Origins of Regio- and Stereoselectivity in Additions of Phenylselenenyl Chloride to Allylic Alcohols and the Applicability of These Additions to a Simple 1,3-Enone Transposition Sequence

Dennis Liotta,*[1] George Zima, and Manohar Saindane

Department of Chemistry, Emory University, Atlanta, Georgia 30322

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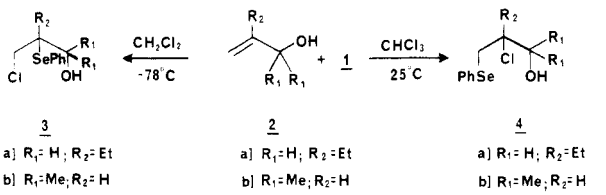
The regio- and stereoselectivity of phenylselenenyl chloride additions to allylic alcohols and their derivatives have been systematically studied. On the basis of the results, a mechanism involving two basic premises is proposed. These are as follows: (a) allylic oxygen's direct selenonium ion formation to the syn face of the double bond; (b) axial attack of the chloride ion is kinetically favored over equatorial attack. A series of rules which are useful for predicting the regio- and stereoselectivity of phenylselenenyl chloride additions to allylic systems are discussed. In addition, these reactions can be used as the key step in a general 1,3-enone transposition sequence. Several examples of this transposition sequence are illustrated.

The synthetic utility of olefin addition reactions involving electrophilic selenium species is now well established.[2,3] Recently, we reported that (a) phenylselenenyl chloride adds to allylic alcohols in a highly regio- and stereoselective fashion and that (b) additions of this type could be used as the key step of a simple 1,3-enone transposition sequence.[4] In this paper we provide insight into the origins of the regio- and stereoselectivity of these addition reactions as well as further demonstrate the generality of the transposition sequence.

The results of our study involving the regio- and stereochemical consequences of phenylselenenyl chloride additions to allylic alcohols and their derivatives are given below. Most of the adducts listed were characterized on the basis of their NMR spectra. By use of this method of analysis, unequivocal assignment of the regio- and stereochemistry of most of the phenylselenenyl chloride adducts could be readily achieved.

PhSeCl Additions to Allylic Alcohols and Their Derivatives

Terminal allylic alcohols are quite unique in their reactions with phenylselenenyl chloride (1). Just as in the reaction of simple terminal olefins with 1, terminal allylic alcohols react with 1[2a,e] under kinetic conditions (−78 °C, CH_2Cl_2) to provide anti-Markovnikov adducts and under thermodynamic conditions (25 °C, $CHCl_3$ or CH_3CN) to produce Markovnikov adducts. If the anti-Markovnikov adducts which are formed under kinetic conditions are not quickly made to undergo a subsequent reaction at low temperature (e.g., oxidative elimination, dehydrohalogenation, etc.), they begin to isomerize to their corresponding Markovnikov adducts. These processes are illustrated below in the reaction of 1 with **2a** and **2b**.



3
a] R_1=H; R_2=Et
b] R_1=Me; R_2=H

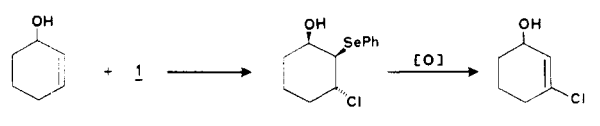
2
a] R_1=H; R_2=Et
b] R_1=Me; R_2=H

4
a] R_1=H; R_2=Et
b] R_1=Me; R_2=H

Additions of 1 to nonterminal, acyclic allylic alcohols usually result in the formation of a mixture of regioisomers. For example, addition of 1 to **5** produces **6** and **7** in a 7:3 ratio (Scheme I), while addition of 1 to **8** produces **9** and **10** in a 3:2 ratio. The ratios of **6** to **7** and **9** to **10** appear to be more or less independent of the reaction conditions employed (i.e., solvent, temperature, and time). The poor regioselectivity observed in additions of 1 to nonterminal, acