6 h, ca. 245 °C).[88] Base-catalyzed fragmentation–re-



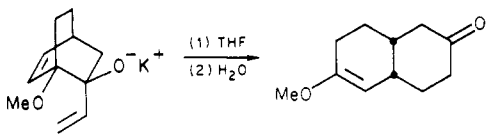
93



94

combination processes (retroaldol followed by Michael addition) were also seen as reasonable alternatives here, and the operation of a Cope rearrangement in this and analogous systems[91,92,93] has not been demonstrated.[94]

Evans and Golub[95] furnished a more convincing example in the rearrangement of the potassium alkoxide, **95** (ca. 98%, THF, 66 °C, half-life = 1.4 min). No

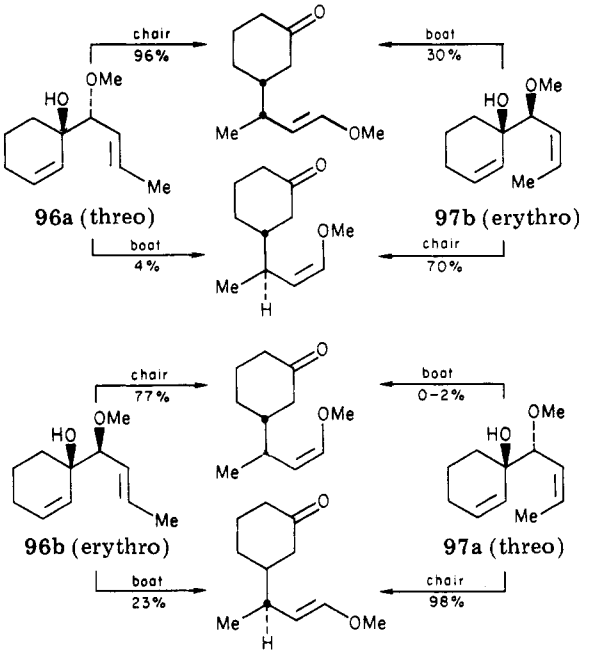


95

reaction under the same conditions was observed with the Li or MgBr salts; the Na salt reacted more slowly (half-life = 1.2 h), and the addition of a crown ether (18-crown-6) to **95** resulted in a 180-fold rate increase. Ion-pair dissociation apparently leads to the largest rate enhancement (first-order reactions observed). Rate accelerations in alkoxides compared to the parent alcohols were dramatic, ranging from 10^{12} at 25 °C for **95** in the presence of 18-crown-6, to 10^{17} at 0 °C for the potassium salt of the unsubstituted analogue of **95** in the presence of crown ether. The epimer of **95** failed to rearrange under comparable conditions, suggesting that a Cope rearrangement was indeed involved here. The geometry of these systems requires reaction by way of a boat transition state.

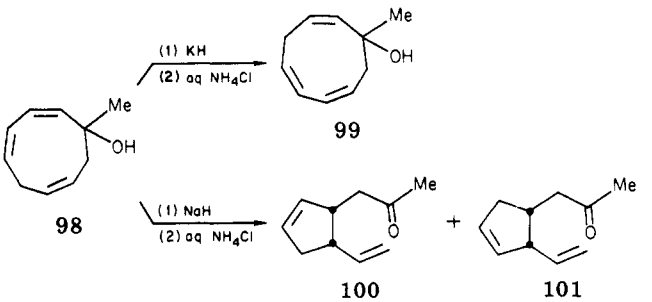
Compelling evidence that anionic reactions of this sort can display typical Cope rearrangement characteristics, including a preference for chair topology in unhindered cases, was obtained by rearrangement of potassium alkoxides derived from four diastereomeric diene alcohols shown in Scheme VII (**96a**, **96b**, **97a**, **97b**).[96] Reactions were carried out in diglyme (100 °C, 38 h, ca. 30–77%). Each diastereomer yielded only two products in the proportions shown,[97] which were indi-

SCHEME VII. Rearrangement as Potassium Alkoxides at 100 °C



cative of the relative extent of reaction through chair or boat geometries. The threo diastereomers displayed a substantial preference for chair transition states. The incursion of significant (23–30%) product formation via boat geometries in the case of the erythro diastereomers could readily be justified by conformational effects in the corresponding transition states. Comparison with thermal oxy-Cope rearrangements in these systems was unfortunately thwarted by preferential formation of byproducts in the thermal reactions.

It has been noted that the hyperbasic reaction conditions that provide the greatest rate enhancements for the anionic oxy-Cope rearrangement do not necessarily lead to the highest yields of [3,3] products, because side reactions may become significant. For example, treatment of **96a,b** with KH in hexamethylphosphoric triamide (HMPT) at 70 °C resulted largely in 1,4-elimination of methanol.[96] The cyclic trienol, **98**, yielded mainly an overall [1,3] hydrogen shift product, **99**, upon treatment with KH in THF (–25 °C, 18-crown-6, 2 h, 86%), whereas about 35% of [3,3] products, **100** and **101** (mixture of unspecified composition), was formed competitively at 0 °C in the absence of crown ether.[98]

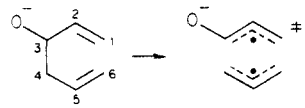


100 101

The [3,3] products predominated (90%) using NaH in THF at reflux (2 h).[99] (Compound **101** was apparently derived from initially formed **99** alkoxide. In the thermal oxy-Cope rearrangements, (205 °C, boat transition states), **98** → **100** and **99** → **101**.) The trend seems to be that reaction conditions promoting the formation of "naked" anions have the potential for fa-

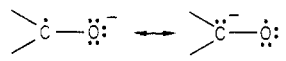
voring side reactions. The relative importance of a number of potentially competitive alkoxide-accelerated pericyclic processes has been explored in other medium-ring alcohols related to **98**.[98]

Numerous other examples of anionic oxy-Cope rearrangements are known, particularly as they relate to organic synthesis, where this reaction is rapidly developing into an important tool.[100] The rate acceleration afforded by a 3-oxido substituent compared to a 3-hydroxy can be rationalized by approaches that model the Cope transition state either as a benzene-like, delocalized $4n + 2$ system, or as a pair of weakly interacting allyl radicals. According to the former approach,[67,68] a comparatively lower activation energy results on going from the localized alkoxide ground state to a charge-delocalized transition state (roughly analogous to delocalization in phenoxide anion; an example of charge-accelerated rearrangement). When a model of interacting allyl radicals is used, a lower activation energy in 3-oxido vs. 3-hydroxy systems is justified on the basis that the C3–C4 bond should have a substantially lower dissociation energy in the former case (cf. **102** → **103**). This conclusion is derived from estimated



102 103

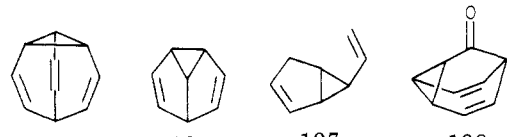
gas-phase bond dissociation energies[101] as well as ab initio theoretical calculations.[102] The lower bond energy is a consequence of enhanced delocalization (cf. **104**) of oxygen electrons in the oxido- vs. hydroxy-substituted radical.[103]



104

H. "Negative Catalysis" in the Cope Rearrangement

A number of cases are reported here in which inhibition of Cope rearrangements was noted, although no attempt has been made for complete coverage of this aspect of the rearrangement. The degenerate rearrangement of bullvalene (**105**, $C_{10}H_{10}$) is inhibited in the complex, $C_{10}H_{10}$·Ag(I),[104] as well as $C_{10}H_{10}$·$Mo(CO)_4$ and $C_{10}H_{10}$·$Cr(CO)_4$.[105] Semibullvalene (**106**) rearrangement



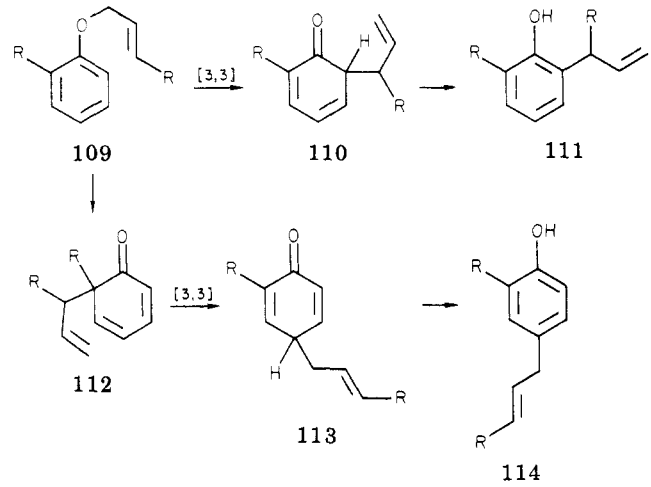
105 106 107 108

is inhibited in its $W(CO)_5$[106] and $Fe(CO)_4$[107] complexes. The (acetylacetonato)rhodium(I) complex of **107** is stable under conditions where the parent hydrocarbon is completely rearranged.[108] Protonation of barbaralone (**108**) inhibits the degenerate Cope rearrangement.[109]

III. Aromatic Claisen Rearrangement

A. Thermal Reactions[1,2]

The initial [3,3] step in the Claisen rearrangement of an allyl aryl ether gives an ortho dienone, which usually rapidly enolizes to the stable product, an *o*-allylphenol (ortho Claisen rearrangement; cf. **109** → **110** → **111**). If the rearrangement is to an ortho position

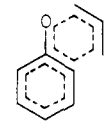


109 110 111

112 113 114

bearing a substituent, a second [3,3] step followed by enolization leads to the *p*-allylphenol (para Claisen rearrangement; cf. **109** → **114**). The ortho Claisen rearrangement predominates in unexceptional cases, but the para process can compete even when both ortho positions are free.[1a] The temperature range for typical reactions is 150–225 °C, with less variability than the Cope rearrangement.

The loss of stereochemical information upon enolization of dienones **110** and **113** makes it impossible to analyze transition-state geometries for the [3,3] step by the same methods applied to the Cope rearrangement. Indirect, kinetic methods are used, as described below in conjunction with catalyzed reactions. These suggest a preference for chair topology, but they provide no information about the specific degree of chair–boat selectivity.[9] (However, the retro-Claisen rearrangement of diastereomeric ortho dienones has been shown to occur with 99.5% chair selectivity or with a preference for boat geometry.[142]) The rearrangement is usually regarded as concerted, with a transition state symbolized by **115**; this is consistent with secondary kinetic deuterium isotope effects in the parent substrate.[110a]

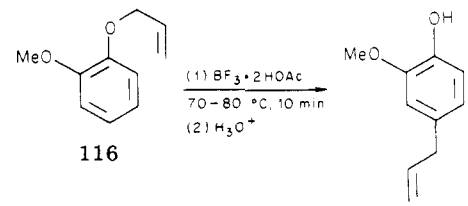


115

B. Catalysis by Lewis Acids

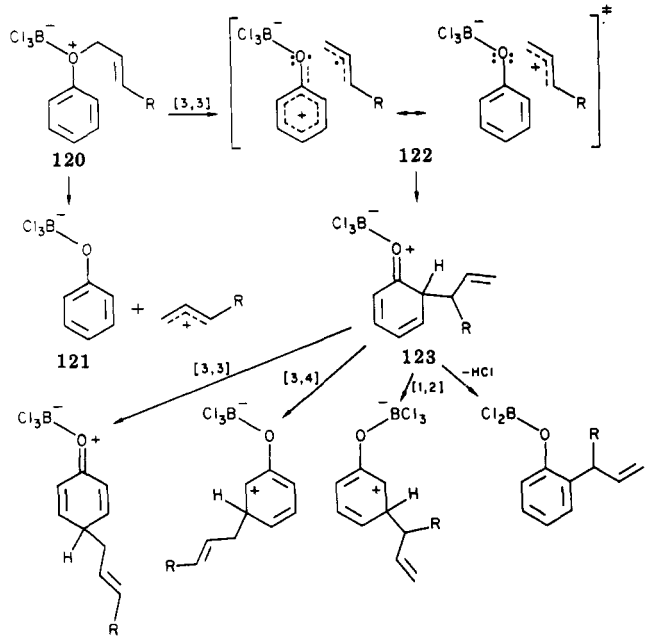
1. Derivatives of Group 2A and 3A Elements

The first reported example of Lewis acid catalysis in the Claisen rearrangement involved the use of BF_3 in the conversion of guaiacol allyl ether (**116**) to eugenol (**117**, 38%).[110b] Later work showed that fewer side

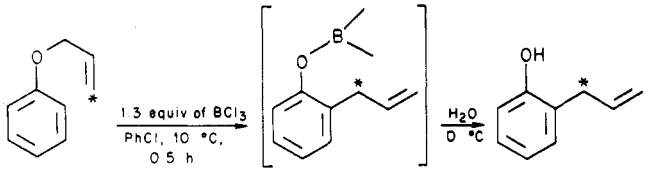


116 117

SCHEME VIII



reactions in general occurred with BCl_3, and the latter has been subjected to the most intensive scrutiny as a catalyst in these systems, largely by Schmid and coworkers.[76,111] The parent Claisen system, allyl phenyl ether, rearranged in high yield with BCl_3 at 10 °C to *o*-allylphenol; the [3,3]-sigmatropic nature of the reaction was confirmed by ^{14}C labeling (**118** → **119**, 89%).[76]



In numerous other cases examined,[76] the reactions were usually carried out at −40 to 0 °C for 0.2–2 h as 0.05–0.2 M solutions in chlorobenzene (dichloromethane also proved satisfactory), by using $^2/_3$–1 equiv of BCl_3. Intermediate boron esters were not isolated, but were converted to phenols by workup with water or methanol at 0 °C. Reaction kinetics were not examined because of complications due to boron speciation; however, a rate enhancement of about 10^{10} was estimated for the above conditions. Stoichiometric amounts of BCl_3 ($^1/_3$ equiv) resulted in incomplete reactions, apparently because intermediates such as $(ArO)_2BCl$ are ineffective as catalysts and don't disproportionate to BCl_3 under the reaction conditions. Products of the "abnormal" Claisen rearrangement[1a] were not observed in the catalyzed reactions.

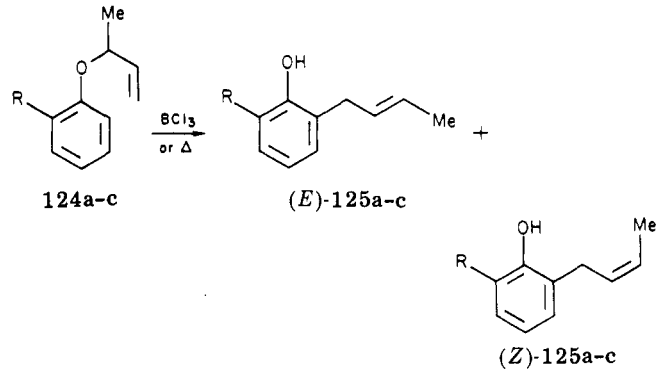
High yields of [3,3] products were observed in many other systems, but more complex product mixtures could result, particularly in substrates with alkyl substituents in the allyl unit. As a focus for further discussion, the proposed [3,3] rearrangement mechanism, essentially a charge-accelerated reaction, is given in Scheme VIII, along with the various competing processes that can rationalize observed side reactions. Thus, an initial ether–BCl_3 complex, **120**, can either cleave to **121** with loss of the allyl cation, leading to cleavage phenols and intermolecular allyl transfers, or undergo [3,3] rearrangement through a charge-delocalized transition state, **122**, to the ortho dienone intermediate, **123** (cf. Scheme VI). Deprotonation of **123** to the boron ester of the product phenol usually occurs rapidly with respect to other potential rearrangements in this species, but if the [3,3] migration terminus does not bear a hydrogen, products of subsequent [3,3], [1,2], or [3,4] rearrangement can be observed. (Scheme VIII is also applicable to other Lewis acids as discussed below.)

TABLE IV. *E*/*Z* Ratio in Ortho Products of 124 Rearrangement

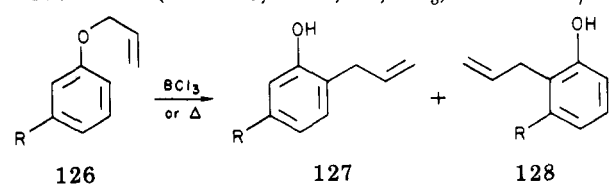
substrate (124)	conditions[a]	*E*/*Z* ratio
a, R = H	thermal	13
	BCl_3	8.5
b, R = Me	thermal	38
	BCl_3	14
c, R = CMe_3	thermal	99
	BCl_3	99

[a] Thermal reactions at 169 °C in *N*,*N*-diethylaniline, 2 h; catalyzed reactions at −31 to 0 °C, 25 min.

The thermal aromatic Claisen rearrangement is deduced to take place preferentially with chair geometry,[9] and the use of analogous experimental probes leads to the same conclusion for the BCl_3-catalyzed reactions.[76] In Table IV are compared the *E*/*Z* ratios for the ortho products of the rearrangement of a series of α-methylallyl aryl ethers (**124** → *E*-**125**, *Z*-**125**), for both the thermal and catalyzed reactions. The increase in the



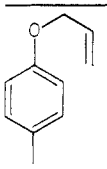
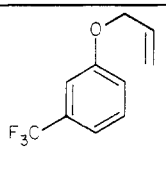
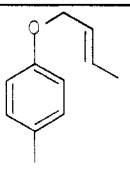
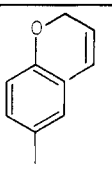
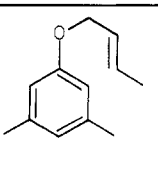
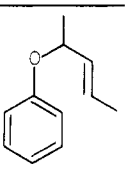
relative amount of *E* product with increasing steric requirements of the R group is consistent with the chair rather than the boat transition state in these systems. Further parallels between the thermal and catalyzed reactions were seen in the [3,3] product ratios of meta-substituted substrates, including the series, **126** → **127** + **128** (R = Me, OMe, Br, CF_3). The **127**/**128**



ratios for thermal and catalyzed reactions were roughly comparable in each case, except for R = OMe, where the catalyzed reaction exhibited a strong preference (85%) for **127**. This was attributed to possible complex formation between BCl_3 and the methoxy group, with resultant steric crowding at the adjacent ortho rearrangement terminus.

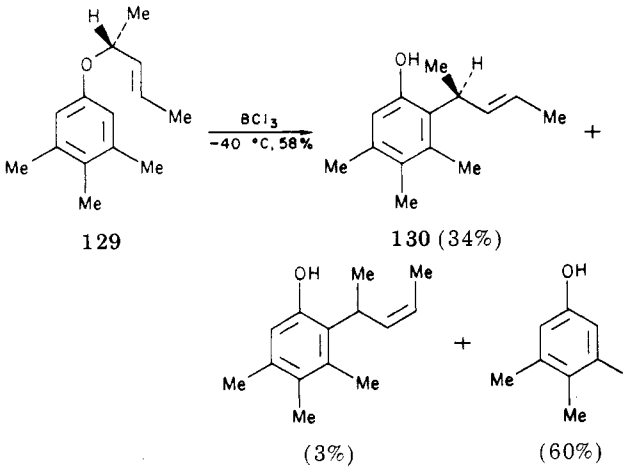
Chirality transfer in the same suprafacial sense as the thermal reaction was observed in BCl_3-catalyzed rear-

TABLE V. Claisen Substrates without Ortho Substituents[a]

Substrates					
					
Cleavage Product					
	25	12	<1	4.5	66
Ortho Product (Inverted)					
92[b]	72[b]	75	91	69	13[b]
Ortho Product (Noninverted)					
b	*b*	4	<1	5	*b*
Para Product					
				16 (*p*-crotyl)	12

[a] Product yields (%) in BCl_3-catalyzed reactions; see text for typical reaction conditions. [b] Product structure does not distinguish between inversion or lack of inversion in the allylic unit.

rangement of the optically active substrate, **129** (0.7 equiv of BCl_3, benzene, −40 °C, 2 h), on the basis of optical rotations observed in the trans product, **130**.[76]

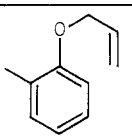
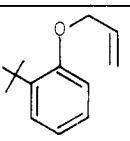
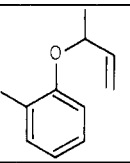
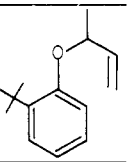


However, about 40% of **130** in the catalyzed reaction was formed with racemization, suggesting intermolecular processes in this system, which is also consistent with the substantial amount of cleavage product formed here.

The results of Schmid and co-workers' extensive investigation of the BCl_3-catalyzed rearrangement have been subdivided and tabulated by them according to the number of available ortho positions in the substrate.[76] Further discussion of the reaction characteristics will be organized along the same lines. A sampling of reactions involving substrates with no ortho substituents is given in Table V. In general, substrates of this type gave high yields of ortho rearrangement product, but cleavage could be a significant side reaction if the aryl group bore a strongly electron-withdrawing substituent or if the allyl group were methyl substituted. Other side reactions included the formation of *p*-allylphenols as well as ortho products with a retained configuration in the allyl unit. *cis*-Crotyl ethers rearranged more cleanly than the *trans*-crotyl.

Substrates with one ortho substituent (Table VI) exhibited characteristics similar to those described above, with the difference that substantial amounts of para rearrangement product could be observed, consistent with the occurrence of a second [3,3] process in intermediates analogous to **123** (Scheme VIII). There was generally a larger relative proportion of para product in the BCl_3-catalyzed reactions than the thermal reactions. This "para effect" was especially pronounced in cases where the allyl group was substituted. The BCl_3-catalyzed reaction of α-methylallyl ethers was generally less stereoselective than the thermal reaction, the latter giving preponderantly *trans*-crotyl ortho rearrangement products.

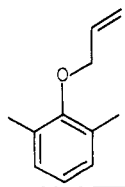
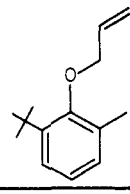
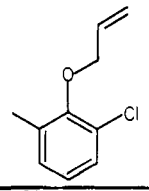
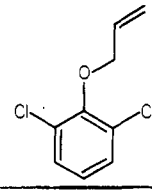
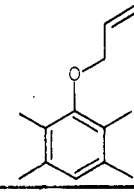
TABLE VI. Claisen Substrates with One Ortho Substituent[a]

sub-strate				
		Cleavage Product		
BCl_3	2	<1	8.5	15.5
Δ				
		Ortho Product		
BCl_3	60	80	39.0 *E*, 2.8 *Z*	16.6 *E*, 0.17 *Z*
Δ	85	100	93.5 *E*, 2.5 *Z*	99.0 *E*, 1.0 *Z*
		Para Product		
BCl_3	32	<1	49[b]	67
Δ	15	<1	4[b]	<0.3

[a] Product yields (%) in thermal and BCl_3-catalyzed reactions. See text for typical conditions for catalyzed reactions; thermal reactions at 170–200 °C. [b] *p*-α-Methylallyl.

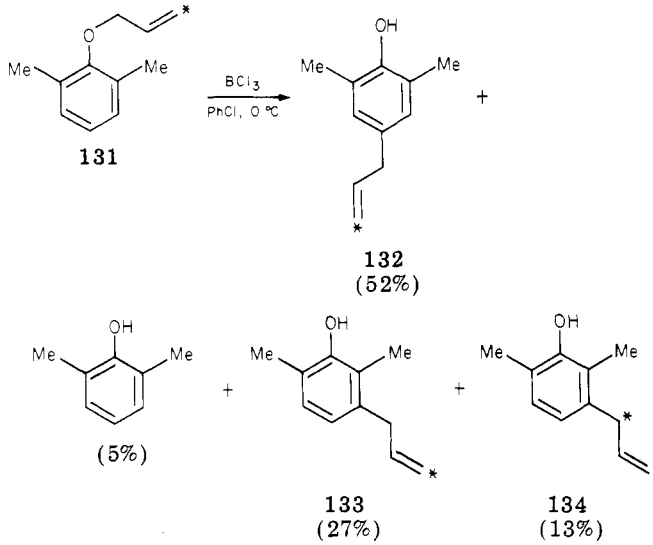
The BCl_3-catalyzed rearrangements were considerably less clean than their thermal counterparts using substrates in which both ortho positions were substituted. The thermal reactions give para products with overall retention of configuration of the allyl group (cf. **109** → **114**); examples of BCl_3-catalyzed rearrangement are given in Table VII. Cleavage is the dominant reaction mode if the aromatic ring bears electron-withdrawing substituents; in other cases the product of rearrangement to the meta position is significant. The distribution of radioactivity in the rearrangement products of ^{14}C-labeled allyl 2,6-dimethylphenyl ether (**131**) is consistent with the operation of [3,3], [3,4], and [1,2]

TABLE VII. Claisen Substrates with Two Ortho Substituents[a]

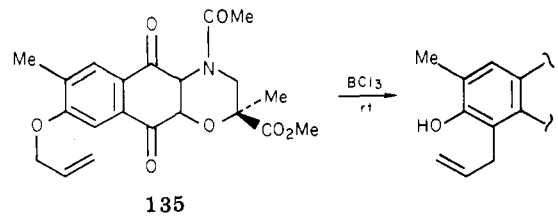
Substrates				
				
Cleavage Products				
5	11.5	43	80	
Para Product				
52	64	42	<0.5	92
Meta Product				
40	5.1	9	<0.5	

[a] Product yields (%) in BCl_3-catalyzed reactions; see text for typical reaction conditions.

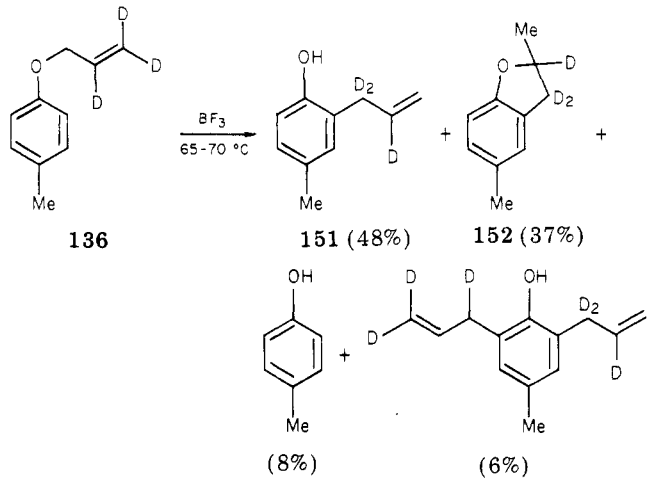
processes in the first-formed ortho dienone intermediate (cf. **123**, Scheme VIII), leading to **132**, **133**, and **134**, respectively. The intramolecularity of the reaction was confirmed by cross experiments.



Schmid and co-workers observed that substitution of BCl_3 by BF_3 or BBr_3 tended to promote side reactions, but that Me_2BBr, on the basis of limited experiments, proved to be satisfactory. The use of BCl_3 in the aromatic Claisen rearrangement might appear to have restricted synthetic utility on the basis of its potential for promoting side reactions of various sorts; however, BCl_3 catalysis in even rather complex systems can lead to the generation of a thermally inaccessible Claisen rearrangement product. For example, thermal treatment of **135** resulted only in decomposition, whereas BCl_3 catalysis (6 equiv, $PhCl/CH_2Cl_2$, rt) furnished the Claisen product in 95% yield.[112]

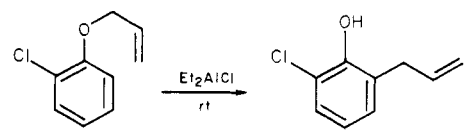


As mentioned earlier, Schmid found BF_3 less successful than BCl_3, but no details were given. From other work,[110b,113] it appears that rearrangement is slower and more complex with BF_3; an example of product mixtures found even in relatively uncomplicated cases is given in the rearrangement of **136** (1 equiv of BF_3, CCl_4, 65–70 °C, 1.5 h, 49%).[113a] The initial **136**/BF_3 adduct could also be significantly diverted to displacement products by the addition of a good nucleophile, tetrahydrothiophene.[113d]



A single case of catalysis by $AlBr_3$ is reported[114] in the rearrangement of allyl phenyl ether. Reaction was "instantaneous" at room temperature (2 equiv of $AlBr_3$, PhCl), but the isolated product was derived from double-bond isomerization in the initial *o*-allylphenol, followed by Friedel–Crafts addition of the resulting olefin to chlorobenzene.

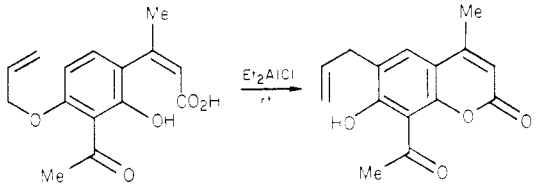
Diethylaluminum chloride appears to be an excellent catalyst on the basis of preliminary investigations involving allyl phenyl ether and derivatives with one to three chlorines on the ring.[115a] Yields were consistently high (89–96%), and only ortho rearrangement products were observed if at least one ortho position was available, as in **137** → **138** (2 equiv of Et_2AlCl, hexane, rt, 0.5 h, then H_3O^+, 94%). Other substrates giving ortho



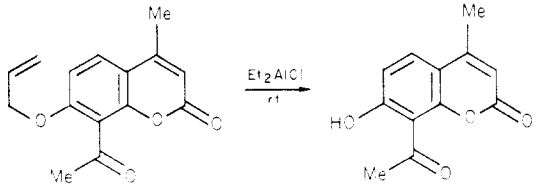
products were as follows: allyl phenyl ether (93%), allyl 3-chlorophenyl ether (92% 2-allyl-5-chlorophenol), allyl 4-chlorophenyl ether (89%), allyl 2,4-dichlorophenyl

ether (95%), allyl 2,4,5-trichlorophenyl ether (96%). Cleavage reactions, which would be significant in these halogenated systems with BCl_3,[76] were not observed except in the case of the ortho-blocked allyl 2,6-dichlorophenyl ether, which gave 50% 2,6-dichlorophenol along with 43% of the para rearrangement product, 4-allyl-2,6-dichlorophenol, and 5% 2-allyl-4,6-dichlorophenol.

Diisobutylaluminum chloride was also a good catalyst for allyl phenyl ether rearrangement; triethyl- or triisobutylaluminum were ineffective (however, see ref 115b), and ethylaluminum sesquichloride or ethylaluminum dichloride caused some cyclization of the first-formed rearrangement product.[115a] In all of these cases, [3,3]-sigmatropic processes have not been proved, but are strongly suggested by the formation of characteristic Claisen products. A recent example involved the rearrangement of the coumarinic acid, **139**, to **140** (87%, 6 equiv of Et_2AlCl, $CHCl_3$, rt, 3 h, then HCl, 5 °C); cyclization also occurred during the reaction.[116] An attempt to carry out an analogous reaction with coumarin **141** resulted in ether cleavage to **142**.



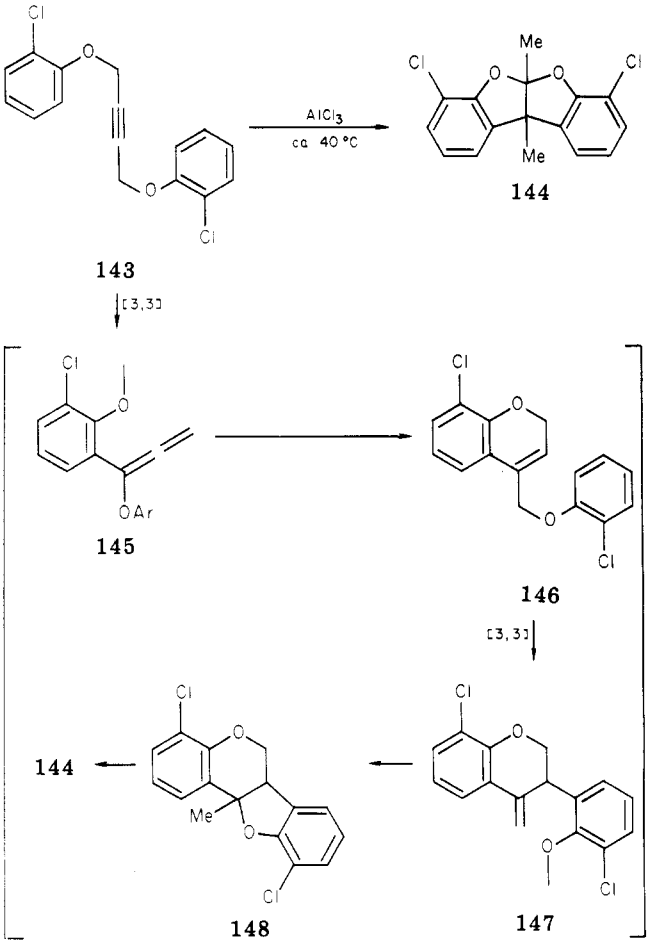
139 **140**



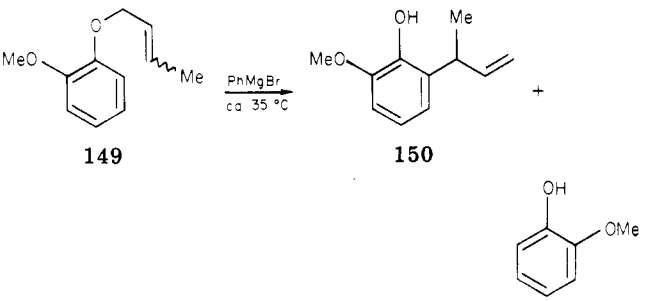
141 **142**

Evidence that $AlCl_3$ is a catalyst for the aromatic Claisen rearrangement of allyl as well as propargyl substrates is given by the conversion of **143** to **144** (30%; 1 equiv of $AlCl_3$, CH_2Cl_2, reflux, 0.5 h, then H_3O^+).[117] The overall reaction is rationalized by a series of steps involving an initial charge-accelerated [3,3] rearrangement to **145** followed by cyclization to **146**, analogous to the product usually obtained in the thermal reactions of simple propargylic aryl ethers.[1a] The presence of the second aryl group in **146** allows a subsequent Claisen rearrangement to **147** followed by cyclization to **148**, which is the type of product found in the thermal reactions of compounds related to **143**.[118] In the above case a catalyzed cationic rearrangement of **148** to **144** was proposed. None of the postulated intermediates was isolated in the rearrangement of **143**, but in separate experiments it was found that both **146** and **148** underwent a facile $AlCl_3$-catalyzed rearrangement to **144** (67% and ca. 85%, respectively). The following compounds related to **143** also rearranged in an analogous manner with $AlCl_3$: 4-OMe (74%), 4-Me (77%), 4-Cl (63%), 2,4-Cl_2 (27%), 2-F (30%). No reaction occurred with the strongly electronegative substituents, 4-NO_2 and 3-CF_3. (See below for Ag(I) and Hg(II) catalysis in these systems.)

Grignard reagents and/or MgX_2 appear to be catalysts for the Claisen rearrangement on the basis of lim-



ited data. The crotyl ether, **149**, on treatment with PhMgBr (Et_2O, reflux, 6.5 h) yielded as a minor product the ortho-substituted phenol, **150**, possessing an inverted allyl group (limited product characterization).[119]



149 **150**

Allyl phenyl ether rearranged to *o*-allylphenol upon treatment with MeMgI, in a process which apparently depends on the MgI_2 present as a component in the equilibrium, $2MeMgI \rightleftarrows Me_2Mg + MgI_2$.[120] This conclusion was based on the fact that the rearrangement rate was first order in added MgI_2. The results here were complicated by the fact that the Claisen rearrangement was not the focus of the study; the Grignard reagent was consumed by the rearrangement product, and the efficacy of MgI_2 by itself was not investigated.

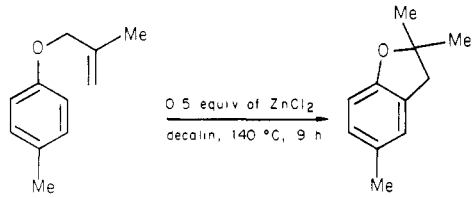
2. Derivatives of Group 4A and 5A Elements

Aside from a brief report that the efficacy of $SbCl_5$ as a catalyst appeared to be comparable to that of BCl_3,[76] to be mentioned here is the $SnCl_4$-catalyzed rearrangement of the deuterium-labeled allyl tolyl ether, **136** (see above).[113a] Reaction with 1 equiv of $SnCl_4$ in decalin at 120 °C for 3.5 h gave in 53% yield a mixture containing 61% of the ortho Claisen product, **151**, as

well as 30% of the product of subsequent cyclization, **152**.

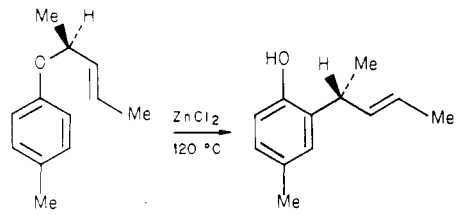
3. Derivatives of Transition Elements

Among the transition-metal derivatives employed as catalysts, $ZnCl_2$ has been the most thoroughly studied, although rate accelerations are modest and the temperature requirements approach those of uncatalyzed rearrangements. The operation of a [3,3] process has been established in some cases, including the deuterated substrate, **136** (see above), which, upon treatment with 1 equiv of $ZnCl_2$ in decalin at 120 °C for 7 h, yielded (32%) a mixture containing **151** (78%) and **152** (12%); the thermal reaction occurred at 180 °C.[113a] In the rearrangement of **153**, the observed product, **154** (98%), was one derived from cyclization of the first-formed intermediate, whereas the thermal reaction (220 °C, decalin, 19 h, 66%) gave the usual ortho rearrangement product.[121] Chirality transfer in the same suprafacial



153 154

sense as that of the thermal rearrangement was seen in the $ZnCl_2$-catalyzed conversion (0.5 equiv, decalin, 120 °C, 6 h, 36%) of **155** to **156**, although racemization to the extent of 70% accompanied the formation of the product.[122] This was attributed to competing ionic and

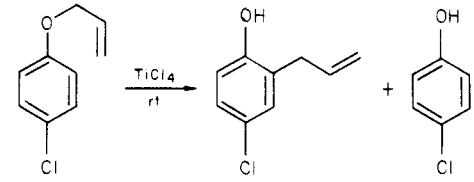


155 156

[3,3] processes, consistent with the appearance of substantial amounts of 2,6-dipentenylated product and partial racemization of starting material.

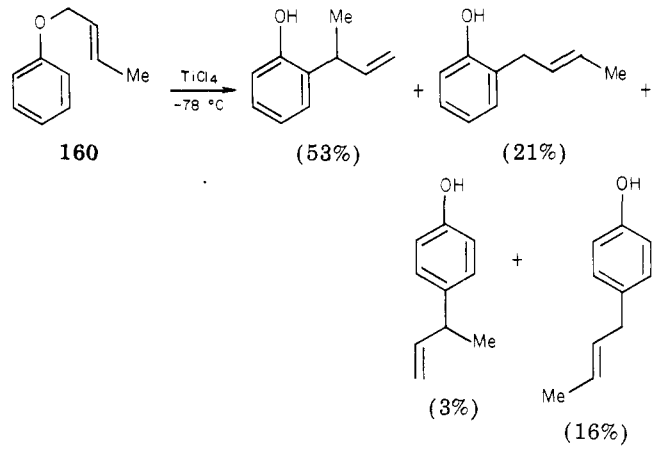
In a study of substituent effects on the rate of $ZnCl_2$-catalyzed rearrangements of ortho- and para-substituted allyl phenyl ethers, electron-withdrawing groups in the para position decreased the reaction rate,[123] consistent with a process similar to that depicted in Scheme VIII. Relative rates of para derivatives were (160 °C): MeO > Me > H > *t*-Bu > Cl > CHO = COMe > NO_2. The order in the ortho series was quite different, with *tert*-butyl the slowest and carbonyl-containing groups among the fastest: MeO > CO_2Me > COMe > Me > CHO > H > Cl > NO_2 > *t*-Bu. Apparently coordination of $ZnCl_2$ to the ether oxygen of the substrate is hindered by bulky ortho substituents and promoted by additional coordination to carbonyl groups at that position.

Titanium tetrachloride appears to have limited utility as a catalyst on the basis of available data. Yields can be high with substrates possessing no alkyl groups in the allylic moiety, and the reaction is usually run in the presence of PhN=C(Me)$OSiMe_3$ to scavenge HCl, which otherwise can add to the double bond of the products. Allyl *p*-chlorophenyl ether (**157**) gave the ortho Claisen product, **158**, in 83% yield along with 10% of cleavage phenol, **159** (2 equiv of $TiCl_4$, 1 equiv of PhN=C(Me)$OSiMe_3$, CH_2Cl_2, rt, 15 h, then H_2O).[124a]



157 158 159

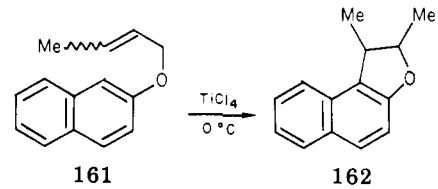
Other substrates that rearranged under similar conditions were: allyl phenyl ether (88%), *p*-Me (95%), *m*-Me (50% ortho product and 29% para product), and 2,4-Cl_2 (36% + 30% cleavage phenol). As was the case with BCl_3 catalysis, electron-withdrawing substituents in the ring promoted the formation of cleavage phenols. Intermolecular processes predominated, even at dry ice temperature, with alkyl-substituted allyl groups, leading to ortho and para products with inverted as well as noninverted allylic units (cf. **160**, 1.5 equiv of $TiCl_4$, 1 equiv of PhN=C(Me)$OSiMe_3$, CH_2Cl_2, −78 °C, 10 min, then H_2O).[124a] However, crotyl 2-naphthyl ether, **161**,



160 (53%) (21%)

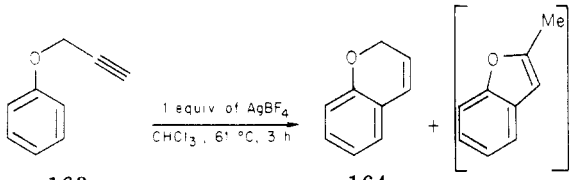
(3%) (16%)

rearranged with $TiCl_4$ (1.5 equiv, CH_2Cl_2, 0 °C, 0.5 h) to **162** (54%), derived from cyclization of the initial Claisen product.[124b] Crotyl 1-naphthyl ether and the allyl naphthyl ethers rearranged in a similar fashion, as did β-bromoallyl 1-naphthyl and 2-naphthyl ethers, in which case the cyclization product contained a double bond from loss of HBr.



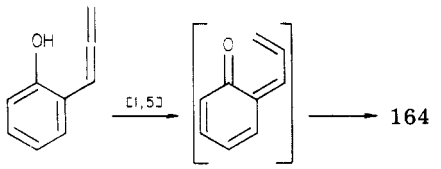
161 162

Silver tetrafluoroborate and trifluoroacetate catalyze the rearrangement of propargyl aryl ethers with yields that are generally only poor to fair because of decomposition of rearrangement products by the catalyst.[125] Propargyl phenyl ether, **163**, rearranged catalytically in chloroform in about 49% yield to 2*H*-chromene, **164**, the same product as that of the thermal rearrangement (190 °C, *o*-dichlorobenzene, half-life = 21 h, 66%[126]). The product composition was solvent dependent; with 0.8 equiv $AgBF_4$ in benzene at 80 °C for 48 h, there was



163 164 165

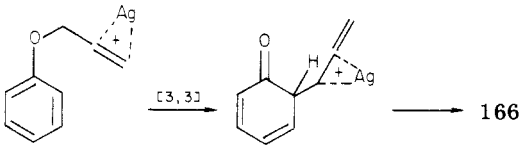
obtained in 48% combined yield a mixture of 25% **164** and 75% of 2-methylbenzofuran (**165**). (However, 2*H*-chromene was the only product of a very slow catalyzed reaction in benzene at room temperature, half-life = 24 days.) 2-Allenylphenol (**166**) is the logical intermediate in these reactions; it yields only 2*H*-chromene in a slow thermal reaction in chloroform or benzene (half-life = 18 h at room temperature), presumably by a [1,5] hydrogen shift followed by cyclization.[127] The presence



166

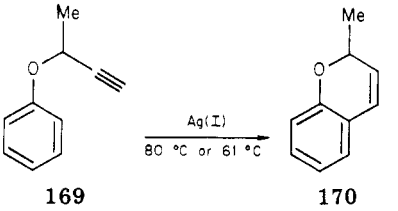
of 0.8 equiv of $AgBF_4$ in $CHCl_3$ catalyzed the **166** → **164** conversion by a factor of about 2. The same rate acceleration was observed with $AgBF_4$ in benzene, but in the latter solvent **166** gave a mixture of **164** (25%) and **165** (75%). The origin of the solvent effect in this system is unclear.[128] Compound **166** is formally a β-allenic alcohol, other examples of which undergo Ag(I)-catalyzed cyclization to six-membered rings.[129]

The mechanism of catalysis by silver ion was formulated as involving initial coordination to the triple bond rather than the oxygen atom or the benzene ring, in view of the inertness of allyl phenyl ether to this catalyst (however, see below, **178** → **179**). For the same reason, the Ag(I) was assumed to complex with those p orbitals not participating in the [3,3] change. Thus, for the reaction of **163**, the π complex, **167**, (in equilibrium with starting materials) undergoes charge-accelerated [3,3] rearrangement to **168**, yielding **166** after enolization and decomplexation. Silver(I)-catalyzed cyclization of **166** would then lead to **164** or **165**.

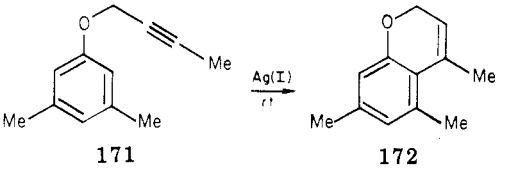


167 168

Catalyzed rearrangement of **169** gave only 25–27% **170** in benzene (80 °C, 48 h) or chloroform (61 °C, 50 h); compound **171** yielded 47% of **172** in chloroform at room temperature (1 h). Higher yields (66%) were observed in the rearrangement of **173** with 2.6–2.8 equiv of $AgBF_4$ in benzene (80 °C) or chloroform (61 °C). In this case, the reaction proceeded only to the allenyl enone, **174**.[130] The use of Ag(I) in the rearrangement of **175** (0.4 equiv of CF_3CO_2Ag, $CHCl_3$, 61 °C, 4 h) permitted the isolation in 92% yield of **176**, which was not accessible in the thermal rearrangement of **175** (ca. 150 °C) because **176** rearranges further under those conditions. Rate enhancements in the catalyzed reactions were estimated to range from 10^3 (for **173** at 80



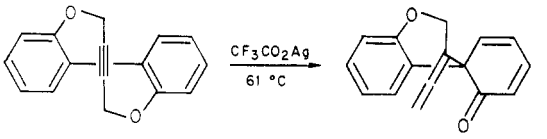
169 170



171 172

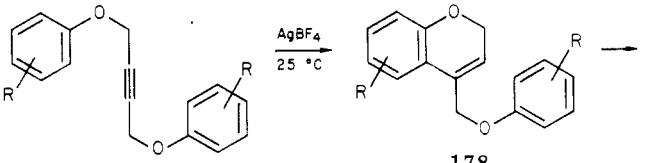
173 174

°C) to 10^5 (for **171** at room temperature).

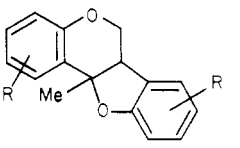


175 176

Catalysis by Ag(I) was also observed in the rearrangement of **177** (R = 4-Me) to **178** or **179**, depending on reaction time (0.5–1 equiv of $AgBF_4$, CH_2Cl_2, 25 °C).[117] At the end of 1 h, the expected 2*H*-chromene derivative, **178** (R = 4-Me), was isolated in 55% yield; after 24 h, the reaction gave 87% of **179** (R = 4-Me).



177 178

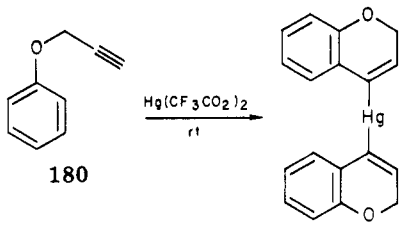


179

The conversion of **178** to **179** was formulated as a Claisen rearrangement followed by cyclization (cf. **146** → **147** → **148**). If this is the case, Ag(I) is also a catalyst for allylic as well as propargylic aryl ethers, in spite of the lack of catalyzed rearrangement with allyl phenyl ether itself,[125] and contrary to the assumption made in formulating the mechanism for catalyzed propargyl phenyl ether rearrangement (**167** → **168**). Other catalyzed rearrangements examined were **177** (R = 4-OMe) → **179** (1 h, 72%, or 24 h, 61%) and **177** (R = 4-Cl) → **178** (24 h, 69%). No reaction occurred with R = 2-OMe. Aluminum chloride was also a catalyst (see above) as was mercuric trifluoroacetate in some cases (see below). Ferric chloride and boron trifluoride were less effective, zinc chloride gave no reaction, and antimony pentafluoride caused extensive decomposition.

Propargylic aryl ethers are also susceptible to catalysis by Hg(II), including **177** (R = 4-OMe), which re-

arranged to 178 with mercuric trifluoroacetate; no reaction occurred with the other substituents reported above for 177.[131] If the alkyne rearrangement terminus is unsubstituted, the reaction takes a more complex course to give mercury derivatives of rearranged substrates; cf. 180 → 181 (75%, $Hg(CF_3CO_2)_2$, CH_2Cl_2, rt, 2 h, then $NaBH_4/OH^-$).[132] The following substituted

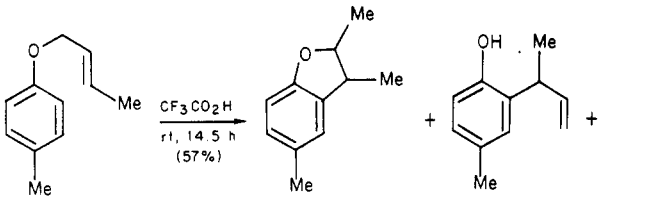


180 181

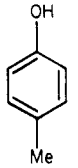
derivatives gave analogous reactions: 4-Me (83%), 4-OMe (97%), and 2-Cl (54%). With 4-Cl and 2,4-Cl_2, the reaction yielded instead the corresponding 2-propanone derived from hydration of the triple bond. The bis(acetylide), $Hg(C{\equiv}CCH_2OPh)_2$, rearranged smoothly to 181 under similar conditions, suggesting that bis(acetylides) were intermediates in these rearrangements. The mechanism for Hg(II) catalysis of the initial [3,3] process was seen as analogous to that suggested for Ag(I) (cf. 167 → 168), with further involvement of Hg(II) assumed in the cyclization of the allenylphenol intermediate.[133] A process involving Friedel–Crafts cyclization catalyzed by Hg(II) was ruled less probable on the basis of experiments which suggested that a five-membered ring would then be the preferred product.

C. Catalysis by Brønsted Acids

Trifluoroacetic acid substantially accelerates the Claisen rearrangement of allyl aryl ethers, but the initially formed allylphenols generally react further under the acidic reaction conditions. The operation of a [3,3] process was confirmed in the catalyzed rearrangement of crotyl tolyl ether (182) in CF_3CO_2H solvent.[134a] It



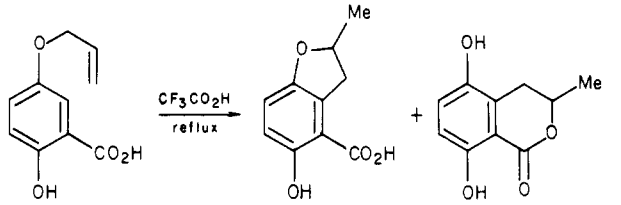
182 183 (69%) 184 (8%)



(8%)

was shown that the principal product, coumaran 183, was derived from cyclization of the Claisen rearrangement product, 184. Under similar conditions (rt, 23 h), allyl phenyl ether gave in 77% yield a mixture containing 28.5% of *o*-allylphenol, 53% 2-methylcoumaran, 8% phenol, 6.5% other products, and 5% unrearranged starting material. These reactions were seen as further examples of charge-accelerated [3,3]-sigmatropic rearrangements (cf. Scheme VIII), and it was noted that the substantial rate acceleration of Claisen rearrangements in phenolic solvents might be a consequence of such a process (e.g., 100-fold acceleration in *p*-chlorophenol vs. tetradecane for rearrangement of allyl tolyl ether at 170 °C[135]).

A similar catalyzed reaction (CF_3CO_2H, ca. 75 °C, 21 h) occurred with the benzoic acid derivative, 185, which yielded 186 (25%) as well as a second cyclization product, 187 (63%), derived from addition of the acid group to the double bond of the Claisen-rearranged intermediate.[134b] The methyl, phenyl, benzyl, isopropyl, and allyl esters of 185 also gave analogous product mixtures in 30–55% combined yields.



185 186 187

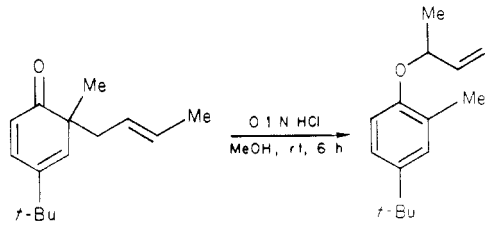
Svanholm and Parker[136] were actually the first to note catalysis by CF_3CO_2H, but their focus was on reaction kinetics, and their limited product descriptions are in some respects inconsistent with the results described above. They observed that the highest yields of 2-allylphenols were obtained at low conversions,[136b] but the complicating side reaction at higher conversion was claimed to be addition of CF_3CO_2H to the double bond of the Claisen rearrangement product, a process not noted by the other workers.[137]

Among the kinetic effects seen by Svanholm and Parker were a rate acceleration in CF_3CO_2H of about 10^5 (60 °C, compared to the thermal reaction in $EtOCH_2CH_2OCH_2CH_2OH$ solvent), relatively slower reaction with electron-withdrawing substituents (allyl *p*-nitrophenyl ether was immeasurably slow), rate increases upon addition of lithium perchlorate, and a rate maximum in water-containing CF_3CO_2H at 5% H_2O. From solvent deuterium isotope effects (k_H/k_D = 1.1–1.4), it was inferred that CF_3CO_2H could be involved in two ways, depending on conditions: equilibration with substrate prior to the rate-limiting step, and/or protonation concerted with rearrangement.

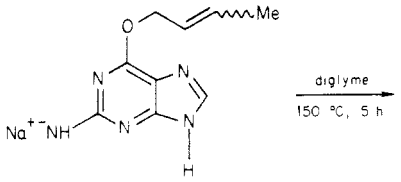
The use of H_2SO_4 as a catalyst leads to product mixtures analogous to that shown above for 182. Allyl *p*-tolyl ether in 69% H_2SO_4 for 6 h (T = ?) yielded (ca. 60%) a mixture containing 8% of 2-allyl-4-methylphenol, 81% of the cyclization product, 2,5-dimethylcoumaran, and 7% of *p*-cresol.[113d] The retro-Claisen rearrangement has also been shown to be acid-catalyzed, as seen in the conversion of ortho dienone 188 to a mixture containing 30% of 189 along with cleavage phenol and other products.[75b] Compound 189 appears to have been formed by an intramolecular process and is also the product of thermal rearrangement of 188 at 120 °C.

D. Catalysis by Base

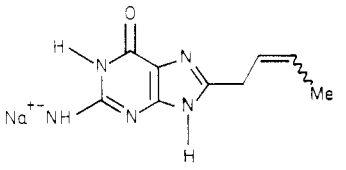
A moderate rate acceleration in the anion as compared to the neutral substrate was seen in the rearrangement of the guanine derivative, 190, to 191 (73%).[138] This and similar reactions were interpreted



188 189



190

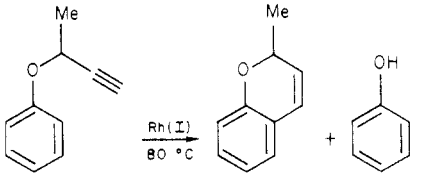


191

as potentially involving a Claisen rearrangement followed by a second [3,3]-sigmatropic shift and tautomerization. An intermolecular process was not strictly ruled out, but the corresponding *O*-methyl and *O*-benzyl derivatives were stable to the reaction conditions.

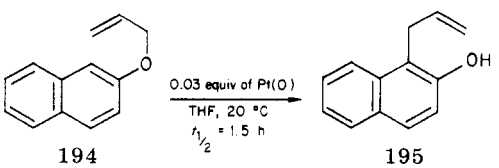
E. Other Catalysts

In this category are included Rh(I) and Pt(0) complexes and silica. Bis(μ-chloro)dirhodium(I) tetracarbonyl catalyzed the transformation in low yield of α-methylpropargyl phenyl ether, **192**, to the rearrangement–cyclization product, **193** (0.02 equiv of Rh(I), PhH, 80 °C, 6 h, 25%).[125] The principal product was



192 193

phenol (53%). A catalyst prepared from equimolar amounts of $[(CH_2{=}CHCH_2)(PPh_3)_2Pt]^+Cl^-$ and sodium acetylacetonate, which presumably generated an active Pt(0) species, $Pt(PPh_3)_2$, facilitated in high yield the conversion of some allyl aryl ethers to Claisen rearrangement products (cf. **194** → **195**, >95%).[139] A [3,3]



194 195

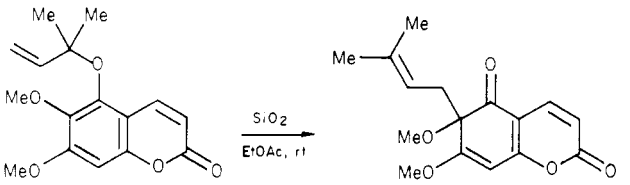
process may be involved in some cases, but diallyl derivatives could be formed in significant amounts, and crotyl phenyl ether under similar conditions yielded only a mixture of ethers derived from allylic isomerization. The reaction was presumed to occur with heterolytic cleavage to aryloxide anions and allylplatinum cations (see below, **230** → **231**).

TABLE VIII. Catalyzed Rearrangement of 200

R_1	R_2	conditions	yield, %	E/Z
n-Bu	Me	*a*, 0.25 h	77	52/48[c]
Ph	H	*a*, 0.5 h	67	*E* only
H	Ph	*a*, 0.25 h	86	
H	Ph	*b*, 0.25 h	87	

[a] Et_2AlSPh (2.5 equiv) in $ClCH_2CH_2Cl$, 25 °C. [b] Et_2AlCl/PPh_3 (2 equiv) in $ClCH_2CH_2Cl$, 25 °C. [c] Thermal reaction (180 °C), >95% *E*.

Silica in the form of silica gel or diatomaceous earth (Celite) effected the clean, high-yield conversion of **196** to **197** at room temperature.[140] (Compound **196** was stable in refluxing ethyl acetate.) Rearrangement of the corresponding dimethylpropargyl derivative was not catalyzed by silica gel.



196 197

IV. Aliphatic Claisen Rearrangement

A. Thermal Reactions[1a,2]

The uncatalyzed [3,3] rearrangement of allyl vinyl ethers, **198** → **199**, occurs at 150–200 °C for unsubstituted or alkyl-substituted acyclic substrates; substituents can bring the rearrangement temperatures down to ambient. Unsaturated, electron-withdrawing sub-

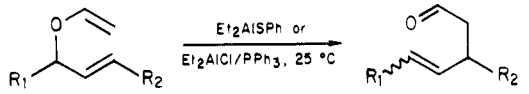
198 199

stituents appear (on the basis of limited data) to have the same activating effects as observed in the Cope rearrangement,[8] and especially facile reactions occur with electron-donor substituents such as dialkylamino, alkoxy, or trimethylsiloxy at C-2.

The rearrangements are highly exothermic; allyl vinyl ether exhibits the secondary kinetic deuterium isotope effects expected for a concerted reaction with an early transition state.[141] Chair selectivity in unhindered cases is slightly lower than in the Cope rearrangement (95–96% chair, 4–5% boat for 2-butenyl 1-propenyl ethers at 145–190 °C),[9] and steric constraints can lead to reactions with boat topology.[142]

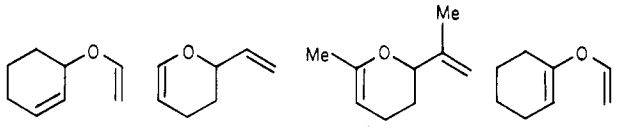
B. Catalysis by Alkylaluminum Derivatives

Catalysis of the aliphatic Claisen rearrangement has received relatively little scrutiny. The most effective and thoroughly examined catalysts are alkylaluminum derivatives, especially Et_2AlSPh and Et_2AlCl/PPh_3.[143] For example, the vinyl heptenyl ether, **200** (R_1 = *n*-Bu, R_2 = H), rearranged within 15 min at 25 °C using Et_2AlSPh (2.5 equiv) in 1,2-dichloroethane to aldehyde **201** (R_1 = *n*-Bu, R_2 = H) (84%, E/Z = 39/61); using Et_2AlCl/PPh_3 (2 equiv) under the same conditions, the yield was 81%, E/Z = 43/57. The thermal rearrangement (180 °C, 20 min) yielded the aldehyde with >95% *E* selectivity. Table VIII gives the results with



200 201

other substituents; the cyclic derivatives, **202–205**, also rearranged under similar conditions. The results provide no information about chair/boat selectivity in the catalyzed reactions; compounds **203** and **204** are sterically constrained to react with boatlike topology. Rate



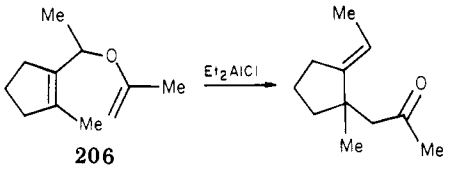
202 203 204 205

enhancements appear to be substantial with these catalysts, particulary in systems such as **203** and **204**, where the thermal reactions are carried out at about 400 °C.[144] No comment about mechanism was offered by the authors, but a charge-accelerated process analogous to that of the aromatic Claisen rearrangement can be proposed (cf. Scheme VIII).

A catalyzed rearrangement also occurred with $(i\text{-Bu})_3Al$, but the carbonyl group of the rearrangement product became reduced to the alcohol (workup with dilute HCl). The yields of alcohols derived from **200–205** ranged from 78 to 97%. The use of $(i\text{-Bu})_2AlH$ also led to reduction products, whereas Me_3Al formed alcohols derived from addition of methyl. In other examples, alkenyl or alkynyl groups on the aluminum added in preference to alkyl.

On the basis of preliminary trials, MeMgI appeared to be a satisfactory catalyst (with subsequent addition to the carbonyl), whereas BF_3, $SnCl_4$ and $ZnBr_2$ gave complex product mixtures.[143]

Catalysis by Et_2AlCl has also been reported for the conversion of **206** to **207** (no details; thermal reaction at 220–320 °C; $AlCl_3$ was not satisfactory).[145] A cata-



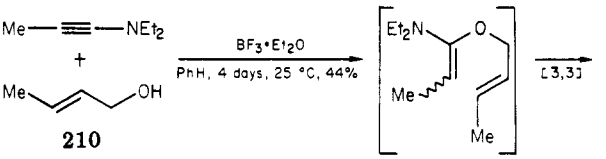
206 207

lyzed **206** → **207** transformation was also presumed to occur in the one-pot conversion of allylic ester, **208**, to the 1,5-diene, **209**, using the Tebbe reagent, $(\eta^5\text{-}C_5H_5)_2TiCH_2AlClMe_2$ (3 equiv, pyridine, toluene–THF, 28 °C, 12 h, then 15% NaOH; 75%).[145] Wittig-like reactions involving the Tebbe reagent with esters or ketones are well-known,[146] so the overall sequence, **208** → **206** → **207** → **209**, is very likely involved here.

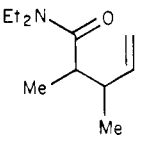
208 209

C. Potential Catalysis of in Situ Claisen Rearrangements

Catalysis of the aliphatic Claisen rearrangement by other Lewis acids or by Brønsted acids has not been systematically investigated. Various in situ methods[1a,2] involve these catalysts, but it is usually not known if the catalyst influences the [3,3] step. For example, the ynamine–Claisen procedure[147] can be carried out without a catalyst in refluxing benzene or toluene, or near room temperature in the presence of trace quantities of $BF_3{\cdot}OEt_2$ (cf. **210** → **211** → **212**).[148] Because inter-

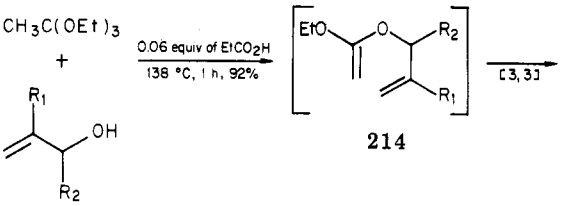


210 211

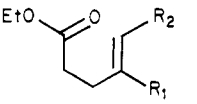


212

mediate Claisen substrates such as **211** have apparently not been isolated using the above or other[149] in situ procedures, their thermal rearrangement characteristics are unknown and the function of BF_3 in the Claisen step is uncertain.[150] The same is true for the ortho ester procedure (cf. **213** → **214** → **215**; R_1 = Me, R_2 = $CH_2CH_2C(Me)=CH_2$)[151] in which a Brønsted acid catalyst could conceivably be involved in the [3,3] step.[152] π-Donor substituents such as alkoxy, di-



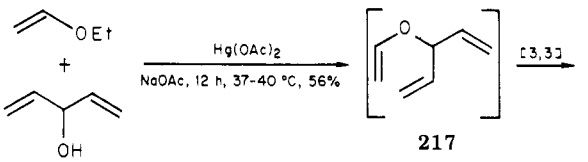
213 214



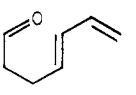
215

alkylamino, and trimethylsiloxy at the 2-position are predicted to accelerate the Claisen rearrangement,[8] in agreement with the observed facile (near room temperature) rearrangements of trialkylsiloxy derivatives in a variation of the enolate Claisen rearrangement.[153] (Also see ref 150.)

Potential in situ catalysis by Hg(II) is illustrated in a transetherification procedure involving ethyl vinyl ether and divinylmethanol (**216**). The intermediate



216 217



218

Claisen substrate, **217**, rearranged to **218** under the very mild reaction conditions, and could be detected only at

TABLE IX. Anionic Claisen Rearrangements

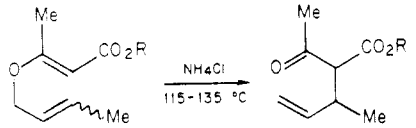
substrate (temp, time)	product (yield)
CH_2=C(CH_2SO_2Ph)OCH_2CH=CH_2 (50 °C, 4 h)	$PhSO_2CH_2COCH_2CH_2CH$=CH_2 (78%)
$PhSO_2CH$=$CMeOCH_2CH$=CH_2 (50 °C, 4 h)	$PhSO_2CH_2COCH_2CH_2CH$=CH_2 (76%)
CH_2=$CH(CH_2SO_2Ph)OCH_2CHMe$=CH_2 (50–62 °C, 4.5–25 h)	$PhSO_2CH_2COCH_2CH_2CMe$=CH_2 (71%)
$PhSO_2CH$=$CMeOCHMeCH$=CH_2 (50 °C, 0.5 h) (20 °C, 4 h)	(*E*)-$PhSO_2CH_2COCH_2CH_2CH$=$CHMe$[a] (89%) (82%)
Me_2C=$C(CH_2SO_2Ar)OCH_2CH$=CH_2[b] (20 °C, 0.25 h)	$ArSO_2CH_2COCMe_2CH_2CH$=CH_2[b] (91%)
(*E*)-CH_2=$C(CH_2SO_2Ph)OCH_2CH$=$CHPh$ (20 °C, 0.5 h)	no [3,3] product[c]

[a] Small amounts of $MeCOCH(SO_2Ph)CH_2CH$=$CHMe$ also formed. [b] Ar = *p*-MeC_6H_4. [c] The reaction took a totally different course.

–10 °C, at which temperature it apparently rearranged slowly.[154] It is questionable that **217** could rearrange thermally at such low temperatures, although π-acceptor substituents at the α-position of the allyl group are known to accelerate the rearrangements.[155] Numerous other examples of Hg(II)-catalyzed transetherifications are known in which the allyl vinyl ether was isolated without complications by in situ rearrangements.[156]

D. Catalysis by NH_4Cl

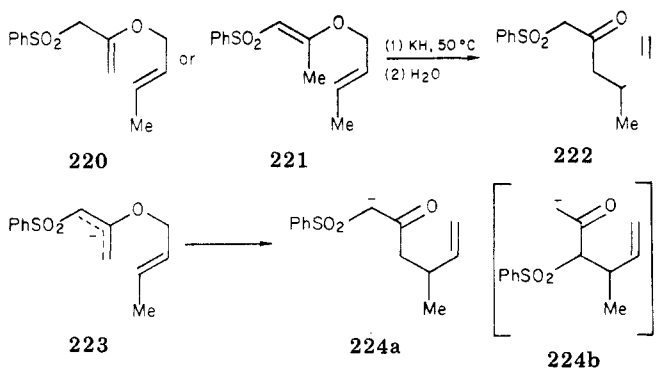
Solid ammonium chloride, in an apparently heterogeneous process, caused a small increase in the rearrangement rate of **219** (R = CH_2CH=CH_2) and other substrates.[157] The catalyst may function as a proton donor under the reaction conditions.



219

E. Catalysis by Base (Anionic Claisen Rearrangement)[158]

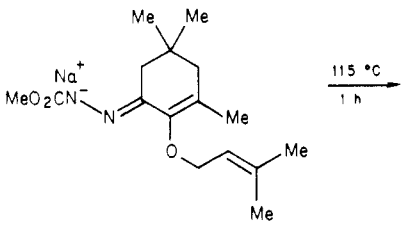
Significant rate enhancements have been reported in an anionic version of the aliphatic Claisen rearrangement involving benzenesulfonyl substituents.[159] Both **220** and **221** yielded **222** (70%) under mild conditions upon treatment with 1.5 equiv of KH in the presence of 18-crown-6 (HMPT/THF, 3/1, 50 °C, 5 h, then H_2O). The reaction very likely involved carbanion **223**,



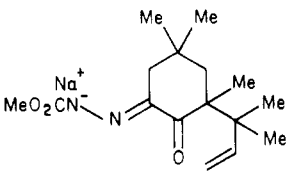
220 **221** **222** **223** **224a** **224b**

which rearranged to **224a**, the more stable of the two possible [3,3] products (cf. **224b**). The [3,3]-sigmatropic nature of the process is confirmed in these transformations. Analogous rearrangements under similar conditions were observed with substrates given in Table IX. Thermal reactions in the absence of base were not reported, but typical temperatures would be expected for these cases. No conclusions about transition-state geometries can be drawn from the data. The rate accelerations were seen as consistent with the expectation that π-donors at the 2-position would lower the activation energy for rearrangement (cf. **211**, **214**).[8] Methyl groups on the vinyl portion of the substrate accelerated the anionic rearrangement.

In a preliminary report, rate acceleration relative to the neutral species was seen in the [3,3] rearrangement of anion **225** to **226** in *N*-methylmorpholine (85%).[160]



225

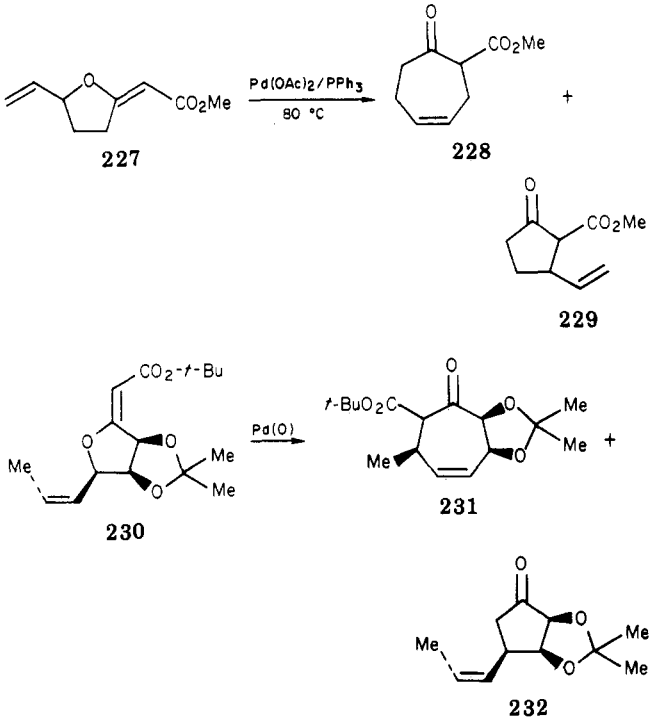


226

F. Catalysis by Pd(II), Pd(0), and Pt(0) Complexes

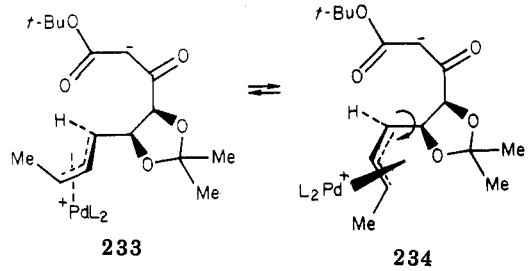
Complexes of Pd(II), Pd(0), and Pt(0) convert certain allyl vinyl ethers into substrates that are formally Claisen rearrangement products, but the generality of the reactions has not been investigated and side reactions can be significant or predominant. Compound **227** rearranged with 0.05–0.1 equiv of $Pd(OAc)_2/PPh_3$ in benzene (reflux, 40 min) to a mixture containing 55% of the [3,3] product, cycloheptenone **228**, and 45% of the [1,3] product, cyclopentanone **229**.[161] In refluxing acetonitrile (1 h) the **228**/**229** ratio was 13/87. The thermal reaction gave exclusively **228** at 195 °C in *N*-methylpyrrolidone; generation of the cis double bond of **228** requires rearrangement via a chairlike transition state;[162] the boat would give a trans cycloheptenone.

The analogous rearrangement was seen by using substrate **230** with Pd(0) complexes.[163] Both **231** (35%)



227 228 229 230 231 232

and **232** (50%) were found with $Pd(PPh_3)_4$ (0.06 equiv, Me_2SO, 60 °C), whereas the sterically less demanding bis[1,2-bis(diphenylphosphino)ethane]palladium at 100 °C gave only **231** in 64% yield (the *Z,Z* isomer of **230** was used in the latter case). The stereochemistry of **231** is that expected from Claisen rearrangement with chair topology, but a process of that sort is prohibited by the congestion created by the acetonide unit, and something quite different must be occurring. The proposed mechanism involves cleavage by Pd(0) to intermediate **233** (L = ligand), possessing a π-allylpalladium unit and a highly delocalized enolate. Isomerization through

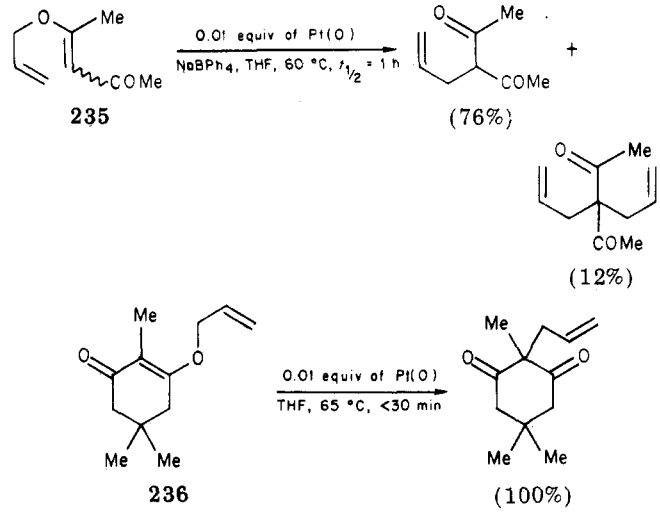


233 234

σ-bonded complexes can eventually lead to **234**, which, following 180° rotation about the C–C bond indicated, can collapse to **231** with backside displacement of palladium. The overall transformation of **230** to **231** by this route involves, in effect, cis → trans isomerization and antarafacial reaction at the allylic center.

Cyclopentanone **232** was proposed to form by collapse of **233** with overall retention. (Decarboxylation also occurred here.) The ratio of five- to seven-membered rings in this and analogous reactions was sensitive to solvent and to steric demands of the catalyst in a way that could be relatively easily rationalized and controlled, and the reaction was seen as a useful approach to the synthesis of these ring systems from readily available starting materials.

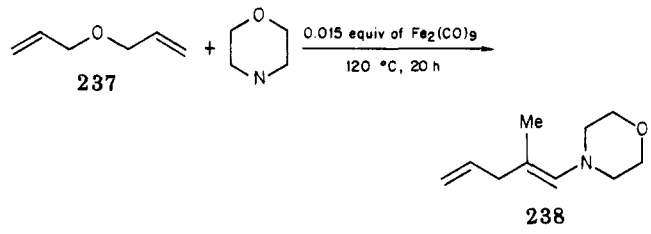
It should be noted that **227** and **230** represent vinylogous esters, which would be readily cleaved compared to typical allyl vinyl ethers, and the potential for catalysis by Pd(0) and Pd(II) in simpler systems is uncertain.[164] In another study involving vinylogous esters **235** and **236**, an overall catalyzed rearrangement was observed with a Pt(0) complex (see above, **194** → **195**).[139] The [3,3]-sigmatropic nature of the reaction was not established by the results, and the incursion of intermolecular processes is obvious from the diallylated side product with **235**. A mechanism analogous to that given above for **230** was suggested.



235 (76%) (12%) 236 (100%)

G. Potential Catalysis by $Fe_2(CO)_9$

Catalysis of a Claisen step by $Fe_2(CO)_9$ in the overall conversion of diallyl ether (**237**) to enamine **238** is possible but not probable.[165] The reaction very likely

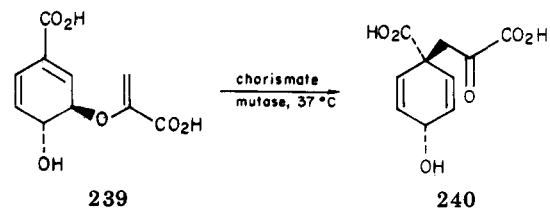


237 238

involves double-bond isomerization followed by Claisen rearrangement to $CH_2{=}CHCH_2CH(Me)CHO$ and reaction with morpholine. In analogous reactions, diallyl ethers are converted to γ,δ-unsaturated carbonyl compounds by using $RuCl_2(PPh_3)_3$[166] or $H_4Ru_4(CO)_8$[(−)-DIOP]$_2$;[167] in the latter case it was shown that the Claisen step is not accelerated by the catalyst.

H. Enzyme Catalysis

In what is claimed to be the only example of an enzyme-catalyzed Claisen rearrangement,[168] chorismic acid (**239**) was converted to prephenic acid (**240**) by chorismate mutase.[169a] At pH 7.5 and 37 °C, the enzyme



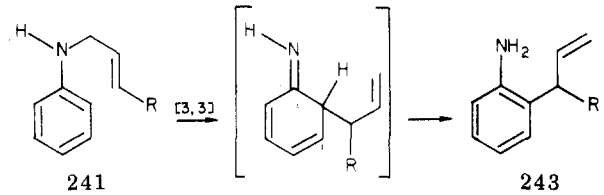
239 240

accelerated the rearrangement by a factor of about 2×10^6. Related compounds that had the potential for Claisen rearrangement were not affected by the enzyme. The reaction occurs with chair topology.[169b]

V. Aromatic Amino-Claisen Rearrangement

A. Thermal Reactions

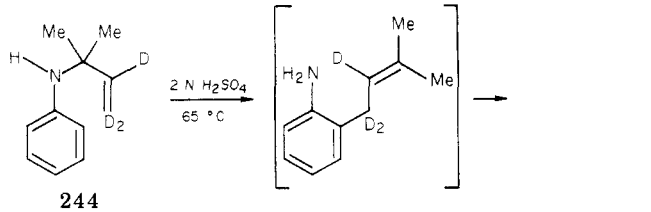
The [3,3]-sigmatropic rearrangement of *N*-allyl-*N*-arylamines, known as the amino-Claisen rearrangement (cf. **241** → **242** → **243**),[170] has until recently received much less attention than its oxygen counterpart, probably because of the more drastic conditions required and the concomitant tendency toward side reactions. Jolidon and Hansen[172] convincingly characterized the thermal reaction as a [3,3] process similar to the Claisen and Cope rearrangements, on the basis of ortho product formation, inversion of allyl groups, strongly negative activation entropies, activation enthalpies that were low with respect to bond dissociation energies, secondary kinetic deuterium isotope effects,[172b] and relatively small solvent effects. The same indirect probes of reaction topology as applied to the aromatic Claisen rearrangement suggested a preferential chairlike transition state for the amino analogue (see below). Thermal rearrangements occurred at 200–350 °C, with cleavage to arylamines sometimes a significant side reaction. (With *N*-allyaniline itself, cleavage and [3,3] rearrangement occurred at about equal rates at 310–340 °C.)



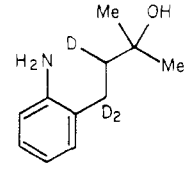
241 242 243

B. Brønsted Acid Catalysis

Catalysis is especially useful in these systems[171] and often permits the occurrence of a reaction that is thermally inaccessible. Brønsted acid catalysis is the most thoroughly investigated, largely due to the exemplary systematic study by Jolidon and Hansen,[172] who observed rate accelerations by factors of 10^5–10^7 (see Table X) with protonated amines compared to neutral substrates in 0.1–2 N H_2SO_4 or 2/1/1 (v/v) CF_3CO_2H/H_2O/dioxane (TWD). Among the examples studied, substrates bearing an α,α-dimethylallyl group rearranged the most readily (60–75 °C), although their rearrangement products were prone to add water, except in 0.1 N H_2SO_4 or TWD. For example, the deuterated substrate, **244**, in 2 N H_2SO_4 at 65 °C for 2 h yielded alcohol **245** (36%).[173] No cross products were

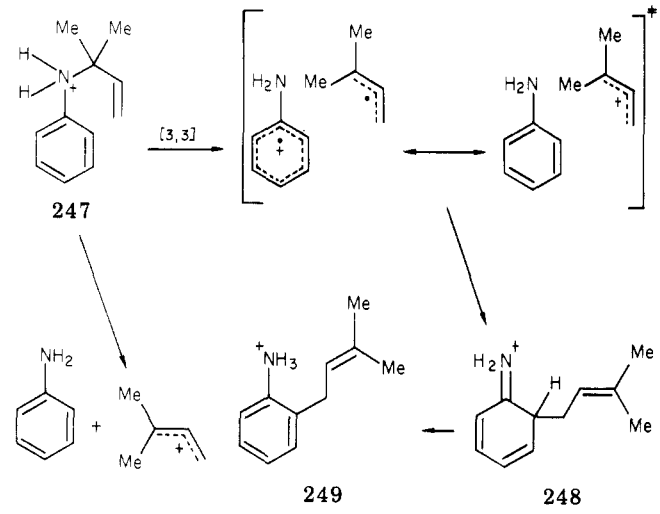


244

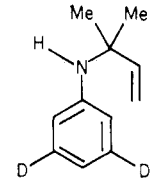


245

SCHEME IX



obtained when **244** was rearranged as a mixture with the dideuterated analogue, **246**, further confirming the [3,3] nature of the reaction. The relative rearrangement rates for a series of para-substituted derivatives in 2 N H_2SO_4 at 60 °C varied as follows: *p*-H (k_{rel} = 1), *p*-CH_3 (0.5), *p*-Cl (0.5), *p*-OCH_3 (0.2). Product yields with



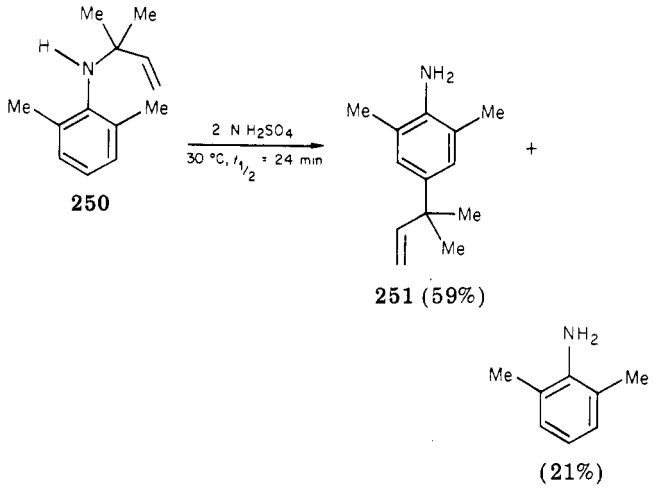
246

these derivatives in H_2SO_4 or TWD under various conditions ranged from 20 to 90% (not optimized); no para products could be detected. Cleavage was an insignificant side reaction in these systems except for *p*-CN, where it was the principal reaction.

Compound **244** exhibited an inverse secondary kinetic deuterium isotope effect in 2 N H_2SO_4 at 67.5 °C (k_H/k_D = 0.84 ± 0.08) comparable to that of its thermal rearrangement at 237.2 °C (k_H/k_D = 0.83 ± 0.11),[172b] indicative in both cases of appreciable bond formation between C-1 and C-6 in the rearrangement transition states. Activation parameters for the catalyzed reaction of undeuterated **244** in 2 N H_2SO_4 or TWD, respectively, were ΔH^*_{60} = 28.1 ± 7.8, 24.4 ± 3.4 kcal/mol, ΔS^*_{60} = +9 ± 23, −2 ± 10 eu. For the thermal reaction in 2-methyl-2-butanol, ΔH^*_{230} = 33.9 ± 2.8 kcal/mol, ΔS^*_{230} = −13 ± 6 eu.

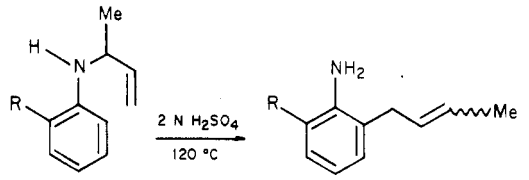
The reactions of the protonated substrates were interpreted as charge-accelerated rearrangements (**247** → **249**, Scheme IX; cf. Scheme VIII) with the lowered activation enthalpy a consequence of charge delocalization in the transition state as well as full inhibition of nitrogen lone pair delocalization in the ground state.[174] Quaternary ammonium salts related to **247** also undergo a facile [3,3] rearrangement.[175]

The para Claisen rearrangement of **250** to **251** represented a case where acid catalysis led to a fair yield of product that was inaccessible by the uncatalyzed route. (Thermal rearrangement of **250** gave a mixture containing cleavage product and *N*-(γ,γ-dimethylallyl)-2,6-dimethylaniline.) Slow chromatography of **250** on silica gel (benzene) also yielded **251** (quantitatively).



250 251 (59%) (21%)

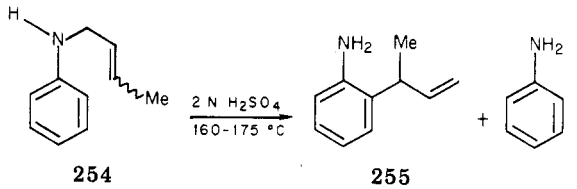
The second step in the reaction of **250**, Cope rearrangement in an intermediate analogous to **248**, is very likely also acid catalyzed (see above). The acid-catalyzed rearrangements of substrates with a single α-methyl group on the allyl unit (**252**, R = H, Me, Me_3C) required higher temperatures (reflux in 2 N H_2SO_4), showed less cleavage than the thermal reactions at 290–310 °C (<0.5% vs. 2–10%), and gave good yields of **253** without the complication of H_2O addition to the double bond; R = H (18 h, 40%), Me (18 h, 75%), Me_3C (20 min, 70%). The E/Z ratios in the catalyzed as well



252 253

as thermal reactions increased with increasing size of the ortho substituent, consistent with a chair transition state in both cases. For the catalyzed reactions at 120 °C, R = H (E/Z = 6.5), Me (12), Me_3C (>81); thermal reactions (291 °C, 2-methyl-2-butanol), R = H (E/Z = 4.9), Me (9.0), Me_3C (36). The thermal and catalyzed rearrangement rates increased in the order H < Me < Me_3C.

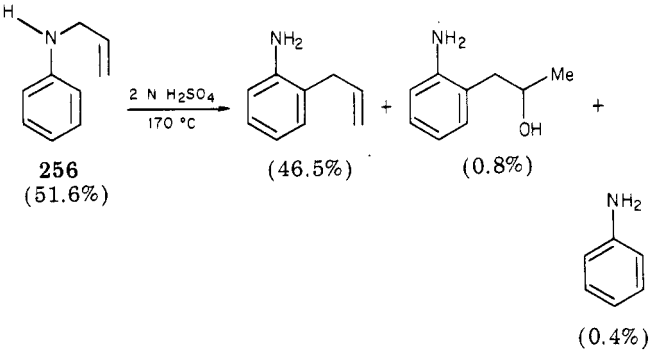
Acid-catalyzed rearrangement of the *N*-crotylanilines, **254** (E or Z), proceeded much more cleanly than the thermal reactions, giving product mixtures which contained about 70% **255** (29% isolated yield from Z-**254**) and less than 1.5% cleavage aniline. The presence of



254 255

a second methyl group at the γ-position, as in *N*-(γ,γ-dimethylallyl)aniline, was, however, sufficient to inhibit fully the [3,3] process to the advantage of cleavage (cf. Scheme IX) in both the thermal and acid-catalyzed reactions.

In the rearrangement of the parent *N*-allylaniline (**256**), cleavage was competitive with rearrangement in the thermal reaction (see above), but was insignificant in the acid-catalyzed reaction (150–170 °C). The reaction mixture composition at one half-life in 2 N H_2SO_4 (170 °C, 14 min) is given below. Roughly comparable results were observed in TWD. Inversion of the

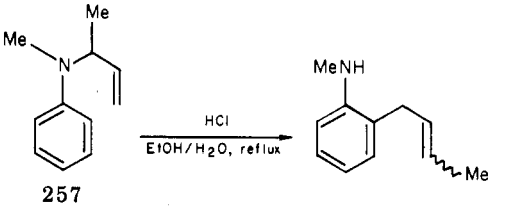


256 (51.6%) (46.5%) (0.8%) (0.4%)

allyl group was demonstrated with γ,γ-d_2-**256**, and a secondary kinetic deuterium isotope effect near unity (k_H/k_D = 0.98 ± 0.13 at 160 °C) was observed with β,γ,γ-d_3-**256**, comparable to the value for the thermal reaction (0.99 ± 0.08, 340 °C).[172b] In contrast to the other cases examined, formation of the new C–C bond in *N*-allylaniline rearrangement is apparently not far advanced in the transition states of either the thermal or acid-catalyzed reactions. *N*-Methyl substitution on **256** led to a product mixture containing 88% 2-allyl-*N*-methylaniline (2 N H_2SO_4, 165 °C, 1.5 h, 57% isolated yield).

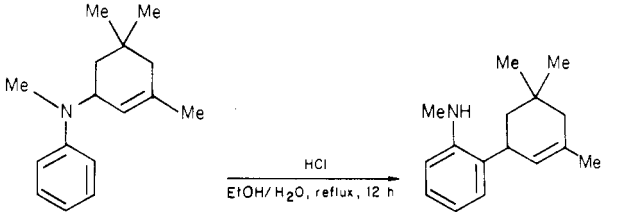
Table X summarizes activation parameters, relative rates and catalytic factors for systems examined by Jolidon and Hansen.

A high yield of [3,3] product was observed with *N*-methyl-*N*-(α-methylallyl)aniline (**257**) in a reaction medium composed of concentrated HCl in ethanol (reflux, 12 h, 90%).[176] Comparable results were ob-



257

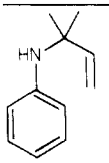
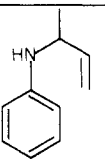
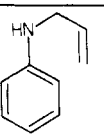
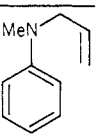
tained with the following ring-substituted derivatives under the same conditions; *p*-Me (95%), *p*-OMe (92%), *m*-Me (90%, mixture), *m*-OMe (80%, mixture); *N*-(α-methylallyl)indoline rearranged in 90% yield. The E/Z ratios were given as 90/10, with no details for individual cases. This reaction medium appears to give better yields than H_2SO_4 or TWD as reported above. As expected, **258** rearranged without inversion of the allyl group,[177] apparently by a cleavage process, but the high yield of ortho product and apparent absence of para product is puzzling. *N*-Crotyl substrates analogous to



258 (90%)

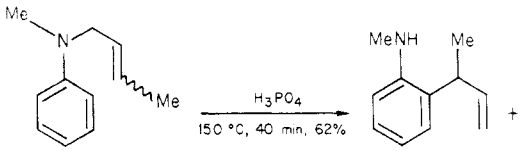
257 required more drastic conditions for rearrangement, consistent with the observations of Jolidon and Schmid. In this case, treatment of **259** with H_3PO_4 gave some cyclization to indolines (**260**) and double bond isom-

TABLE X. Kinetic Parameters for Thermal and Acid-Catalyzed Amino-Claisen Rearrangements

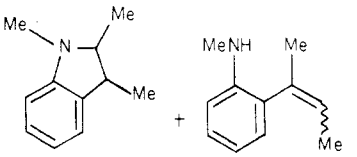
		Substrate			
					
temp, °C	Δ	200–260	290–310	310–340	310–330
	H^+	50–70	105–125	150–170	145–170
ΔH^*, kcal/mol	Δ	33.9	34.4	37.6	40.2
	H^+	28.1	27.3	27.1	30.3
ΔS^*, eu	Δ	−13	−19	−17	−14
	H^+	+9	−4	−12	−3
ΔG^*, kcal/mol	Δ	40.6	45.6	47.5	48.5
	H^+	25.3	28.9	32.3	31.8
k_{rel}	Δ (330 °C)	122	4.3	1.0	0.4
	H^+ (160 °C)	13000	48	1.0	2.1
k_{H^+}/k_Δ[a]		2×10^7	7×10^5	7×10^4	1×10^6

[a] Calculated for the temperatures of the thermal reactions.

erization (**261**) of the initial [3,3] product, in the proportions shown. The *p*-Me and *p*-OMe derivatives



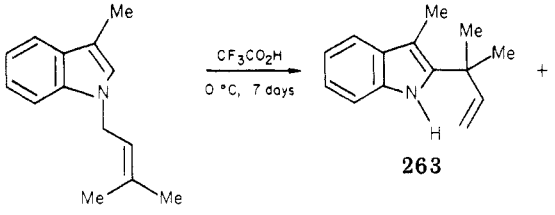
259 (65%)



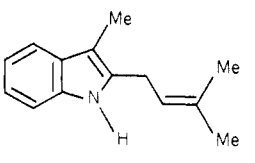
260 (29%) 261 (<5%)

gave comparable results. Catalyzed amino-Claisen rearrangements may be involved in the conversion of *N*-allylanilines to indoles and/or indolines upon heating with acids,[178] but in a related reaction using BF_3·MeOH, it was shown that the process was more complex (see below).[179]

Acid treatment of a series of 3-alkyl-1-allylindoles (cf. **262**) yielded 3-alkyl-2-allylindoles with inverted (**263**) as well as noninverted (**264**) allyl groups (**263**/**264** = 65/35).[180] The absence of cross products from mixtures



262 263



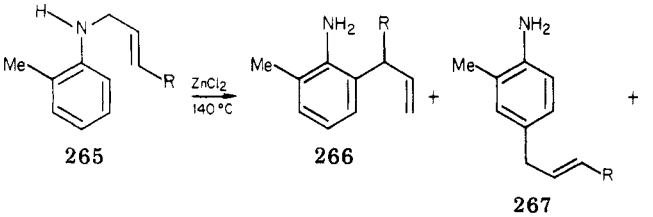
264

of **262** and deuterated **262**, as well as other examples, implicated intramolecular processes. It has been proposed[181] that **263** arises by acid-catalyzed [3,3] rearrangement followed by a [1,2] shift (a [1,2] shift in C-protonated **262** was suggested for the formation of **264**); however, the relative reactivities with differing allyl substitution ($CH_2CH{=}CMe_2$ > $CH_2CH{=}CHMe$ > $CH_2CH{=}CH_2$) were the reverse of those typically observed for [3,3] rearrangements, including the acid-catalyzed amino-Claisen.[172] The rearrangements of **262** and related compounds were also catalyzed by BF_3, $SnCl_4$, and $AlCl_3$ (see below).

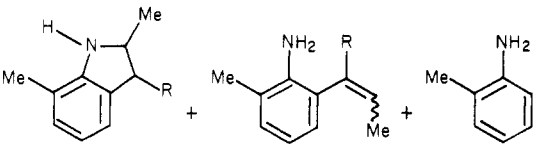
Aniline hydrochloride has been used as a catalyst.[182]

C. Lewis Acid Catalysis

Among the Lewis acid catalysts for the aromatic amino-Claisen rearrangement, anhydrous $ZnCl_2$ has received the most attention,[183] although it is not always the most effective (see below, BF_3). Rearrangements are usually carried out in refluxing xylene, followed by workup with aqueous sodium hydroxide (assumed for all equations below). Its earliest reported use[184] was in the rearrangement of *N*-allylaniline in 42% yield to *o*-allylaniline (0.7 equiv of $ZnCl_2$, xylene, reflux, 3 h). The [3,3]-sigmatropic nature of the process was later demonstrated in the conversion of the *N*-crotyl derivative, **265** (R = Me) (1 equiv of $ZnCl_2$, xylene, 140 °C, 4.5 h) in 69% overall yield to a mixture containing 78% ortho product, **266**, 12% para product, **267**, as well as small amounts of material (4% **268**, 2% **269**, 4% **270**) derived respectively from cyclization or isomerization of **266**, and cleavage of **265**.[175] The noninverted crotyl



265 266 267

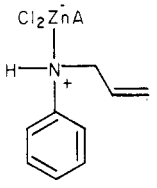


268 269 270

group in **267** is consistent with two sequential [3,3] rearrangements. In the reaction under similar conditions of *N*-allyl-2-methylaniline, **265** (R = H), there was formed in 70% combined yield a mixture consisting of

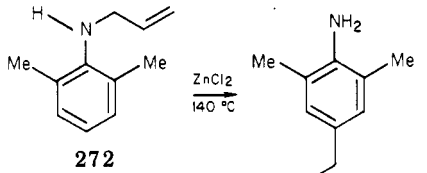
81% **266**, 10% **267**, 8% **268**, and 1.5% **270**. Likewise *N*-allyl-*N*-methylaniline rearranged in 73% combined yield to a mixture containing 96% of 2-allyl-*N*-methylaniline; *N*-(β-methylallyl)-*N*-methylaniline rearranged less cleanly, with most of the [3,3] product undergoing cyclization under the reaction conditions. In all cases it was shown that cyclization (cf. **268**) and double-bond isomerization (cf. **269**) products were derived from the initial [3,3] rearrangement products.

Specific tests for intramolecularity or for inversion of unsubstituted allyl groups (using labeling) were not carried out, but [3,3] processes were justifiably assumed, and the $ZnCl_2$-catalyzed reactions were seen as examples of charge-accelerated sigmatropic rearrangements (cf. Scheme VIII).[175] On the basis of the known composition of the $ZnCl_2$–aniline complex, the complexes undergoing rearrangement in these cases were presumed to possess two amines coordinated to the zinc (cf. **271**, A = amine).



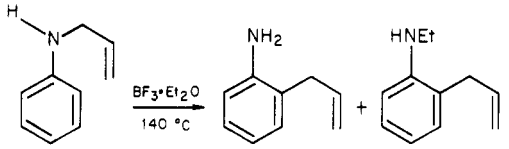
271

tems,[175] the $ZnCl_2$-catalyzed [3,3]-sigmatropic rearrangement of *N*-(γ,γ-dimethylallyl)aniline was not competitive with other processes;[185] the same was true for *N*-cinnamylaniline.[184] Catalyzed rearrangement of a 2,6-disubstituted substrate, **272** (1.2 equiv of $ZnCl_2$, toluene, 140 °C, 4 h), gave 73% of para product, **273**.[186]



272 **273**

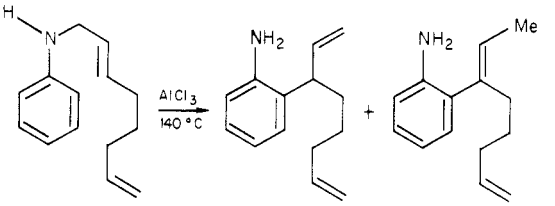
The use of BF_3 as a catalyst for the amino-Claisen rearrangement has received little attention, although it proved to be the superior catalyst in one systematic comparison with $ZnCl_2$.[187] Thus, *N*-allylaniline (**256**) rearranged to *o*-allylaniline in 73% yield with BF_3·Et_2O in refluxing xylene, compared to 40% with $ZnCl_2$. The



256 **274**

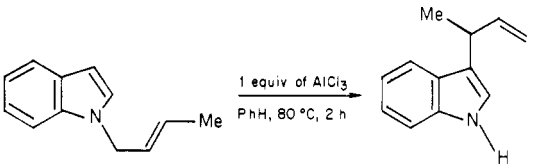
principal side product was the N-ethylated aniline, **274** (8%), undoubtedly formed by nucleophilic displacement on the ether complex. Comparative yields (BF_3·Et_2O vs. $ZnCl_2$) for other reactions carried out under similar conditions are *N*,*N*-diallylaniline to 2,6-diallylaniline (62% vs. 14%), *N*,2-diallylaniline to 2,6-diallylaniline (62% vs. 37%), and *N*,2,6-triallylaniline to 2,4,6-triallylaniline (76% vs. 22%). In these cases, 1–3% of N-ethylated product was also observed. A charge-accelerated [3,3] process is very likely involved here. The rearrangement of **262** was also catalyzed by BF_3 (ethyl ether, room temperature, 24 h), giving **263** and **264** in equal amounts.[180] The conversion of *N*-(β-haloallyl)anilines into indoles with BF_3·MeOH (120–140 °C) may involve a catalyzed amino-Claisen rearrangement,[179] but tracer studies were not consistent with a [3,3] process as being the only source of the indoles.

Other examples of Lewis acid catalysis include the use of $AlCl_3$ (0.64 equiv, PhMe, 140 °C, 2 h) in the rearrangement of **275** in 81% yield to a mixture of the [3,3] product, **276**, with its double bond isomer, **277** (workup with NaOH).[182b] (Both $ZnCl_2$ and $AlBr_3$ were



275 **276** **277**

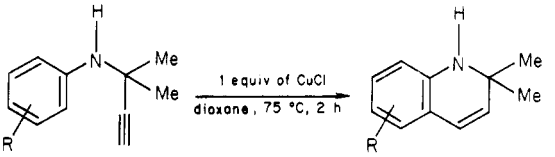
less effective here.) Inversion of the allyl moiety was also seen in the $AlCl_3$-catalyzed rearrangement of *trans*-1-crotylindole (**278**, 43%, workup with HCl);[188] 1-allylindole rearranged analogously in 58% yield.



278

(The thermal reactions occur at 405–470 °C.[189]) Other catalysts examined for the indole rearrangements were $TiCl_4$ (satisfactory, but not as good as $AlCl_3$), $ZnCl_2$ (very poor), and $SbCl_5$ (tars). The $AlCl_3$-catalyzed rearrangement of **262** (hexane, room temperature, 72 h) gave **263**/**264** in the ratio 1/3; the same conditions with $SnCl_4$ gave **263**/**264** in the ratio 35/65.[180]

Copper(I) is apparently a catalyst for the acetylenic amino-Claisen rearrangement, on the basis of the conversion of **279** with CuCl to the 1,2-dihydroquinoline, **280**.[190] The reaction was carried out with a series of

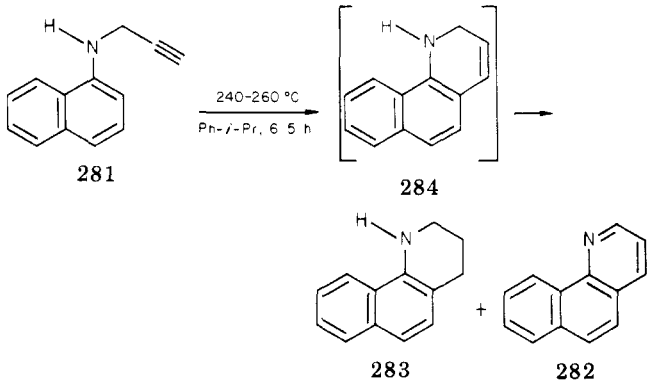


279 **280**

monosubstituted (R = H, *p*-Me, *p*-OMe, *o*-Et, *o*-Cl) and disubstituted (R = 2,3-Me_2, 2,4-Me_2, 2,5-Me_2, 2-Me-3-Cl) substrates, with yields ranging from 66% (R = H) down to 25%. The *p*-methoxy derivative rearranged at room temperature. Contrary to an earlier report,[191] copper powder (purified) was not also a catalyst; dioxane was a more effective solvent than the wet ether used earlier. The *N*-methyl derivative of **279**, R = H, gave only cleavage under the same conditions.

Thermal reactions were not reported. *N*-Propargylaniline itself undergoes cleavage rather than rearrangement when heated, and examples of thermal acetylenic amino-Claisen rearrangements are apparently confined to *N*-propargylnaphthylamines (cf. **281**), which rearrange at 240–260 °C to mixtures of benzoquinolines (**282**) and benzotetrahydroquinolines (**283**), presumably

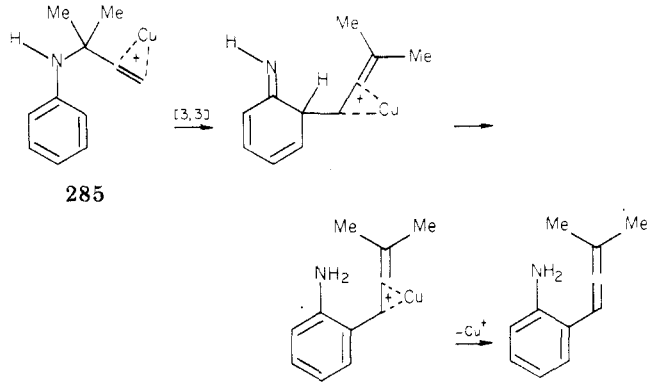
by disproportionation of an intermediate benzodihydroquinoline (**284**) corresponding to **280**.[192] Com-



281 284 283 282

pound **284** (as well as **280**) is analogous to the chromenes observed as products of acetylenic oxygen-Claisen rearrangements, and its formation following an initial [3,3] step was seen as analogous to that of the oxygen counterpart (see above).

Hence, **280** is a logical product for the catalyzed reaction of **279**. The proposed mechanism (**285** → **286**) for the initial Claisen step[190] is analogous to that of the Ag(I)-catalyzed oxygen-Claisen counterpart (see above).



285 286

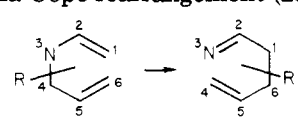
The participation of Cu(I) was also invoked in the cyclization of **286** to **280**, but no evidence bears on this point. (Silver ion has a very slight accelerating effect on the cyclization of *o*-allenylphenol; see above.)

The Cu(I)-catalyzed acetylenic amino-Claisen rearrangement does not appear to have been further explored. Because thermal reactions are so unfavorable in *N*-propargyl-*N*-arylamines, these substrates are good candidates for further studies of catalysis.

VI. Aliphatic Amino-Claisen (3-Aza-Cope) Rearrangement

A. Thermal Reactions

The nitrogen counterpart of the aliphatic Claisen rearrangement is known as the amino-Claisen, aza-Claisen, or 3-aza-Cope rearrangement (**287** ⇢ **288**). On

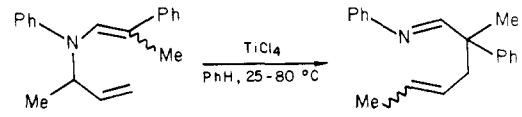


287 288

the basis of the relatively few cases examined, it has the features of a [3,3]-sigmatropic process;[1a,171] thermal reactions have been observed at 170–250 °C, higher temperatures than those required for oxygen analogues, and a preference for chair topology has been established.

B. Catalyzed Reactions

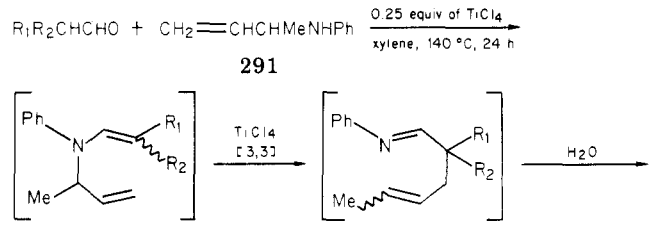
The use of $TiCl_4$ as catalyst allows the rearrangement to occur in refluxing benzene or slowly at room temperature. For example, the conversion of **289** to **290** using 0.25 equiv of $TiCl_4$ in benzene was complete in 24 h at reflux, 68% complete in 24 h at 50 °C, and 67% complete in 72 h at 25 °C;[193] the thermal reaction took place at 170–175 °C.[1a] The *E*/*Z* ratio in **290** (90 ± 3:10



289 290

± 3) was the same within experimental error for the thermal and catalyzed reactions. Chirality transfer occurred to the extent of 67% (in *E*-**290**) using optically active substrate, and established the same preference for chair topology as the thermal reaction (69% chirality transfer). The $TiCl_4$ very likely functions by interaction with the nitrogen, and the catalyzed reaction was interpreted as a charge-accelerated [3,3]-sigmatropic rearrangement.

The $TiCl_4$ was also a catalyst for the preparation of the Claisen substrates (which are *N*-allyl enamines) from aldehydes and allylamines, so that the preparation and rearrangement occurred under the same conditions; hydrolysis of the purified rearrangement products then yielded the appropriately substituted aldehydes (cf. **291** → **293**). In this way the following aldehydes were



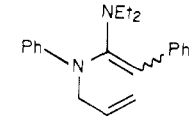
291 292

CHMe=CHCH$_2$CR$_1$R$_2$CHO

293

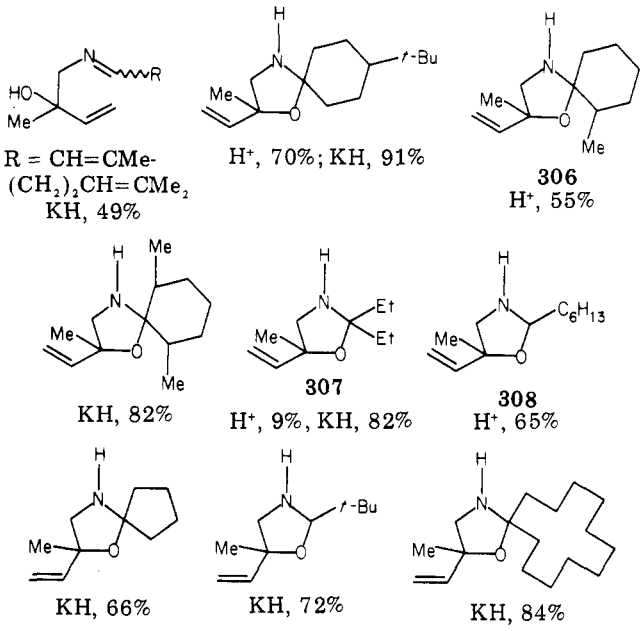
substituted with a crotyl group in the α-position: propanal (26%), 2-phenylpropanal (27–68%), cyclohex-3-enecarbaldehyde (31%), 2,2-dimethylcyclopentanecarbaldehyde (61%). Two linear aldehydes gave products resulting from substitution of two crotyl groups (butanal, 16%; hexanal, 27%) apparently because the initially formed imine (**292**) reacted further with amine to form a second *N*-allyl enamine, which then rearranged. Acetophenone and cyclohexanone did not react under comparable conditions.

Boron trifluoride is apparently not a catalyst for the amino-Claisen rearrangement of **294**, as this substance is prepared by the BF_3-catalyzed addition of *N*-allylaniline to phenyl(diethylamino)acetylene at 30 °C.[194]



294

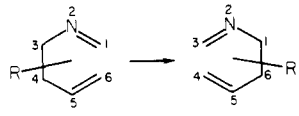
SCHEME X



The drastic conditions required for the partial thermal rearrangement of **294** (280 °C, 4 h) are somewhat unexpected in view of the accelerating effect of the diethylamino group in the equivalent position of an aliphatic Claisen substrate (see above).

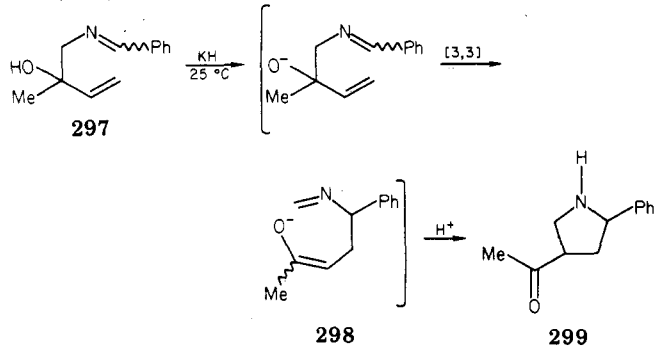
VII. 2-Aza-Cope Rearrangement

The 2-aza-Cope rearrangement is defined by the transformation, **295** → **296**, the few examples of which include thermal rearrangements of *cis*-vinylcyclopropyl isocyanates[195a] and 1,3,4,6-tetraaryl-2-azahexa-1,5-dienes.[195b] Also known is an anionic 4-oxy-2-aza-Cope



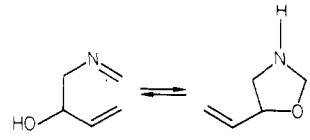
295 **296**

version, illustrated by the reaction of **297** in the presence of 1.5 equiv of KH and 0.1 equiv of 18-crown-6 (THF, 25 °C, 24 h, workup with solid NH_4Cl/$Na_2SO_4 \cdot 10H_2O$).[196] The rearranged anion, **298**, was converted in the course of the process to the 3-acylpyrrolidine, **299**. No thermal reaction was reported.



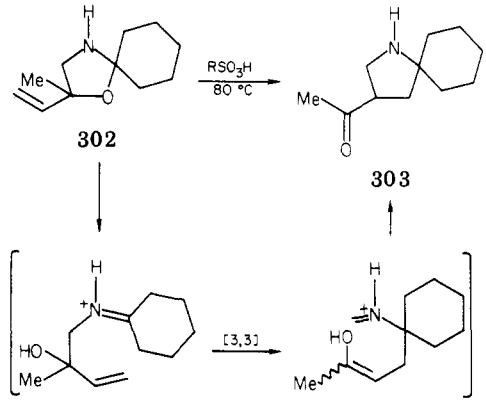
297 **298** **299**

Sodium hydride or *n*-butyllithium were ineffective, reminiscent of the counterion dependence of the anionic oxy-Cope rearrangement (see above). Hydroxyimines having the structural features of **297** can exist in equilibrium with 5-vinyloxazolidines (**300** ⇄ **301**, the position of equilibrium depending on the substituents), so that the latter can also be employed for the anionic rearrangements. Examples of substrates used are given in Scheme X. Rate accelerations in these systems can be accounted for on the same basis as the anionic oxy-Cope rearrangements.



300 **301**

5-Vinyloxazolidines can also be converted to 3-acylpyrrolidines by a Brønsted acid catalyzed process, presumably involving a cationic, charge-accelerated rearrangement.[197] Substrate **302** yielded **303** (69%) on treatment with 1 equiv of *d*-10-camphorsulfonic acid in refluxing benzene (24 h, workup with NaOH), presumably by way of the ring-opened intermediates, **304** → **305**. The treatment of **302** with KH/18-crown-6



302 **303**

304 **305**

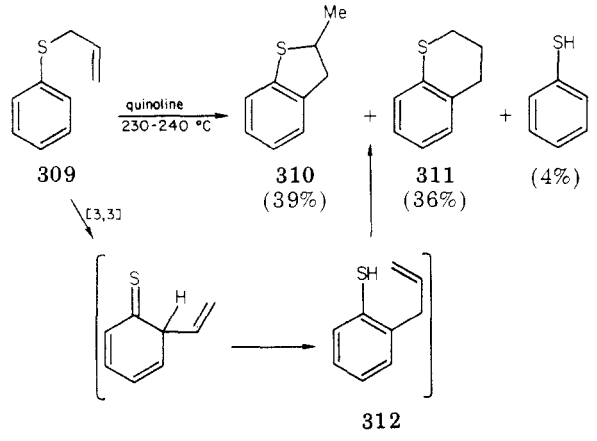
gave 79% **303**.[196] Scheme X illustrates other substrates converted to 3-acylpyrrolidines, in the yields given, by the anionic (KH)[196] and/or cationic (H^+)[197] processes. (The acid employed for **306**–**308** was a catalytic amount of *p*-toluenesulfonic acid.)

A process analogous to **304** → **305**, followed by hydrolysis, very likely occurred in the reactions of 3-butenylamines with formaldehyde in the presence of acids.[198] Cationic 2-aza- and 3-aza-Cope rearrangements involving quaternary nitrogen are well-known.[171]

VIII. Thio-Claisen Rearrangement[199]

A. Aromatic Substrates

Examples of catalysis or potential catalysis in the thio-Claisen rearrangement are few and unspectacular. In the aromatic series, allyl phenyl sulfides undergo double-bond isomerization and cleavage at about 300 °C, as well as [1,3] shifts at lower temperatures;[200] however, the thio-Claisen rearrangement can be the predominant reaction in the presence of nucleophiles or in nucleophilic solvents such as amines.[201] For example, allyl phenyl sulfide itself (**309**) was converted in quinoline at 230–240 °C (7 h) to 2-methyl-1-thiacoumaran (**310**) and 1-thiachroman (**311**),[202] presumably by cyclization of the Claisen product, *o*-allylthiophenol (**312**). This presumption was supported by the observation that preformed **312**, a relatively labile substance, cyclized upon injection into quinoline at ca. 240

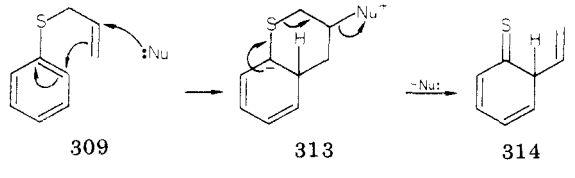


°C to a mixture of **310** and **311**, whose ratio was similar to that observed in the rearrangement of **309**.[201] Compounds **310** and **311** were stable to the reaction conditions. The [3,3] nature of the process was verified with crotyl *m*-tolyl sulfide.[202]

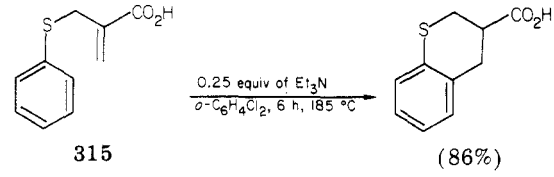
Kwart and Schwartz subsequently found that the rearrangement of **309** could be carried out in "inert" solvents such as diethylcarbitol [$(EtOCH_2CH_2)_2O$] so long as a nucleophile was present, and it was concluded that the aromatic thio-Claisen rearrangement was susceptible to nucleophilic catalysis.[201] Determination of rate accelerations was complicated by the fact that the uncatalyzed thio-Claisen rearrangement did not compete with cleavage and double-bond isomerization; however, catalytic factors of 20–100 can be estimated, relatively modest, but sufficient to render the rearrangement competitive with side reactions and a viable preparative process.

Rearrangement of **309** in diethylcarbitol in the presence of pyridine was first order in both components. Relative rates of catalyzed reactions were determined with eight amines and three anions (PhS^-, PhO^-, $MeCOO^-$); there was no correlation with aqueous basicities, but a rough correlation with nucleophilicities. The relative catalyzed rates at 228 °C varied by a factor of 8 in going from the least effective catalyst (aniline) to the most effective (1,4-diazabicyclooctane). The effectiveness of nonnucleophilic anions was not examined.

The proposed mechanism for catalysis by nucleophiles involves a concerted bimolecular process in which the nucleophile and substrate approach each other to achieve what is essentially the [3,3] transition state (chair geometry assumed) with the nucleophile weakly bonded to carbon, backside to the sulfur.[201] As the reaction progresses, the nucleophile moves away. No theoretical justification for a lowering of the activation energy by this means was offered. Also considered was a cyclization-induced process, **309** → **313** → **314**, which was rejected on the grounds that substituent effects were inconsistent with the development of a full negative charge on the ring, and no kinetic secondary deuterium isotope effect was observed with β-deuterioallyl phenyl sulfide (k_H/k_D = 1.053 ± 0.007, 204 °C).[203] An

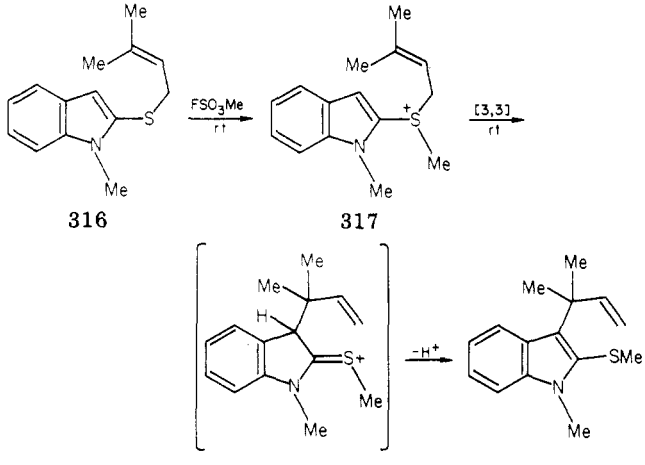


intramolecular verison of the above backside-bonding mechanism was offered to rationalize the effect of added triethylamine on the rearrangement of the carboxyl-substituted substrate, **315**, in refluxing *o*-dichlorobenzene.[204] No reaction occurred in the absence of the base, and it was proposed that a carboxylate anion participated intramolecularly. A strained geometry would thus be generated, however, and there is no reason to assume here anything other than the usual effect of nucleophiles in the medium.



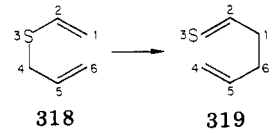
The rearrangement of **309** was not catalyzed by acids[201] or Et_2AlCl.[115a] Although the thio-Claisen rearrangement is frequently carried out in amine solvents or in the presence of amines,[199] no investigation of nucleophilic catalysts has been carried out in other systems (e.g., with heterocyclic aromatic components, which tend to facilitate reaction).

In spite of the fact that **309** did not appear to be susceptible to electrophilic catalysis, contrary to experience with oxygen and nitrogen counterparts, there is evidence for a cationic, charge-accelerated process in the facile rearrangement of **316** via its sulfonium salt, **317**, at room temperature.[205] The reversible thermal thio-Claisen rearrangement of **316** itself also occurred at room temperature, but more slowly.[206]



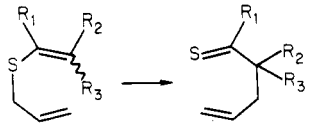
B. Allphatic Substrates (3-Thia-Cope Rearrangement)

The aliphatic thio-Claisen (3-thia-Cope) rearrangement, **318** → **319**, has presented a somewhat confusing picture in attempts to define the conditions for a "typical" thermal reaction, but it is now apparent that the reaction can be considerably more facile than the oxygen or nitrogen analogues. For example, substrates



320a–c rearrange more or less readily at room temperature in benzene (a, R_1 = *t*-Bu, R_2 = R_3 = H; b, R_1 = *i*-Pr, R_2 = R_3 = Me; c, R_1 = *t*-Bu, R_2 = H, R_3 = Me);

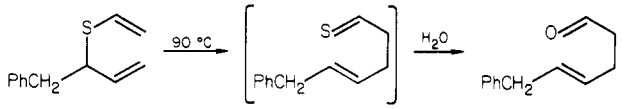
the substitution of crotyl in place of allyl leads to a less clean, incomplete reaction, but inversion of the crotyl group is observed.[207] The rearrangement of **320b** is



320

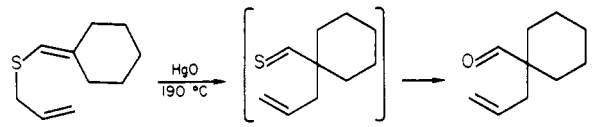
actually reversible, and shows activation parameters characteristic of a [3,3] process (ΔH^*_{80} = 20.0 ± 1.0 kcal/mol, ΔS^*_{80} = −19.0 ± 2.9 eu).[208] The presence of a β-phenyl substituent in the allyl group of **320b** leads to an even faster rearrangement, and is suggestive of a cyclic 1,4-diradical intermediate (cf. **4**) in that case.[209] Reaction of a 2-methylthio substrate (cf. **318**) occurred at −25 °C,[210] and reaction with preponderantly chair topology was observed in the rearrangement of 2-dimethylamino derivatives in refluxing THF.[211]

Reports of unsuccessful reactions even at high temperatures probably stem from lability of the products rather than sluggishness of the rearrangements themselves, and can often be circumvented by in situ diversion of products to more stable substances. For example, whereas heating **321** at 180–200 °C (with or without HgO) gave an intractable tar, reaction in $MeOCH_2CH_2OMe/H_2O$ (3/1) at reflux (ca. 90 °C) for 12 h in the presence of $CaCO_3$ yielded 62% of aldehyde **322**, presumably by hydrolysis of the intermediate thioaldehyde, **323**.[212] A similar strategy had been used



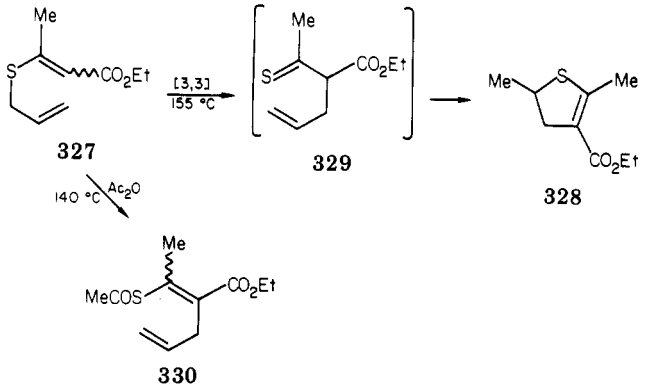
321 323 322

earlier in the converison of sulfide **324** to aldehyde **325** (82%) in the presence of red HgO (3 equiv, 190 °C, 10 min); heating **324** at 160–180 °C in the absence of HgO gave tars and starting material.[213] In this case, HgO may possibly catalyze the [3,3] step to **326** as well as promote further reaction of **326**, but no conclusion can be reached on the basis of existing data. Various other sulfides were converted to aldehydes in the same way.

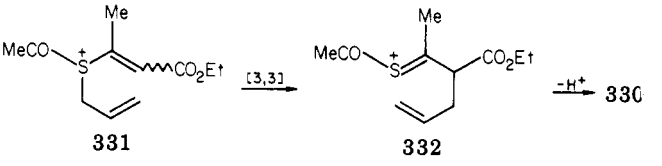


324 326 325

Another strategy for in situ capturing of labile rearrangement products, which also has the potential for promoting the [3,3] rearrangement, involves running the reaction in acetic anhydride or other acid anhydrides.[199] Sulfide **327**, for example, gave **328** (29%) in quinoline at 155 °C (6.5 h), presumably by way of thioketone **329**;[214] but in acetic anhydride (140 °C, 3 h) **327** gave 75% of ester **330**. It was assumed that **330** was formed from **329**, but the milder conditions and higher yield suggest that a charge-accelerated reaction may be taking place, following reaction of **327** itself with acetic anhydride (**331** → **332** → **330**). Again, a firm conclusion regarding such a process in this and other systems can not be reached from available data.

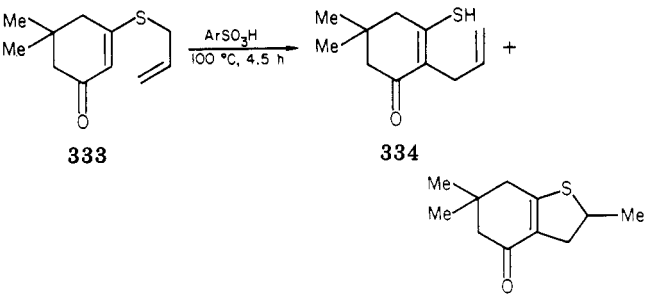


327 329 328 330



331 332

Potential acid catalysis in the rearrangement of **333**, a 1-acyl-substituted substrate, to **334** and **335** (no yield data) cannot be evaluated because of lack of controls, but the reaction conditions in the presence of a trace of *p*-toluenesulfonic acid were milder than under various other rearrangement conditions.[215]



333 334 335

IX. Polyhetero-Cope and Claisen Rearrangements[216]

A. Introduction

In this section the terms Cope and Claisen rearrangement are stretched to include rearrangements that are not commonly identified as such; an alternative heading, "polyhetero-[3,3]-sigmatropic rearrangements," would also serve. Examples are confined to systems containing two of the same or different heteroatoms, subdivided according to the identity of the heteroatom and its position in the rearrangement substrate, based on structure **336**, which represents the minimum degree of unsaturation in the examples reported. (For formal

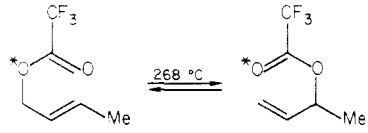
336

suggestions on the classification of polyhetero-[3,3]-sigmatropic shifts, see ref 217 and references cited.) This section is less comprehensive in discussions and coverage of the literature than earlier sections of this review.

B. 1-O,3-O Systems

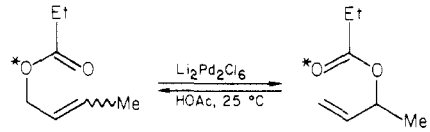
1. Allyl Esters (Carboxylates)[37b]

^{18}O-labeling and product studies have demonstrated that simple allylic esters undergo a [3,3] rearrangement in the gas phase at about 300 °C (cf. **337** ⇄ **338**).[218]



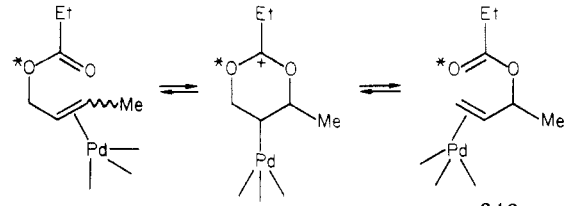
337 338

Substituent effects suggested that the transition state possesses significant polar character;[219] no information is available about transition-state geometry. A similar strategy employing labeled crotyl propionate showed that Pd(II) catalysis of allylic ester isomerization using $Li_2Pd_2Cl_6$ also represented a [3,3] process (**339** ⇄ **340**).[220] The suggested mechanism (later termed cy-



339 340

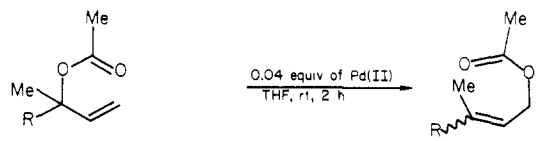
clization-induced rearrangement; see above) involved the action of Pd(II) as a Lewis acid to promote cyclization of complex **341** to the 1,3-acetoxonium intermediate, **342**, followed by ring opening to **343**. A



341 342 343

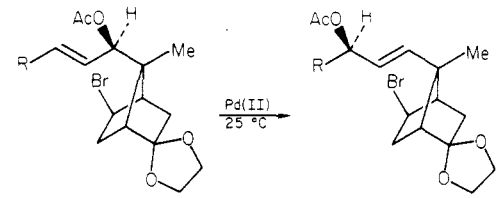
500-fold rate decrease when Et was replaced by CF_3 is consistent with this proposal. In the presence of added LiCl and LiOAc, which acted as inhibitors, the rate law for isomerization had the form: $v = k[Li_2Pd_2Cl_6][\text{ester}]/\{[LiCl](1 + k'[LiOAc])\}$. Inhibition by LiOAc was assumed to involve attack of acetate on intermediate **342**, whereas LiCl was thought to displace the following olefin–Pd(II) equilibrium toward unreactive forms: $Li_2Pd_2Cl_6 + C{=}C \rightleftarrows C{=}C{\cdot}Pd_2Cl_5^- + Li^+ + LiCl$.

A series of preparative runs using acetate esters and $PdCl_2(MeCN)_2$ in THF gave high yields of rearrangement products.[221] In addition to the transformation shown, **344** → **345** (88%, E/Z = 78/22), esters of the following alcohols were rearranged under similar conditions: 1-vinylcyclohexanol (93%); 5,8-dimethoxy-2-vinyl-2-hydroxy-1,2,3,4-tetrahydronaphthalene (87%, $E + Z$); α-phenylallyl alcohol (96%, E/Z = 98/2); hex-1-en-3-ol (95%, equilibrium mixture with 59% $E + Z$, 41% starting ester). Complete suprafacial chiralty



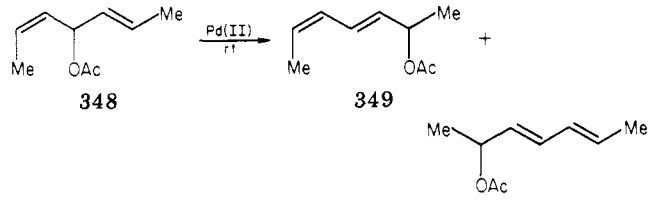
344 (R = $CH_2CH_2CH_2CHMe_2$) 345

transfer, consistent with a [3,3] process, was observed under comparable conditions (0.04 equiv of $PdCl_2(MeCN)_2$, THF, 25 °C, 1.5 h) in the rearrangement of acetate **346** to **347** (R = n-C_5H_{11}) in 93% yield.[222] The corresponding cis isomer and a related compound exhibited similar chirality transfer, as did compounds analogous to **346** having Me = OCH_2Ph,[223] as well as derivatives of Δ^{23}-22-acetoxycholesterol.[224] (Transition-state geometry is not defined by these experiments.)



346 347

Palladium(II)-catalyzed allylic ester isomerization occurs preferentially at E-disubstituted double bonds rather than Z-disubstituted, as seen in the rearrangement of (*E,Z*)-4-acetoxyhepta-2,5-diene (**348**, 0.05 equiv of $PdCl_2(MeCN)_2$, THF, rt, 5 min) to a mixture of **349** (74%) and **350** (18%).[225] The new double bond in this



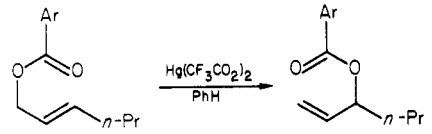
348 349

350

and related acetoxy dienes was exclusively E. High yields of a single isomer were obtained under comparable conditions with (*E,E*)- and (*Z,Z*)-**348**; (*E,Z*)-$R_1CH{=}CHCH(OAc)CH{=}CHR_2$, where R_1,R_2 = Me,Bu or Bu,Me, gave mixtures comparable to those obtained with (*E,Z*)-**348**. Rearrangement occurred at disubstituted double bonds in preference to monosubstituted, with (*E*)-$CH_2{=}CHCH(OAc)CH{=}CHMe$ giving 95% (*E*)-$CH_2{=}CHCH{=}CHCH(OAc)Me$ (**351**); the corresponding Z 1,4-diene gave 60% of **351** along with 30% (*E,E*)- and 10% (*E,Z*)-$AcOCH_2CH{=}CHCH{=}CHMe$. A cyclization-induced mechanism was assumed.

The stereochemical course of the above rearrangements was quite different employing a Pd(0) complex, $Pd(PPh_3)_4$ (0.05 equiv, benzene, rt). All three stereoisomers of **348** gave only the *E,E* product, **350**, within a few minutes; both (*E*)- and (*Z*)-3-acetoxyhexa-1,4-diene gave >80% (*E,E*)-1-acetoxyhexa-2,4-diene.[225] It is questionable that [3,3] processes are involved with the Pd(0) complex; it is known that antarafacial allylic ester isomerization can occur with $Pd(PPh_3)_4$.[226] The same question regarding mechanism applies to the rearrangements of a series of α-cyanoallyl acetates catalyzed by $Pd(PPh_3)_4$; yields ranged from 50 to 91%, and Pd(II) derivatives were less effective here.[227]

Mercuric trifluoroacetate was reported to be ineffective for the rearrangement of **344** (24 h, rt)[221] and other carboxylate esters,[228a,b] although anisate **352** (Ar = C_6H_4-4-OMe) was converted in 85% yield to a mixture containing 69% **353** upon treatment with 1.0 equiv of $Hg(CF_3CO_2)_2$ in benzene for 53 h.[228a] A [3,3] process was assumed. In a preliminary account, clean suprafacial topology was reported in the Hg(II)-catalyzed allylic rearrangement of (*E*)-MeCH=CHCH(OAc)-

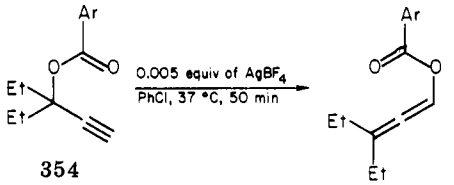


352 353

$CHMeCO_2Me$.[229a] 1,1-Dideuterio- and 3,3-dideuterioallyl acetate were equilibrated in 11–17 days at 160 °C in the presence of $Hg(CH_3CO_2)_2$.[141] Mercuric acetate was an efficient catalyst for allylic rearrangement of 1-methyl-2-propenyl acetate in acetic acid (75 °C), presumably by an addition–elimination mechanism under these conditions.[229b]

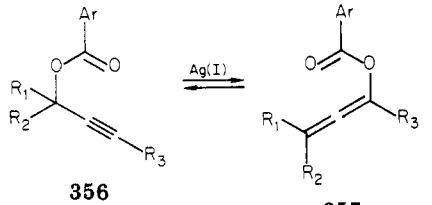
2. Propargyl and Allenyl Esters (Carboxylates)

Catalyzed rearrangement of propargyl esters using silver salts was first reported by Saucy et al.,[230] then systematically studied and characterized as a [3,3] process by Schmid and co-workers,[231] who observed, among other rearrangements, that of **354** to **355** (68%, Ar = *p*-nitrophenyl). Other rearrangements were less



354 355

successful from a preparative point of view because of incomplete conversions and reversibility, and can be generalized by the equilibrium, **356** ⇄ **357**, where R = alkyl or hydrogen. Esters of *p*-nitrobenzoic acid were normally used because they were solids, although in one comparison an acetate rearranged considerably faster.

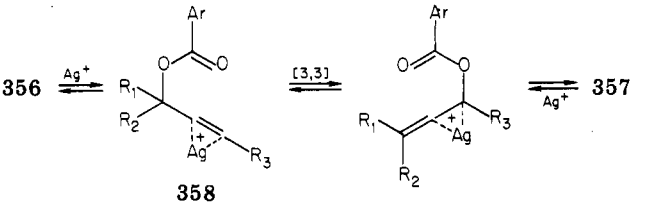


356 357

The reactions were run with 0.005–0.3 equiv of Ag(I), typically 0.03–0.05 equiv, at 35–95 °C for 15–90 min. Catalyst systems were $AgBF_4$, its benzene complex, or $AgCF_3CO_2$ in dry chlorobenzene, or $AgNO_3$ in 96% aqueous dioxane. The latter was especially suitable when $R_1 = R_2 = R_3$ = alkyl. Silver trifluoroacetate was the least successful because it catalyzed the further rearrangement of the allenes to 1,3-dienes.

The position of the propargyl–allenyl equilibrium could be roughly correlated with the substitution pattern, assuming steric congestion involving the *p*-nitrobenzoate group and the substituent(s) on the carbon atom to which it was attached. When $R_1 = R_2$ = alkyl, R_3 = H, the reaction was essentially irreversible; for R_1 = Me, $R_2 = R_3$ = H, the reaction mixture contained 60% allenyl ester at equilibrium (dioxane, 96 °C); for $R_1 = R_2 = R_3$ = Me, the value was 47% (dioxane, 96 °C); the same equilibrium composition was attained starting with either **356** or **357**. An optically active substrate, **356**, R_1 = Me, R_2 = Et, R_3 = H, rearranged without loss of activity in unreacted material, but the allenyl ester, **357**, R_1 = Me, R_2 = Et, R_3 = H, was totally racemic. This was attributed to a fast Ag(I)-catalyzed isomerization of the allenic double bond, which could be independently confirmed in a different system.

Cross reactions and ^{18}O-labeling showed without question that the catalyzed rearrangements were [3,3] processes. Thermal reactions were not reported and are apparently unknown except for isolated cases associated with ambiguities.[232] No rearrangement of **354** occurred in refluxing chlorobenzene (ca. 135 °C) in the absence of Ag(I). The catalytic effect of silver ion was seen to be analogous to that proposed for the Ag(I)-catalyzed acetylenic Claisen rearrangement (see above); the kinetics were consistent with a rate-limiting charge-accelerated [3,3] rearrangement taking place in complex **358**, formed in a rapid preequilibrium with substrate **356**. The silver ion was assumed to complex with those

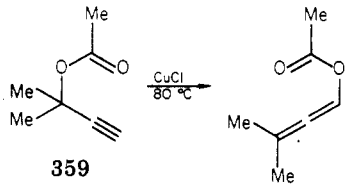


358

p orbitals not involved in the [3,3] transition state, consistent with the fact that no Ag(I)-catalyzed allyl ester isomerization could be observed with α,α-dimethylallyl *p*-nitrobenzoate ($AgBF_4$, PhCl, 130 °C, 6 h)[231] and that the presence of Ag(I) inhibited the degenerate Cope rearrangement of bullvalene.[104]

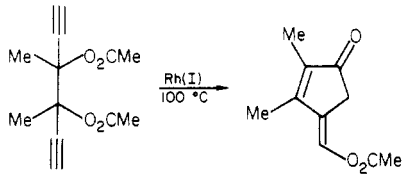
Oelberg and Schiavelli[233a] devised a more convenient reaction procedure for these systems, using $AgClO_4$ or $AgBF_4$ in CH_2Cl_2; yields were poor to fair in an extensive series of reactions. On the basis of these and earlier results, the characteristics of the rearrangements could be summarized as follows: terminal alkynes give better yields than internal; tertiary esters rearrange with higher yields and shorter reaction times than secondary; no reaction seems to occur with aromatic substituents as R_1, R_2, or R_3 (see **356**).

In the earlier work of Saucy et al.,[230] analogous tertiary acetylenic acetates were rearranged in acetic acid in the presence of silver acetate. The reaction was complicated by the concurrent addition of acetic acid to the allenyl acetates. Silver nitrate was also effective, as were, in varying degrees, copper powder, copper oxide, copper salts, and gold salts (no details). Cuprous chloride has had only limited use as a catalyst, but was superior to $AgBF_4$ in the rearrangement of **359** to **360** (100%, benzene, reflux); the yield with $AgBF_4$ (benzene) was 60%.[233b]



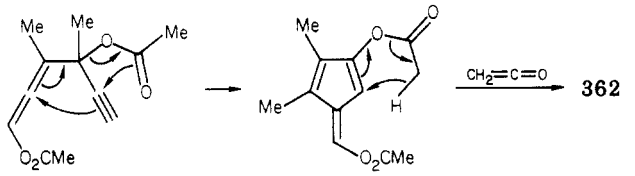
359 360

Attempts to catalyze the rearrangements of simple propargyl esters with Rh(I) were unsuccessful; α,α-dimethylpropargyl acetate yielded a very complex reaction mixture on treatment with $[Rh(CO)_2Cl]_2$ in chloroform.[234] However, treatment of the 3,4-diacetoxyhexa-1,5-diyne, **361**, with the same catalyst (0.05 equiv, $CHCl_3$, 100 °C, 4.5 h) gave 35% of **362**. The overall



361 362

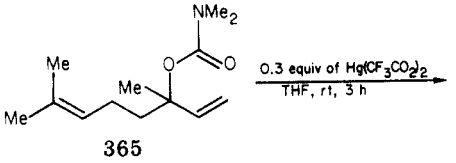
transformation was proposed, on the basis of product structure only, to involve Rh(I)-catalyzed [3,3] rearrangement to **363**, followed by further rearrangement to **364** and a retroene reaction to give **362**. Related substrates exhibited analogous Rh(I)-catalyzed reactions.



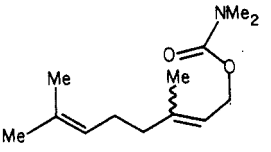
363 364

3. Allyl N,N-Dialkylcarbamates[37b]

Mercuric trifluoroacetate catalyzed the rearrangement of allylic *N,N*-dimethylcarbamates, including the conversion of **365** to **366** (E/Z = 7:3) at room temperature in 70% yield.[228a] Similar rearrangements in high

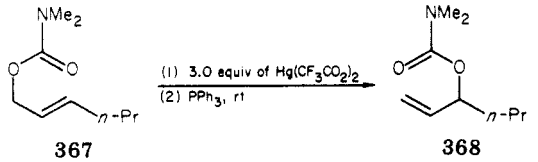


365



366

yield were also observed with carbamates derived from 1-vinylcyclohexanol (95%), 3,7-dimethyloct-1-en-3-ol (92%), 2-methylbut-3-en-2-ol (98%), and a tertiary C-20 sterol (96%). Mercuric nitrate and perchlorate were less effective than the trifluoroacetate. The reactions were worked up with excess PPh_3, which could increase yields by liberating products bound as covalent complexes of Hg(II). In the cases mentioned, the reaction occurred in a thermodynamically favorable sense, in that terminal double bonds were converted to the more stable internal double bonds. However, a contrathermodynamic isomerization could be achieved in certain systems by employing an excess of mercuric trifluoroacetate followed by quenching with PPh_3. Carbamate **367**, for example, was converted with 3.0 equiv of $Hg(CF_3CO_2)_2$ in THF at room temperature for 24 h in 75% isolated yield to an isomer mixture containing 95% **368** and 5% **367**. A preparatively useful contrathermody-

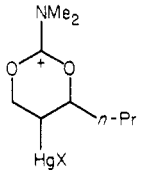


367 368

namic isomerization was also achieved with carbamate derived from (*E*)-4-phenyl-2-butenol, but not with other substrates tested. Displacement of the equilibrium by excess $Hg(CF_3CO_2)_2$ to the side of the less stable olefin is consistent with the fact that formation constants for covalent alkene–$Hg(CF_3CO_2)_2$ adducts generally increase with decreasing double-bond substitution.

Various carbamates derived from methyl *cis*-3-hydroxy-4-cyclohexenecarboxylate rearranged with suprafacial stereochemistry by using 0.25 equiv of $Hg(CF_3CO_2)_2$ in THF at reflux.[228c]

Thermal rearrangements of allylic carbamates have not been reported, but a catalytic factor of 10^{12}–10^{14} was estimated[228a,b] for these reactions by comparison with the thermal rearrangements of allylic carboxylates (cf. **337** → **338**). Although labeling studies to demonstrate inversion of the carbamate moiety were not carried out, a [3,3] process was assumed on the basis that no products of allyl cation intermediates were observed, and the analogous allylic thionocarbamates (see below) rearranged with inversion of the thionocarbamate unit. A cyclization-induced process analogous to **341** → **343** was proposed for these rearrangements, involving a highly charge-delocalized intermediate such as **369**, consistent with the known capacity for Hg(II) salts to promote the reversible addition of nucleophiles to double bonds. A charge-accelerated rearrangement following initial complexation of Hg(II) with oxygen was considered less likely in view of the lack of catalysis by CF_3CO_2H, and the much slower catalysis by BF_3, which also gave evidence of allyl cation intermediates.

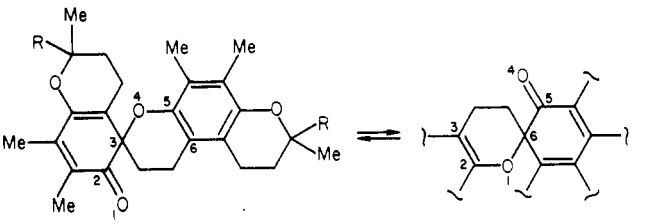


369

C. 1-O,4-O Systems

1. α-Tocopherol Spiro Dimer

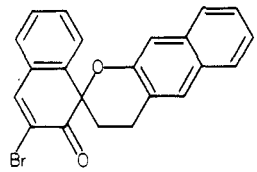
The title compound, **370**, R = $C_{16}H_{33}$, as well as a related substance, R = Me, undergo a degenerate rearrangement that is detected by NMR, with coalescence of signals at about 70 °C (chloroform, benzene).[235] The



370

rearrangement is intramolecular on the basis of cross reactions, and was formulated as a [3,3]-sigmatropic shift;[235a] the structure imposes a boatlike transition state analogous to that for related 1-O,4-O systems such as methacrolein dimer.[236] The rearrangement was acid catalyzed, with coalescence of signals occurring at "constant temperature" in 0.2 M trichloroacetic acid in benzene.[237] Acid catalysis was accounted for by a heterolytic process involving a univalent oxygen cation (phenoxylium ion),[235b] but a charge-accelerated [3,3] rearrangement analogous to that observed in the re-

tro-Claisen rearrangement of cyclohexadienones (cf. **188**) may well be involved here. The picture is complicated by the fact that the [3,3] rearrangement of spiro dienone **371**, whose rate was measured at 50 °C (nitrobenzene), was not accelerated by the presence of 0.2 M trichloroacetic acid.[238]

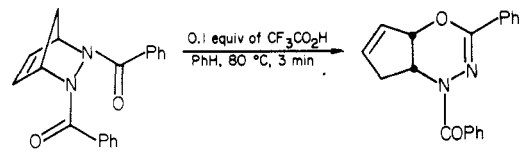


371

D. 1-O,3-N Systems

1. N-Allyl Amides

The Diels–Alder adducts of cyclopentadiene and azodiacyls [R(CO)N=N(CO)R] undergo in high yield a [3,3]-sigmatropic rearrangement catalyzed by Brønsted and Lewis acids.[239] Compound **372**, for example, was rapidly converted to the cis oxadiazine, **373** (90%), by catalytic amounts of CF_3CO_2H.[239a] The



372 373

half-life for the catalyzed reaction at 62 °C was 1.3 s in 0.13 M CF_3CO_2H, or 1.3 min in 1.3 × 10^{-2} M HCl, compared to 11 h for the thermal reaction (hexane solvent in all cases). Both BF_3·Et_2O (0.2 equiv, $CDCl_3$) and $SnCl_4$ (1.0 equiv, CH_2Cl_2) were also very effective catalysts; *p*-toluenesulfonic acid (0.2 equiv, CD_3SOCD_3) was less so, and acetic acid (2.8 M, heptane) was marginally effective. A low degree of asymmetric induction was observed in the rearrangement of **372** catalyzed by (+)-camphor-10-sulfonic acid (0.08 equiv, $CHCl_3$, rt, 15 min).[240] The more basic amides were the more susceptible to acid catalysts; rate enhancements (catalyzed vs. thermal) increased markedly in the order: *p*-nitrophenyl < phenyl < *p*-methoxyphenyl (cf. **372**).

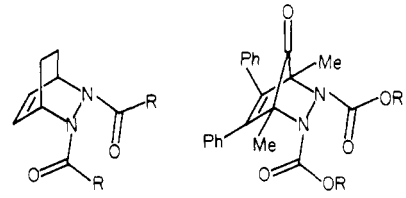
The thermal rearrangements of these and related systems have been well characterized as [3,3] processes;[241] the rigid structure of the substrate imposes a boatlike geometry. The catalyzed reactions were seen essentially as charge-accelerated analogues, although open structures involving allylic cations could not be totally discounted. The question of initial O- vs. N-protonation(complexation) could not be resolved.

Catalysis was less successful with the bicyclo[2.2.2] derivatives, **374**, which were also resistant to thermal rearrangement.[239a] Acid catalysis was apparently operative in the rearrangement of the acyloxyl derivatives, **375**; however, both the catalyzed and thermal reactions here followed a more complex course than those of **372**.[242]

E. 1-N,3-O Systems

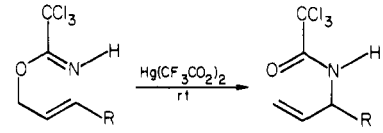
1. Allyl Trichloroacetimidates[37b]

The irreversible thermal rearrangements of allylic trichloroacetimidates to amides (cf. **376** → **377**), which



374 375

represent a specific case of allylic imidate rearrangement, have been well characterized as [3,3]-sigmatropic processes.[243] Temperature requirements range from



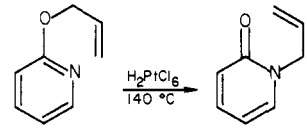
376 377

about 80 to 140 °C; the lower values are suitable for trichloroacetimidates of tertiary allylic alcohols, whereas derivatives of primary and secondary alcohols require the intermediate or higher temperatures, respectively. The stereoselectivity in the formation of *E* or *Z* alkenes is consistent with a chair transition state, although the chair/boat selectivity in these systems can't be rigorously established by the usual methods.

The rearrangements can be catalyzed by Hg(II)[244] or Pd(II)[245] salts (no details for the latter). For example, treatment of **376** (R = C_3H_7) with $Hg(CF_3CO_2)_2$ (0.1 equiv, THF, rt, 1 h) yielded 79% of **377**; the thermal reaction occurred at 140 °C (*m*-xylene, 9 h, 81%). Analogous reactions occurred with R = Me (78%), R = Ph (45%), and the substrate derived from geraniol (79%). In the latter case, the catalyzed reaction could be carried out at −60 °C, with an estimated rate enhancement of >10^{12} (1 M catalyst). (Quenching with pyridine or PPh_3 in all cases.) The scope of the catalyzed reaction was somewhat limited, in that it was synthetically viable only for substrates derived from primary allylic alcohols; in other cases, fragmentation to trichloroacetamide seemed to be the predominant reaction. The reaction mechanism was formulated as a cyclization-induced process analogous to that proposed for allylic carbamate rearrangement (see above).

2. 2-(Allyloxy)pyridines

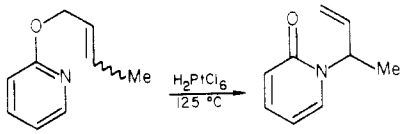
Treatment of neat 2-(allyloxy)pyridine (**378**) with 1% of H_2PtCl_6 at 140 °C, 40 h, yielded >85% of *N*-allyl-α-pyridone (**379**).[246] No reaction occurred without the



378 379

catalyst; higher temperatures (240 °C) were required for the thermal rearrangement, which gave low yields of all possible Claisen-type products. Analogous high yield rearrangements occurred with 1% of Na_2PtCl_4, BF_3·Et_2O, or $SnCl_4$. Various other catalysts were less effective, probably because of insolubility in the medium. Rearrangement of the unsubstituted allyl group does not require a [3,3] process, but inversion was observed in the conversion of **380** to **381** (93%) with 0.3%

H_2PtCl_6 (125 °C, 36 h). Treatment of **380** with BF_3·



380 381

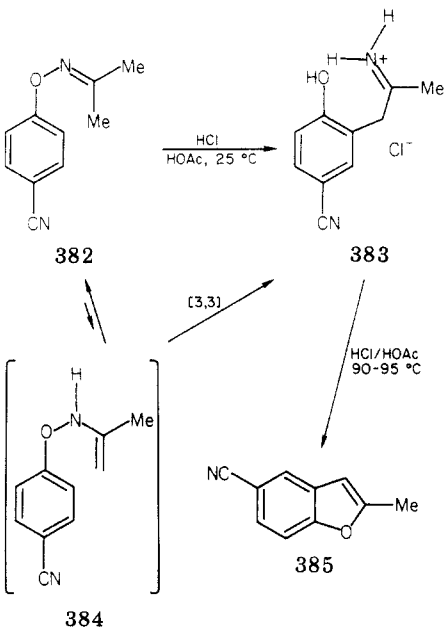
Et_2O under the same conditions, however, gave a mixture of products with noninverted crotyl substituents.

With $Pt(PPh_3)_4$ as catalyst, the rearrangement of **378** to **379** could be carried out at lower temperatures (dimethylformamide, 65 °C, 1 h, 100%), but treatment of **380** with the same catalyst gave a product mixture with inverted (**381**, 86%) and noninverted (14%) allyl groups.[247] A mixture of the same composition was obtained starting with 2-((α-methylallyl)oxy)pyridine. In summary, the rearrangement of **378** and **380** catalyzed by H_2PtCl_6 very likely involves a [3,3] process; the same may be true for the rearrangement of **378** with the other catalysts, but no supporting evidence is available. The presence of an alkyl substituent on the ally group, as in **380**, can lead to reaction by other routes.

F. 3-N,4-O Systems

1. N-(Aryloxy) Enamines

Rearrangement of the *O*-aryl oxime, **382**, in the presence of 2 equiv of HCl in acetic acid at 25 °C gave in high yield iminium salt **383**, presumably by equilibration of **382** with the less stable, tautomeric *N*-(aryloxy) enamine, **384**, followed by [3,3] rearrangement.[248] Treatment of **383** with HCl/HOAc at 90–95



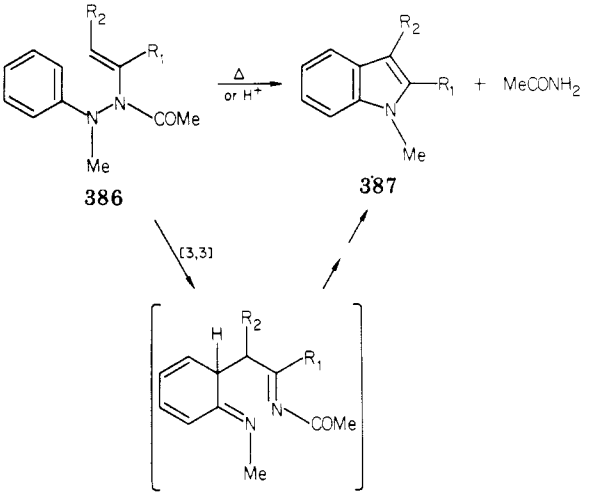
382 383 384 385

°C gave benzofuran **385**, which was also formed when **382** was subjected to the latter conditions. The overall **382** → **385** transformation represents a synthesis of benzofurans from *O*-aryl oximes, of which numerous examples are known;[249] the intermediate iminium derivative is generally not isolated, and the transformation is also catalyzed by BF_3.[249a] The [3,3] step in these conversions is very likely a charge-accelerated rearrangement, although this is not confirmed. Heating the *O*-aryl oximes in the absence of catalysts leads to tars.[249c]

G. 3-N,4-N Systems

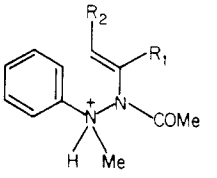
1. N-Aryl-N'-enylhydrazines

Both the aromatic and aliphatic versions of the 3,4-diaza-[3,3]-sigmatropic shift are known. An example of the former is the first step in the conversion of enylhydrazines to indoles. For example, the acyl enylhydrazine, **386** (R_1 = Et, R_2 = Me), rearranged to **387** (49%) at 170 °C (half-life = 30 min), very likely by way of intermediate **388**.[250a] The reaction was strongly



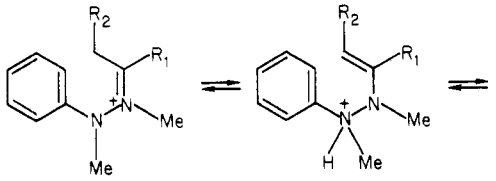
386 387 388

acid catalyzed, yielding 80% of **387** at 25 °C (half-life = 2 s) in 0.5 N Cl_2CHCO_2H in anhydrous MeCN. In a series of reactions with other R groups, thermal rearrangements gave 14–59% of the indoles (10–70 min half-lives), whereas the acid-catalyzed processes gave 79–91% (2–2700 s half-lives). No intermediates were detected, suggesting that the [3,3] step was rate-limiting. The catalyzed reactions were interpreted as charge-accelerated rearrangements of **389** (protonation at the most basic site).

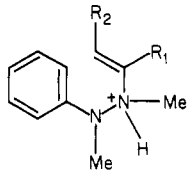


389

A similar series of transformations was carried out with substrates having Me in place of acetyl (**386**, COMe = Me).[250b] The thermal reactions gave 26–57% of **387** (110 °C, 8–30 min half-lives), whereas 36–87% yields were observed in acid-catalyzed rearrangements at 25 °C (half-life = <1–26 min) or 60 °C (half-life = 2–48 min). Protonation of the substrate occurred predominantly at carbon to give **390**, which could be obtained as stable salts. However, the [3,3] shift requires the N-protonated forms, **391** or **392**; these were undetectable, but substituent effects were consistent with **391** and/or **392** as the reactive species. Enylhydrazine **393** rearranged to indole **394** (95%), using 1 equiv of *tert*-butylammonium chloride in acetic acid, 30–35 °C, 15 min, in a process that was about 10^6 times faster than the thermal reaction.[251] Stronger acids under a variety of conditions were strangely much less effective. It was suggested that preferential N-protonation to a reactive

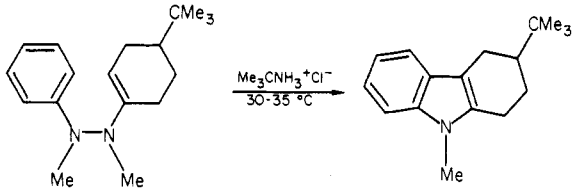


390 391



392

form occurred only with the weaker ammonium salt, but this seems improbable.

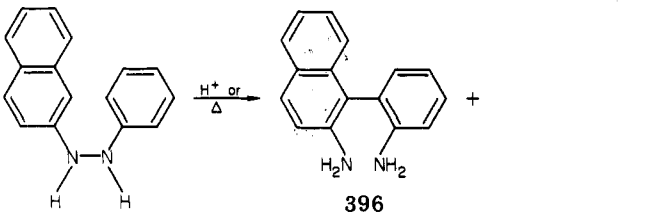


393 394

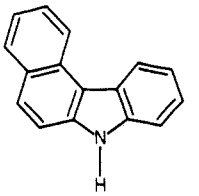
Other thermal and catalyzed reactions of the above type are reviewed in ref 171. They are intimately related to the Fischer synthesis of indoles from arylhydrazones.[252] This process involves conversion of the arylhydrazones to the less stable, tautomeric *N*-aryl-*N'*-enylhydrazines, which are then transformed to indoles as above, in a sequence of reactions initiated by a [3,3] shift. The various Brønsted and Lewis acids employed as catalysts in the Fischer indole synthesis very likely promote charge-accelerated [3,3] rearrangement of the enylhydrazine intermediates, in addition to catalyzing other steps in the overall sequence.

2. *N,N'-Diarylhydrazines (Hydrazoarenes)*

Another version of an aromatic 3,4-diaza-[3,3]-sigmatropic shift is represented by the thermal and acid-catalyzed intramolecular rearrangement of *N*-2-naphthyl-*N'*-phenylhydrazine, **395**. The thermal reaction gave 90–95% of **396**, derived from tautomerization of an initial [3,3] intermediate, along with 4–9% of benzocarbazole **397**, at 80 °C or 110 °C in a variety of solvents.[253] Acid catalysis with 0.05–0.50 N $HClO_4$ in 60% aqueous dioxane at 0 °C or 20 °C gave 96–99% **396** with only traces of **397**.[254] The rearrangement was first order in acid at low acidities, increasing to second order at higher acid strength, suggesting that a charge-accelerated reaction takes place here with both the mono- and diprotonated substrates.



395 396

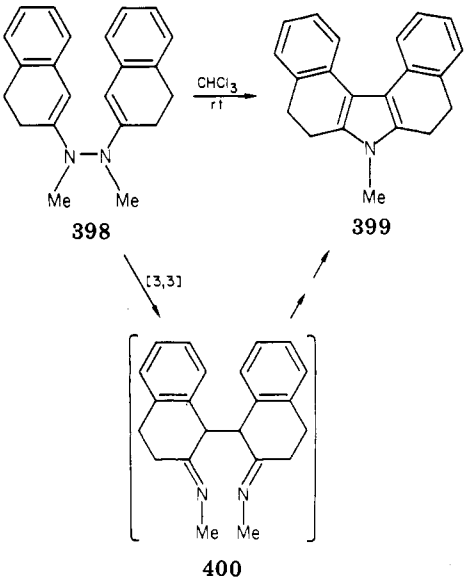


397

Various other hydrazonaphthalenes and *N*-naphthyl-*N'*-phenylhydrazines rearranged in a similar fashion, although generally less cleanly in both the thermal and acid-catalyzed reactions.[255] In most cases, products of [5,5]-sigmatropic rearrangement were observed. The reactions are related to the ortho and para benzidine rearrangements,[256] which formally involve [3,3]- and [5,5]-sigmatropic processes, respectively. The acid-catalyzed para benzidine rearrangement has been shown to be concerted on the basis of nitrogen, deuterium, and carbon isotope effects,[257] and it is reasonable to regard the related ortho processes as charge-accelerated [3,3]-sigmatropic shifts.[258] Cyclic compounds such as **397** can occur in substantial amounts,[255] and are known not to be formed from the aromatized [3,3] product (cf. **396**). They are very likely generated from the initial [3,3] intermediate in a process analogous to that occurring in the Fischer synthesis of indoles or the formation of indoles from enylhydrazines (see above).

3. *N,N'-Bis(enyl)hydrazines*

The bis(enyl)hydrazine, **398**, derived from 2-tetralone and *N,N'*-dimethylhydrazine, is a crystalline material that slowly rearranged at room temperature to pyrrole **399**, presumably by way of an initial [3,3] reaction to **400** (half-life = 5 h at rt).[259] The rearrangement was



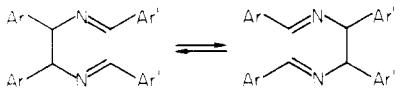
398 399 400

apparently catalyzed by acetic acid, although details are unclear. *N,N'*-Bis(enyl)hydrazines like **398** are generally not isolable with respect to rearrangement products, especially in the presence of acids, unless a stabilizing feature is present, such as conjugation of the double bonds. *N,N'*-Bis(enyl)hydrazines are presumed to be intermediates in the Piloty–Robinson synthesis of pyrroles from azines,[260] in a process which is analogous to the Fischer indole synthesis, and in which Brønsted and Lewis acid catalysis of the [3,3] step is very likely involved.

H. 2-N,5-N Systems

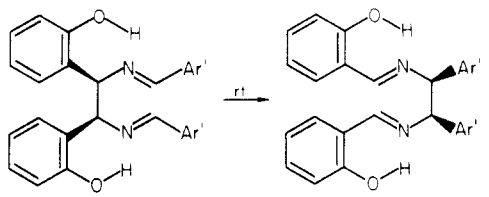
1. 2,5-Diaza-1,5-dienes

Vögtle et al. have uncovered a number of 2,5-diaza-Cope rearrangements, among them a general [3,3] rearrangement of 1,3,4,6-tetraaryl double Schiff bases, **401** → **402**.[261] The reversibility of the reaction depended



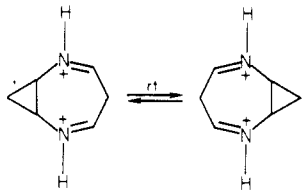
401 402

on substituents, and meso substrates generally rearranged by way of boat transition states to meso products, whereas the *dl* diastereomers rearranged with chair topology to *dl* products. Reaction temperatures ranged from ambient to 140 °C (the racemization of *d*- or *l*-tetraphenyl-**401** (Ar = Ar′ = Ph) occurred with chair topology at 40–50 °C[262]); the lowest temperatures and irreversible reactions were observed when Ar = *o*-hydroxyphenyl, employing a wide range of aryl and other groups on the double bond (cf. *meso*-**403** → *meso*-**404**). A charge-accelerated rearrangement involving intramolecular catalysis by phenolic protons has been proposed for those substrates.[171]



meso-403 *meso*-404

The degenerate rearrangement of the doubly charged cation, **405**, took place at room temperature in equal parts of sulfuric and trifluoroacetic acids.[263] Rate acceleration in the charged system could not be established because the uncharged Cope substrate exists preferentially as a tautomer possessing a carbon–carbon double bond.

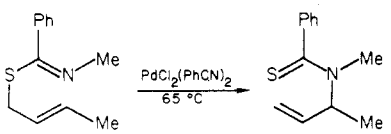


405

I. 1-N,3-S Systems

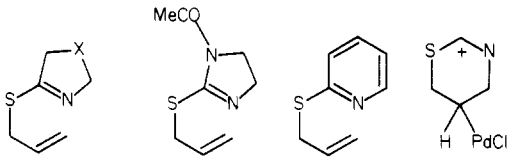
1. S-Allyl Thioimidates[37b]

A pronounced catalytic effect of Pd(II) salts has been observed in the rearrangement of *S*-allyl thioimidates to *N*-allyl thioamides. The involvement of a [3,3] process was confirmed in the rearrangement of **406** to **407** (98%) with 0.01 equiv of $PdCl_2(PhCN)_2$ in refluxing THF, 24 h; the corresponding *S*-(α-methylallyl) thioimidate rearranged analogously (2 h, 94%, *E*?).[264]



406 407

Thermal rearrangements in these systems can be complicated (see below), but no thermal reaction of **406** occurred at 170 °C, and the related *S*-allyl derivative yielded predominantly the product of allyl → propenyl isomerization at 150 °C (the catalyzed reaction of the *S*-allyl derivative, 18 h, gave 99% of the *N*-allyl thioamide). Substrates **408–410** also rearranged with yields as indicated. The rearrangement of **410** represented



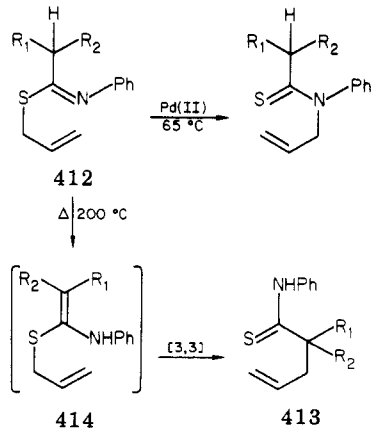
408 409 (91%) 410 (96%) 411

X = CH_2, 71%
X = $(CH_2)_3$, 93%

a contrathermodynamic process, and was effected by using 1 equiv of the catalyst, which preferentially complexed the rearrangement product (which was then liberated with pyridine). Neither Pd(0), as $Pd(PPh_3)_4$, nor $NiCl_2$, $CuCl_2$, or $HgCl_2$ were effective as catalysts.

A cyclization-induced mechanism involving **411** was proposed,[264] analogous to the various other Pd(II)-catalyzed rearrangements discussed in this review. No catalyzed reaction occurred in substrates with a substituent (Me, Ph, or Cl) at the β-position of the allyl group, which would require a tertiary Pd–C bond in the cyclized intermediate, **411** (H = R). The absence of Pd(II)-catalyzed reactions in such cases is characteristic of other systems previously described.

A related series of Pd(II)-catalyzed reactions under similar conditions yielded *N*-allyl thioamides from substrates substituted as in **412**: R_1, R_2 = H (81%); R_1, R_2 = Me (85%); R_1 = H, R_2 = *n*-Pr (80%); R_1 = H, R_2 = Ph (80%).[265] The thermal reactions (200 °C) took a different route, giving *C*-allyl products (**413**) in 73–94% yield, undoubtedly by initial isomerization of **412** to the ketene S,N-acetal, **414**, followed by the [3,3] shift. No *N*-allyl product was observed in the thermal

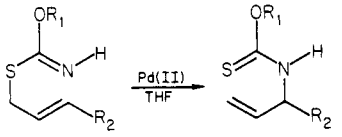


412 414 413

reactions, and only 0–15% of *C*-allyl in the catalyzed rearrangements, so that S → N or S → C allylic rearrangement could be selected by the choice of conditions. The relative "softness" of the catalyst as a Lewis acid seemed to influence the ratio of *C*- vs. *N*-allyl products. Treatment of **412**, R_1 = R_2 = Me, Ph = Me, with 0.02 equiv of $PdCl_2$ (THF, 65 °C, 16 h) gave *C*-allyl/*N*-allyl = 81/19; with the softer $Pd(OAc)_2$ (0.1 equiv, 24 h), the ratio was 4/96.

2. O-Alkyl S-Allyl Iminothiocarbonates[37b]

Palladium(II)-catalyzed S → N [3,3] rearrangements were also observed in the conversion of the related *O*-alkyl *S*-allyl iminothiocarbonates, **415** (R_1 = menthyl), to *O*-alkyl *N*-allylthiocarbamates, **416**, employing $PdCl_2(MeCN)_2$ in THF: R_2 = *E*-Me (0.01 equiv of Pd(II), 65 °C, 10 h, 68%); R_2 = *E*-Ph (1.0 equiv of Pd(II), 15 °C, 66 h, 60%); R_2 = *E*-CH_2Ph (1.0 equiv of Pd(II), 15 °C, 20 h, 52%).[266] Yields were low if the allyl



415 416

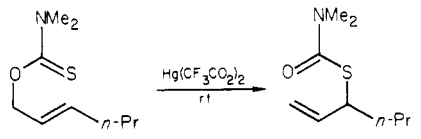
group was unsubstituted (R_2 = H, 24%), or of the *Z* configuration (12% with R_2 = *Z*-CH_2Ph); fragmentation occurred in a case where the allyl group was γ,γ-disubstituted (R_1 = neopentyl; (*S*)-geranyl). In cases where stoichiometric amounts of catalyst were used, the product was liberated from its complex with pyridine or PPh_3. Mercuric trifluoroacetate was ineffective as a catalyst, as were $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, and a number of other transition-metal salts and complexes. No thermal rearrangement occurred at 100 °C with **415** (R_1 = menthyl, R_2 = Me); at 125 °C the compound decomposed. A cyclization-induced mechanism was assumed for Pd(II) catalysis.

A low degree of asymmetric induction (3–5% enantiomeric enrichment) was observed with optically active substrates (R_1 = menthyl). In a case where R_1 = dehydroabietyl, R_2 = Me, treatment with 0.1 equiv of $PdCl_2(MeCN)_2$ at 65 °C gave 64% of product with a 2.1% optical yield. The use of 1.0 equiv of catalyst at room temperature gave 48% product with 3.6% optical yield, but with the opposite sign of rotation.

J. 1-S,3-O Systems

1. Allyl Thionocarbamates[37b]

In a reaction cited as supporting the assumption of [3,3] processes in the Hg(II)-catalyzed rearrangement of allyl carbamates (see above), it was shown that the allyl thionocarbamate, **417**, is converted to thiocarbamate **418** (52%) with 0.3 equiv of $Hg(CF_3CO_2)_2$ in THF, rt, 12 h, then PPh_3.[228a] The thiocarbamate



417 418

with a noninverted allyl group was formed in trace amounts only. The thermal rearrangement occurred at 135 °C (2 h).[267]

X. References and Notes

(1) Cope and Claisen rearrangement reviews: (a) Rhoads, S. J.; Raulins, N. R. *Org. React. (N.Y.)* **1975**, *22*, 1–252. (b) Mechanistic aspects in: Gajewski, J. "Hydrocarbon Thermal Isomerizations"; Academic Press: New York, 1981.

(2) Claisen rearrangement reviews: (a) Bennett, G. B. *Synthesis* **1977**, 589–606. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227–232. (c) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 1–72.

(3) The conventional use of the terms Cope and Claisen rearrangement, as outlined in ref 1a, is employed in this review. The rearrangement of 1, X = nitrogen or sulfur, is sometimes called a 3-aza- or 3-thia-Cope rearrangement, respectively.

(4) Hetero-Cope, polyhetero-Cope and Claisen rearrangements; see below.

(5) Dewar, M. J. S.; Wade, L. E. *J. Am. Chem. Soc.* **1977**, *99*, 4417–4424; **1973**, *95*, 290–291.

(6) (a) Gajewski, J. *Acc. Chem. Res.* **1980**, *13*, 142–148. (b) Gajewski, J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 6693–6704. (c) Wehrli, R.; Schmid, H.; Bellus, D.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 1325–1356. (d) Wehrli, R.; Bellus, D.; Hansen, H.-J.; Schmid, H. *Chimia* **1976**, *30*, 416–423.

(7) Cf.: Doering, W. v. E. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 5279–5283.

(8) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983–6984, 6984–6986.

(9) Reviewed in: Hansen, H.-J.; Schmid, H. *Tetrahedron* **1974**, *30*, 1959–1969.

(10) Cited in ref 157.

(11) The yields cited are not necessarily those for isolated or purified products.

(12) Woodward, R. B.; Hoffman, R. "The Conservation of Orbital Symmetry"; Verlag Chemie/Academic Press: Weinheim, 1970.

(13) In no case has a process involving one-electron transfer been proposed for a catalyzed reaction. Calculations suggest that a cation-radical Cope rearrangement may be a facile process. Cf.: Bauld, N. L.; Bellville, D. J.; Pabon, R.; Chelsky, R.; Green, G. *J. Am. Chem. Soc.* **1983**, *105*, 2382–2388.

(14) Reference 171, p 658.

(15) Or, better, cyclization-accelerated rearrangement? Cf. ref 228a.

(16) Doering, W. v. E.; Toscano, V. G.; Beasley, G. H. *Tetrahedron* **1971**, *27*, 5299–5306.

(17) Brown, J. M.; Golding, B. T.; Stofko, J. J., Jr. *J. Chem. Soc., Chem. Commun.* **1973**, 319–320.

(18) Cheng, A. K.; Anet, F. A. L.; Mioduski, J.; Meinwald, J. *J. Am. Chem. Soc.* **1974**, *96*, 2887–2891.

(19) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67–74.

(20) Lutz, R. P.; Bernal, S.; Boggio, R. J.; Harris, R. O.; McNicholas, M. W. *J. Am. Chem. Soc.* **1971**, *93*, 3985–3990.

(21) (a) Jolly, P. W.; Wilke, G. "The Organic Chemistry of Nickel"; Academic Press: New York, 1974 (Vol. 1), 1975 (Vol. 2). (b) Malatesta, L.; Cenini, S. "Zerovalent Compounds of Metals"; Academic Press: New York, 1974.

(22) Heimbach, P.; Jolly, P. W.; Wilke, G. *Adv. Organometal. Chem.* **1970**, *8*, 29–86.

(23) (a) Heimbach, P.; Brenner, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 800. (b) Brenner, W.; Heimbach, P.; Hey, H.; Muller, E. W.; Wilke, G. *Liebigs Ann. Chem.* **1969**, *727*, 161–182.

(24) Heimbach, P.; Brenner, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 800–801.

(25) Hammond, G. S.; DeBoer, C. D. *J. Am. Chem. Soc.* **1964**, *86*, 899–902.

(26) The catalyzed reactions were first order in catalyst and zero order in diene, indicating that all of the catalyst was in the form of reactive intermediates. Quantitative comparison with the first-order thermal process requires specification of diene as well as catalyst concentration. A first-order thermal rate constant at 24 °C was estimated from activation parameters quoted in ref 25.

(27) Heimbach, P.; Hey, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 528–529.

(28) (a) Heimbach, P. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 975–989. (b) Heimbach, P. In "Aspects of Homogeneous Catalysis"; Ugo, R., Ed.; Reidel: Boston, 1974; Vol. 2, Chapter 3.

(29) The Ni(0) complexes can be prepared in several ways,[23b] including in situ reduction of Ni(II) in the presence of reactants and the phosphine or phosphite ligand. In every case the Ni/P molar ratio is 1/1, with other coordination sites occupied by any available double bonds.

(30) Heimbach, P.; Molin, M. *J. Organometal. Chem.* **1973**, *49*, 483–494.

(31) Steric effects are apparently responsible. There are tentative indications that *cis,trans*-cycloocta-1,5-diene (3% at 108 °C) is formed in the thermal rearrangement of *cis*-1,2-divinylcyclobutane.[25]

(32) Formation of cycloocta-1,5-diene from butadiene could be a consequence of direct catalyzed dimerization or Cope rearrangement of preformed *cis*-1,2-divinylcyclobutane. The nearly constant ratio of 8/9 observed in the dimerization of butadiene up to 85% conversion[23] indicates that both processes occur simultaneously.

(33) Including the remarkable double isomerization of *cis,cis*-1,4-dideuterio-1,3-butadiene exclusively to the trans,trans isomer.[34]

(34) Graham, C. R.; Stephenson, L. M. *J. Am. Chem. Soc.* **1977**, *99*, 7098–7100.
(35) Alternatively, the initial complex could involve a different conformer of the divinylcyclobutane followed by isomerization of nickel intermediates to **14b**. (See ref 34.)
(36) For example, *cis,trans*-cyclodeca-1,5-diene and related compounds. (a) Heimbach, P.; Wilke, G. *Liebigs Ann. Chem.* **1969**, *727*, 183–193. (b) *Ibid.* 194–207. (c) Brenner, W.; Heimbach, P.; Ploner, K. J.; Thoemel, F. *Ibid.* **1973**, *11*, 1882–1892.
(37) (a) Maitlis, P. M. "The Organic Chemistry of Palladium"; Academic Press: New York, 1971; Vol. 1 and 2. (b) For a review by L. E. Overman covering research on Pd(II) and Hg(II) catalysis in [3,3]-sigmatropic rearrangements, see: *Acc. Chem. Res.*, in press.
(38) Trebellas, J. C.; Olechowski, J. R.; Jonassen, H. B. *J. Organometal. Chem.* **1966**, *6*, 412–420.
(39) Heimbach, P. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 702–703.
(40) Heimbach, P.; Molin, M. *J. Organometal. Chem.* **1973**, *49*, 477–482.
(41) Brown, E. D.; Sam, T. W.; Sutherland, J. K.; Torre, A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2326–2332.
(42) The stereochemical assignment was based on limited data but is consistent with the Cope rearrangement stereochemistry found for related germacrane-type sesquiterpenes. Cf.: Takeda, K. *Tetrahedron* **1974**, *30*, 1525–1534.
(43) Heimbach, P.; Molin, M. *J. Organometal. Chem.* **1973**, *49*, 483–494.
(44) It was later reported[28] that isomer **13** yielded 7% *cis,trans*-1,5-diene at 95 °C. (See above.)
(45) Pd(II)-catalyzed double bond isomerization in **24** and **25** can account for nonstereospecific product formation, but it is not clear why isomerization would be confined to these compounds among those examined to date. Alternatively, nonstereospecificity can be due to competitive catalyzed reactions via boat and chair geometries. For example, **26** can be derived from **24** when the reaction takes place with boat geometry. A chair transition state would give a *cis,trans*-cycloocta-1,5-diene corresponding to **27**. Pd(II)-catalyzed trans → cis double bond isomerization in this relatively strained ring system would yield **27**.
(46) Overman, L. E.; Knoll, F. M. *J. Am. Chem. Soc.* **1980**, *102*, 865–867.
(47) The Pd(II)-catalyzed reaction is apparently first order in catalyst and diene, in contrast to the Ni(0)-catalyzed process, which is zero order in diene.
(48) Overman, L. E.; Jacobsen, E. V. *J. Am. Chem. Soc.* **1982**, *104*, 7225–7231.
(49) Cf.: Hill, R. K.; Gilman, N. W. *J. Chem. Soc., Chem. Commun.* **1967**, 619–620.
(50) Overman, L. E.; Renaldo, A. F. *Tetrahedron Lett.* **1983**, *24*, 3757–3760.
(51) Conia, J.-M.; LePerchec, P. *Bull. Soc. Chim. Fr.* **1966**, 273–277.
(52) Overman, L. E.; Renaldo, A. F. *Tetrahedron Lett.* **1983**, *24*, 2235–2238.
(53) Bluthe, N.; Malacria, M.; Gore, V. *Tetrahedron Lett.* **1983**, *24*, 1157–1160.
(54) Discussed in ref 48.
(55) Pd(IV) complexes of this type are apparently unknown. See ref 46 for citations dealing with related complexes.
(56) Hamilton, R.; Mitchell, T. R. B.; Rooney, J. J. *J. Chem. Soc., Chem. Commun.* **1981**, *10*, 456–457.
(57) Overman, L. E.; Campbell, C. B.; Knoll, F. M. *J. Am. Chem. Soc.* **1978**, *100*, 4822–4832.
(58) Henry, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 5200–5206.
(59) Lutz, R. P.; Berg, H. A. J.; Wang, P. J. *J. Org. Chem.* **1976**, *41*, 2048–2049.
(60) Reference 52 and citations therein.
(61) Bluthe, N.; Malacria, M.; Gore, V. *Tetrahedron Lett.* **1982**, *23*, 4263–4266.
(62) Yates, P.; Eaton, P. *Tetrahedron Lett.* **1960**, 5–9.
(63) Cookson, R. C.; Hudec, J.; Williams, R. O. *Tetrahedron Lett.* **1960**, 29–32.
(64) Woodward, R. B.; Katz, T. J. *Tetrahedron* **1959**, *5*, 70–89.
(65) Breslow, R.; Hoffman, J. M., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 2111–2112.
(66) (a) Reference 171. (b) Jolidon, S.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 978–1032. (c) Also referred to as charge-induced rearrangements: Widmer, U.; Zsindely, J.; Hansen, H.-J.; Schmid, H. *Ibid.* **1973**, *56*, 75–105.
(67) Carpenter, B. K. *Tetrahedron* **1978**, *34*, 1877–1884.
(68) For another opinion, see: Ahlgren, G. *Tetrahedron Lett.* **1979**, 915–918.
(69) Dauben, W. G.; Chollet, A. *Tetrahedron Lett.* **1981**, *22*, 1583–1586.
(70) Inversion of both allylic moieties is not demonstrated by the results.
(71) Miller, B. *Acc. Chem. Res.* **1975**, *8*, 245–256.
(72) Fahrni, P.; Habich, A.; Schmid, H. *Helv. Chim. Acta* **1960**, *43*, 448–452.
(73) Leitich, J. *Monatsh. Chem.* **1961**, *6*, 1167–1175.
(74) Miller, B. *J. Am. Chem. Soc.* **1965**, *87*, 5115–5120.
(75) (a) Miller, B. *J. Am. Chem. Soc.* **1970**, *92*, 6246–6252. (b) Miller, B. *J. Am. Chem. Soc.* **1969**, *91*, 2170–2172.
(76) Borgulya, T.; Madeja, R.; Gahrni, P.; Hansen, H.-J.; Schmid, H.; Barner, R. *Helv. Chim. Acta* **1973**, *56*, 14–75.
(77) Wunderli, A.; Zsindely, J.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 989–1011. BF_3 seems to be preferable to BCl_3 as a catalyst.
(78) Widmer, U.; Zsindely, J.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 75–105.
(79) Curiously, 6-allyl-6-methyl-2-*tert*-butylcyclohexa-2,4-dien-1-one yields 95% [3,3] product with either BCl_3 or HCl in chlorobenzene.[76]
(80) Schmid, H.; Zsindely, J.; Hansen, H.-J. *Special Lect. Int. Congr. Pure Appl. Chem.* **1971**, *1*, 251–274.
(81) Wunderli, A.; Winkler, T.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 2436–2459.
(82) Unpublished results mentioned in: Hansen, H.-J.; Schmid, H. *Tetrahedron* **1974**, *30*, 1959–1969.
(83) (a) Vittorelli, P.; Peter-Katalinic, J.; Mukherjee-Muller, G.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1975**, *58*, 1379–1425. (b) Hansen, H.-J.; Sutter, B.; Schmid, H. *Ibid.* **1968**, *51*, 828–867.
(84) Several examples given by Miller.[71]
(85) Miller[71] has suggested that interaction of an electrophile with the n or π electrons of the carbonyl group may lead to two distinct intermediates, the former prone to rearrange like a Cope system, the latter like a carbonium ion.
(86) Schmid, M.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1971**, *54*, 937–951.
(87) Reviewed in ref 1a. Cf. references given by Evans and Golub.[95]
(88) Swaminathan, S.; Srinivasan, K. G.; Venkataramani, P. S. *Tetrahedron* **1970**, *26*, 1453–1461.
(89) Swaminathan, S.; John, J. P.; Ramachandran, S. *Tetrahedron Lett.* **1962**, 729–734.
(90) John, J. P.; Srinivasan, K. G.; Venkataramani, P. S.; Swaminathan, S. *Tetrahedron* **1969**, *25*, 2661–2666.
(91) Raju, N.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron Lett.* **1980**, 1577–1580.
(92) Rao, C. S. S.; Kumar, G.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron* **1982**, *38*, 2195–2199.
(93) Tice, C. M.; Heathcock, C. H. *J. Org. Chem.* **1981**, *46*, 9–13.
(94) Chandrasekaran, S.; Venkataramani, P. S.; Srinivasan, K. G.; Swaminathan, S. *Tetrahedron Lett.* **1973**, 991–994.
(95) Evans, D. A.; Golub, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765–4766.
(96) Evans, D. A.; Nelson, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 774–782.
(97) Preparative yields were 75–80% from a mixture of **96a,b** and about 30% from **97a,b**.
(98) (a) Paquette, L. A.; Crouse, G. D.; Sharina, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 4411–4423. (b) Crouse, G. D.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 3167–3170.
(99) The use of $Na^+{}^-CH_2SOCH_3$ in THF at 0 °C resulted in 93% of **99**.[98a]
(100) See examples given in: Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190–3192. For synthetic applications of a vinylogous anionic oxy-Cope ([5,5]-sigmatropic) rearrangement, see: Wender, P. A.; Sieburth, S. M.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967–3975.
(101) Evans, D. A.; Baillargeon, D. J. *Tetrahedron Lett.* **1978**, 3319–3322.
(102) Streigerwold, M. L.; Goddard, W. A., III; Evans, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 1994–1997. These calculations reproduce the observed tendency for greater reactivity in the more "naked" anions.
(103) However, see ref 1b, p 175.
(104) (a) Allerhand, A.; Gutowsky, H. S. *J. Am. Chem. Soc.* **1965**, *87*, 4092–4096. (b) McKechnie, J.; Paul, I. C. *Chem. Commun.* **1968**, 44–45.
(105) Aumann, R. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 800–801.
(106) Moriarty, R. M.; Yeh, C.-L.; Yeh, E.-L.; Ramey, K. C. *J. Am. Chem. Soc.* **1972**, *94*, 9229–9230.
(107) Aumann, R. *J. Organometal. Chem.* **1974**, *66*, C6–C10.
(108) Aris, V.; Brown, J. M.; Golding, B. T. *J. Chem. Soc., Chem. Commun.* **1972**, 1206–1207.
(109) Ahlberg, P.; Brutzner, J. B.; Harris, D. L.; Winstein, S. *J. Am. Chem. Soc.* **1970**, *92*, 3478–3480.
(110) (a) McMichael, K. D.; Korver, G. L. *J. Am. Chem. Soc.* **1979**, *101*, 2746–2747. (b) Bryusova, L. Y.; Ioffe, M. L. *Zh. Obshch. Khim.* **1941**, *11*, 722–728; *Chem. Abstr.* **1942**, *36*, 430[3].
(111) (a) Fahrni, P.; Habich, A.; Schmid, H. *Helv. Chim. Acta* **1960**, *43*, 448–452. (b) Schmid, H. *Gazz. Chim. Ital.* **1962**, *92*, 968–982; *Chem. Abstr.* **1963**, 8882.

(112) Kozikowski, A. L.; Sugiyama, K.; Huie, E. *Tetrahedron Lett.* **1981**, *22*, 3381–3384.
(113) (a) Feoktistov, V. M.; Bunina-Krivorukova, L. I. *Zh. Org. Khim.* **1978**, *14*, 807–811. (b) Aleksandrova, E. K.; Bunina-Krivorukova, L. I.; Bal'yan, Kh. V. *Ibid.* **1980**, *16*, 459–460. (c) Aleksandrova, E. K.; Bunina-Krivorukova, L. I. *Ibid.* **1982**, *18*, 855–859. (d) Bunina-Krivorukova, L. I.; Feoktistov, V. M.; Aleksandrova, E. K.; Bal'yan, Kh. V. *Ibid.* **1982**, *18*, 859–865.
(114) Petropoulos, J. C.; Tarbell, D. S. *J. Am. Chem. Soc.* **1952**, *74*, 1249–1253.
(115) (a) Sonnenberg, F. M. *J. Org. Chem.* **1970**, *35*, 3166–3167. (b) Alberola, A.; Bolado, B.; Gonzalez-Nogal, A. M. *An. Quim., Ser. C* **1982**, *78*, 57–66; *Chem. Abstr.* **1982**, *97*, 38593.
(116) Bender, D. R.; Kanne, D.; Frazier, J. D.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 2709–2719.
(117) Bates, D. K.; Janes, M. W. *J. Org. Chem.* **1978**, *43*, 3856–3861.
(118) Thyagarajan, B. S.; Balasubramanian, K. K.; Rao, R. B. *Tetrahedron* **1967**, *23*, 1893–1899.
(119) Meltzer, R. I.; King, J. A. *J. Am. Chem. Soc.* **1953**, *75*, 1355–1359.
(120) Blomberg, C.; Vreugdenhil, A. D.; Vink, P. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1409–1417.
(121) Bunina-Krivorukova, L. I.; Rossinakii, A. P.; Bal'yan, Kh. V. *Zh. Org. Khim.* **1978**, *14*, 586–593.
(122) Aleksandrova, E. K.; Bunina-Krivorukova, L. I.; Moshimskaya, A. V.; Bal'yan, Kh. V. *Zh. Org. Khim.* **1974**, *10*, 1039–1046.
(123) Hayashi, T.; Goto, M. *Nippon Kagaku Kaishi* **1978**, 1007–1012; *Chem. Abstr.* **1978**, *89*, 128852.
(124) (a) Narasaka, K.; Bald, E.; Mukaiyama, T. *Chem. Lett.* **1975**, 1041–1044. (b) Saidi, M. R. *Heterocycles* **1982**, *19*, 1473–1475.
(125) Koch-Pomeranz, U.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 2981–3004.
(126) Harfenist, M.; Thom, E. *J. Org. Chem.* **1972**, *37*, 841–848.
(127) Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1510–1514.
(128) It is curious that the $AgBF_4$-catalyzed reaction of propargyl phenyl ether in benzene at room temperature gave only 2*H*-chromene, whereas 2-allenylphenol, the presumed intermediate in the rearrangement, gave both 2*H*-chromene and 2-methylcoumaran under similar conditions. Many side products were produced in the Ag(I)-catalyzed reaction of 2-allenylphenol.
(129) Olsson, L. I.; Claesson, A. *Synthesis* **1979**, 743–745.
(130) The same product was formed in the thermal reaction (160 °C, decane, half-life = 34 min).[125] Rearrangement to the alternate, unsubstituted [3,3] terminus would lead to complete loss of aromaticity in the intermediate.
(131) Reference 117. Experimental details were not given, but are presumed to be similar to those employed in other Hg(II)-catalyzed rearrangements reported by the same authors.[132] Cf.: Majunder, K. C.; Thyagarajan, B. S. *J. Heterocycl. Chem.* **1972**, *9*, 489–494.
(132) Bates, D. K.; Jones, M. C. *J. Org. Chem.* **1978**, *43*, 3775–3776.
(133) Gelin, R.; Albrand, M.; Gelin, S. *C. R. Seances Acad. Sci., Ser. C* **1969**, *269*, 241–244.
(134) (a) Widmer, U.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 2644–2648. (b) Harwood, L. M. *J. Chem. Soc., Chem. Commun.* **1982**, 1120–1122; **1983**, 530–532.
(135) White, W. N.; Wolfarth, E. F. *J. Org. Chem.* **1970**, *35*, 2196–2199.
(136) (a) Svanholm, U.; Parker, V. D. *Chem. Commun.* **1972**, 645–646. (b) Svanholm, U.; Parker, V. D. *J. Chem. Soc., Perkin Trans. 2* **1974**, 169–173.
(137) Apparently Svanholm and Parker did not take into account the possible formation of secondary cyclization products, and probably misinterpreted changes in NMR spectra during reaction. The product of CF_3CO_2H addition to the double bond may indeed have been isolated, but, with the very long reaction times employed (2 weeks in CF_3CO_2H at room temperature),[136b] it was probably formed indirectly from cyclization products related to 2-methylcoumaran.
(138) Frihart, C. R.; Leonard, N. J. *J. Am. Chem. Soc.* **1973**, *95*, 7174–7175.
(139) Balavoine, G.; Bram, G.; Guibe, F. *Nouv. J. Chim.* **1978**, *2*, 207–209.
(140) Murray, R. D. H.; Sutcliffe, M.; Hasegawa, M. *Tetrahedron* **1975**, *31*, 2966–2971.
(141) Gajewski, J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 6693–6704.
(142) Wunderli, A.; Winkler, T.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 2436–2459.
(143) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 3985–3988. (For additional work by these authors abstracted after the submission date of this review, see: Nozaki, H.; Utimoto, K.; Oshima, K.; Takai, K. *Kenkyu Hokoku - Asahi Garasu Kogyo Gijutsu Shoreikai* **1982**, *40*, 83–89; *Chem. Abstr.* **1983**, *99*, 138954q.)
(144) Buchi, G.; Powell, J. E., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 3126–3133.
(145) Stevenson, J. W. S.; Bryson, T. A. *Tetrahedron Lett.* **1983**, *23*, 3143–3146.
(146) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270–3272.
(147) Ficini, J. *Tetrahedron* **1976**, *32*, 1449–1486.
(148) Bartlett, P. A.; Hahne, W. F. *J. Org. Chem.* **1979**, *44*, 882–883.
(149) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030–1042.
(150) The BF_3 undoubtedly catalyzed the addition of the alcohol to the ynamine. With reactive ynamines such as methyl(*N,N*-diethylamino)acetylene, the addition of alcohol followed by rearrangement occurs without catalyst using undiluted reagents, in an exothermic process whose temperature is not allowed to exceed 40–45 °C (Ficini, J., Université Pierre et Marie Curie, Paris, personal communication, 1983). This establishes that the Claisen rearrangement here occurs under very mild conditions, and renders unlikely, but does not rigorously rule out, the involvement of BF_3 in the rearrangement step. Treatment of **200** (R_1 = *n*-Bu, R_2 = H) with BF_3 gave a complex mixture containing no detectable [3,3] product.[143]
(151) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brockson, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.
(152) Experiments relating to the thermal rearrangements of 2-methoxy substrates analogous to **214** are reported to be in progress.[8]
(153) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.
(154) Reed, S. R., Jr. *J. Org. Chem.* **1965**, *30*, 1663–1665.
(155) With the corresponding cyano derivative, a kinetic study was carried out at 55–100 °C.[8]
(156) For recent examples, see ref 143.
(157) Ralls, J. W.; Lundin, R. E.; Bailey, G. F. *J. Org. Chem.* **1963**, *28*, 3521–3526 and earlier references cited.
(158) The Claisen analogue of the oxy-Cope or anionic oxy-Cope rearrangement of 3-hydroxyhexa-1,5-dienes is not feasible because of the lability of the species involved.
(159) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972–4974. An investigation of stereoselectivity was reported after the submission date of this article in: Denmark, S. E.; Harmata, M. A. *J. Org. Chem.* **1983**, *48*, 3369–3370. For potential anionic rearrangement with an analogous phenyl sulfoxide, see: Cookson, R. C.; Gopalan, R. *J. Chem. Soc., Chem. Commun.* **1978**, 608.
(160) Ponaras, A. A. *Abstr. Pap—Am. Chem. Soc.* **1983**, *186th* ORG 236. Details were published after the submission of this article in: Ponaras, A. A. *J. Org. Chem.* **1983**, *48*, 3866–3868.
(161) Tsuji, J.; Kobayshi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, 1475–1478.
(162) Rhoads, S. J.; Watson, J. M. *J. Am. Chem. Soc.* **1971**, *93*, 5813–5815.
(163) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 2485–2487.
(164) Allyl phenyl ether is smoothly cleaved by $PdCl_2(PhCN)_2$ without competing Claisen rearrangement: Bruce, J. M.; Roshan-Ali, Y. *J. Chem. Res. Synop.* **1981**, 193.
(165) Kiji, J.; Nishimura, S.; Yamamoto, K.; Furukawa, J. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3417–3418.
(166) Reuter, J. M.; Salomon, R. G. *J. Org. Chem.* **1977**, *42*, 3360–3364.
(167) Gladiali, S.; Faedda, G. A.; Botteghi, C.; Menchi, G. *Chim. Ind. (Milan)* **1981**, *63*, 506–511.
(168) Walsh, C. "Enzymatic Reaction Mechanisms"; W. H. Freeman: San Francisco, 1979; Chapter 20.
(169) (a) Ife, R. J.; Ball, L. F.; Lowe, P.; Haslam, E. *J. Chem. Soc.* **1976**, 1776–1783. (b) Sogo, S. G.; Widlanski, T. S.; Hoare, J. H.; Grimshaw, C. E.; Berchtold, G. A.; Knowles, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 2701–2703.
(170) Reviewed in ref 171. Cf. ref 172.
(171) Heimgartner, H.; Hansen, H.-J.; Schmid, H. In "Iminium Salts in Organic Chemistry"; Böhme, H., Viehe, H., Eds.; Wiley-Interscience: New York, 1979; Part 2, pp 655–731.
(172) (a) Jolidon, S.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 978–1032. (b) A reviewer made the following comments about the secondary kinetic deuterium isotope effects reported in this reference: "The discussion of transition state structure in these amino-Claisen rearrangements based on the KIE's reported is tarnished by the data. The large error limits that Lutz reported indicate that the effects should not and cannot be interpreted. In fact, it does a disservice to those of us who sweat blood and tears to measure these effects to much higher precision to even discuss the relevance of these KIE's."
(173) Unprotonated forms are shown in equations, although the amines were fully protonated in 1 N H_2SO_4. Alkaline workup gave the neutral products.

(174) In the thermal reactions, the achievement of a chair transition state requires that the nitrogen lone pair resonance become sterically inhibited. This is apparently the source of the higher activation enthalpies for thermal amino-Claisen rearrangements compared to oxygen counterparts.[172]
(175) Schmid, M.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 105–124.
(176) Krowicki, K.; Paillous, N.; Riviere, M.; Lattes, A. *J. Heterocycl. Chem.* **1976**, *13*, 555–560.
(177) de Saqui-Sannes, G.; Riviere, M.; Lattes, A. *Tetrahedron Lett.* **1974**, 2073–2076.
(178) (a) Bader, R.; Bridgewater, R. J.; Freeman, P. R. *J. Am. Chem. Soc.* **1961**, *83*, 3319–3323. (b) McDonald, B. G.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1446–1450. (c) Towne, E. B.; Hill, H. M. U.S. Patent 2607779, 1952; *Chem. Abstr.* **1953**, *47*, 5452.
(179) George, C.; Gill, E. W.; Hudson, J. A. *J. Chem. Soc. C* **1970**, 74–78.
(180) (a) Casnati, B.; Marchelli, R.; Pochini, A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 754–757. (b) Casnati, B.; Pochini, A. *Chem. Commun.* **1970**, 1328–1329.
(181) Reference 171. Cf. ref 172.
(182) (a) Abdrakhmanov, I. B.; Sharafutdinov, V. M.; Sagitdinov, I. A.; Tolstikov, G. A. *Zh. Org. Khim.* **1979**, *15*, 2601–2604. (b) Abdrakhmanov, I. B.; Fakhretdinov, R. N.; Khusnutdinov, R. N.; Dzhemilev, U. M. *Ibid.* **1981**, *17*, 2604–2608.
(183) Briefly reviewed in ref 171.
(184) Hurd, C. D.; Jenkins, W. W. *J. Org. Chem.* **1957**, *22*, 1418–1423.
(185) (a) Takamatsu, N.; Kishi, Y. *Tetrahedron Lett.* **1971**, 4661–4664. (b) Tanaka, J.; Takabe, K.; Taniguchi, K.; Katagiri, T. *Nippon Kagaku Kaishi* **1981**, 1043–1045; *Chem. Abstr.* **1981**, *95*, 219818.
(186) Elliot, M.; James, N. F. *J. Chem. Soc. C* **1967**, 1780–1782. Cf. ref 185a, 187.
(187) Inoue, S.; Takamatsu, N.; Kishi, Y. *Yakagaku Zasshi* **1977**, *97*, 553–557.
(188) Inada, S.; Nagai, K.; Takayanagi, Y.; Okazaki, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 833–834.
(189) Patterson, J. M.; Wa, A.; Kook, C. S.; Smith, W. T. *J. Org. Chem.* **1974**, *39*, 486–488.
(190) Dillard, R. D.; Parey, D. E.; Beuslay, D. N. *J. Med. Chem.* **1973**, *16*, 251–253.
(191) Easton, N. R.; Cassady, D. R. *J. Org. Chem.* **1962**, *27*, 4713–4714.
(192) Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 478–489.
(193) Hill, R. K.; Khatri, H. N. *Tetrahedron Lett.* **1978**, 4337–4340.
(194) Ficini, J.; Barbara, C. *Tetrahedron Lett.* **1966**, 6425–6429.
(195) (a) Reference 1a, p 66. Rearrangement occurred at room temperature or refluxing xylene, depending on substituents. (b) Brombach, D.; Vogtle, F. *Synthesis* **1977**, 800–802. Temperature requirements were modest; some samples rearranged at 34 °C.
(196) Kakimoto, M.; Okawara, M. *Chem. Lett.* **1979**, 1171–1174.
(197) Overman, L. E.; Kakimoto, M.; Okawara, M. *Tetrahedron Lett.* **1979**, 4041–4049. Experimental details have appeared in: Overman, L. E.; Kakimoto, M.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622–6628.
(198) (a) Horowitz, R. M.; Gerisman, T. A. *J. Am. Chem. Soc.* **1950**, *72*, 1518–1522.
(199) For reviews: (a) Morin, L.; Lebaud, J.; Paguer, D.; Chaussin, R.; Barillier, X. *Phosphorus Sulfur* **1979**, *7*, 69–80. (b) Reference 1a.
(200) Kwart, H.; Johnson, N. A.; Eggerichs, I.; George, T. J. *J. Org. Chem.* **1977**, *42*, 172–174.
(201) Kwart, H.; Schwartz, J. L. *J. Org. Chem.* **1974**, *39*, 1575–1583.
(202) Kwart, H.; Evans, E. R. *J. Org. Chem.* **1966**, *31*, 413–419.
(203) Kwart, H.; Miles, W. H.; Horgan, A. G.; Kwart, L. D. *J. Am. Chem. Soc.* **1981**, *103*, 1757–1760.
(204) Gopalan, B.; Rajagopalan, K.; Swaminathan, S.; Balasubramanian, K. K. *Synthesis* **1976**, 409–411.
(205) Bycroft, B. W.; Landon, W. *J. Chem. Soc., Chem. Commun.* **1970**, 967–968.
(206) Bycroft, B. W.; Landon, W. *J. Chem. Soc., Chem. Commun.* **1970**, 168–169.
(207) Barillier, D.; Morin, L.; Paquer, D.; Rioult, P.; Vazeux, M.; Andrieu, C. G. *Bull. Soc. Chim. Fr.* **1977**, 688–692.
(208) Metzner, P.; Pham, T. N.; Vialle, J. *Nouv. J. Chim.* **1978**, *2*, 179–182.
(209) Metzner, P.; Pham, T. N.; Vialle, J. *J. Chem. Res. Synop.* **1978**, 478–479.
(210) Takahashi, H.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 5803–5804.
(211) Tamura, Y.; Harada, T.; Nishi, S.; Mizutana, M.; Hioki, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1980**, *102*, 7806–7808.
(212) Oshima, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 2693–2694.
(213) Corey, E. J.; Shulman, J. I. *J. Am. Chem. Soc.* **1970**, *92*, 5522–5523.
(214) Dalgaard, L.; Lawesson, S. O. *Tetrahedron* **1972**, *28*, 2051–2063.
(215) Dalgaard, L.; Lawesson, S. O. *Acta Chem. Scand., Ser. B* **1974**, *B28*, 1077–1090.
(216) Winterfeldt, E. *Fortschr. Chem. Forsch.* **1970**, *16*, Part 1, 75–102.
(217) Vögtle, F.; Goldschmitt, E. *Chem. Ber.* **1976**, *109*, 1–40.
(218) Lewis, E. S.; Hill, J. T. *J. Am. Chem. Soc.* **1969**, *91*, 7458–7462.
(219) Leavell, K. H.; Lewis, E. S. *Tetrahedron* **1972**, *28*, 1167–1171.
(220) Henry, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 5200–5206. This paper also cites earlier references to Pd(II) catalysis.
(221) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, 321–324.
(222) Grieco, P. A.; Takigawa, T.; Bongers, S. L.; Tanako, H. *J. Am. Chem. Soc.* **1980**, *102*, 7587–7588.
(223) Grieco, P. A.; Tuthill, P. A.; Sham, H. L. *J. Org. Chem.* **1981**, *46*, 5006–5007.
(224) Takatsuto, S.; Ishiguro, M.; Ikekawa, N. *J. Chem. Soc., Chem. Commun.* **1982**, 258–260.
(225) Golding, B. T.; Pierpoint, C.; Aneja, R. *J. Chem. Soc., Chem. Commun.* **1981**, 1030–1031.
(226) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. *Tetrahedron Lett.* **1979**, 2301–2304.
(227) Mandai, T.; Hashio, S.; Goto, J.; Kawada, M. *Tetrahedron Lett.* **1981**, *22*, 2187–2190.
(228) (a) Overman, L. E.; Campbell, C. B.; Knoll, F. M. *J. Am. Chem. Soc.* **1978**, *100*, 4822–4832. (b) Overman, L. E.; Campbell, D. B. *J. Org. Chem.* **1976**, *41*, 3338–3340. (c) Trost, B. M.; Timko, J. M.; Stanton, J. L. *J. Chem. Soc., Chem. Commun.* **1978**, 436–438.
(229) (a) Eschenmoser, A., Peter A. Leermakers Symposium Lecture, Wesleyan, CT; reported in ref 37b. (b) Rappaport, Z.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1972**, *94*, 2320–2329.
(230) Saucy, G.; Marbet, R.; Lindar, H.; Isler, O. *Helv. Chim. Acta* **1959**, *42*, 1945–1955.
(231) Schlossarczyk, H.; Sieber, W.; Hesse, M.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 875–944.
(232) Cited in ref 231.
(233) (a) Oelberg, D. G.; Schiavelli, M. D. *J. Org. Chem.* **1977**, *42*, 1804–1806. (b) Cookson, R. C.; Cramp, M. C.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1980**, 197–198.
(234) Paulo, S.; Pryde, A.; Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1978**, *61*, 266–278.
(235) (a) Lloyd, H. A.; Sokolski, E. A.; Strauch, B. S.; Fales, H. M. *J. Chem. Soc., Chem. Commun.* **1969**, 299–301. (b) Chauhan, M.; Dean, F. M.; Hindley, K.; Robinson, M. *Ibid.* **1971**, 1141–1143.
(236) Lutz, R. P.; Roberts, J. D. *J. Am. Chem. Soc.* **1961**, *83*, 2198–2199.
(237) Reference 235b. The term "constant temperature" probably means standard NMR probe temperature.
(238) Dixie, C. J.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1972**, 646–647. In the unsubtituted derivative (Br = H), there was no change in the NMR spectrum up to 200 °C.
(239) (a) Chung, C. Y.-J.; Mackey, D.; Sauer, T. D. *Can. J. Chem.* **1972**, *50*, 1568–1573. (b) Barrett, W. G.; Mackey, D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1046–1052.
(240) Jennison, C. P. R.; Mackey, D. *Tetrahedron* **1973**, *29*, 1255–1258.
(241) Campbell, J. A.; Harris, I.; Mackey, D.; Sauer, T. D. *Can. J. Chem.* **1975**, *53*, 535–541.
(242) (a) Mackey, D.; Pilger, C. W. *Can. J. Chem.* **1974**, *52*, 1114–1121. (b) Cf.: Dao, L. H.; Mackey, D. *Ibid.* **1978**, *56*, 1724–1728.
(243) Reviewed in ref 244c; cf. ref 244b.
(244) (a) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597–599. (b) Overman, L. E. *Ibid.* **1976**, *98*, 2901–2910. (c) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218–224.
(245) Reference 19 in ref 244c.
(246) Stewart, H. F.; Seibert, R. P. *J. Org. Chem.* **1968**, *33*, 4560–4561.
(247) Balavoine, G.; Guibe, F. *Tetrahedron Lett.* **1979**, 3949–3952.
(248) Mooradian, A.; Dupont, P. E. *Tetrahedron Lett.* **1967**, 2867–2870.
(249) (a) Sheradsky, T. *Tetrahedron Lett.* **1966**, 5225–5227. (b) Mooradian, A. *Ibid.* **1967**, 407–408. (c) Mooradian, A.; Dupont, P. E. *J. Heterocycl. Chem.* **1967**, *4*, 441–444. (d) Kaminsky. D.; Shavel, J., Jr.; Meltzer, R. I. *Tetrahedron Lett.* **1967**, 859–861.
(250) (a) Schiess, P.; Sendi, E. *Helv. Chim. Acta* **1978**, *61*, 1364–1372. (b) Schiess, P.; Grieder, A. *Ibid.* **1974**, *57*, 2643–2657.
(251) Posvic, H.; Dombro, R.; Ito, H.; Telinski, T. *J. Org. Chem.* **1974**, *39*, 2575–2580.
(252) Reviews cited in ref 171 and 250. Cf.: Robinson, B. "The Fischer Indole Synthesis"; Wiley: New York, 1983.

(253) Banthorpe, D. V. *J. Chem. Soc.* **1964**, 2854–2860.
(254) Banthorpe, D. V. *J. Chem. Soc.* **1962**, 2429–2435.
(255) Reviewed in: Shine, H. In "Mechanisms of Molecular Migrations"; Thyagarajan, B. S., Ed.; Wiley Interscience: New York, 1969; Vol. 2, pp 191–247.
(256) Reference 255. See ref 257 for more recent reviews.
(257) Shine, H. J.; Zinuda, H.; Park, K. H.; Kwart, H.; Horgan, A. G.; Collins, C.; Maxwell, B. E. *J. Am. Chem. Soc.* **1981**, *103*, 955–956.
(258) Association of these reactions with the Claisen rearrangement has already been made.[255]
(259) Sucrow, W.; Chondromatidis, G. *Chem. Ber.* **1970**, *103*, 1759–1766.
(260) Discussed in ref 171.
(261) Reference 217 and earlier references cited. No rearrangements occurred with 3,4-diphenyl-2,5-diazahexa-1,5-dienes with one or two alkyl groups on each double bond.
(262) Vögtle, F.; Goldschmitt, E. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 480–482.
(263) Quast, H.; Stawitz, J. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 643–645.
(264) Tamaru, Y.; Kagotani, M.; Yoshida, Z. *J. Org. Chem.* **1980**, *45*, 5221–5223. (Additional work appeared after the submission data of this review in: Mizutani, M.; Sanemitsu, Y.; Tamaru, Y.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 4585–4589.)
(265) Tamaru, Y.; Kagonati, M.; Yoshida, Z. *Tetrahedron Lett.* **1981**, *22*, 4245–4248.
(266) Jones, D. S. Ph.D. Dissertation, University of Utah, Salt Lake City, UT, 1982; *Diss. Abstr. Int. B.* **1982**, *43*, 428.
(267) Hackler, R. E.; Balko, T. W. *J. Org. Chem.* **1973**, *38*, 2106–2109.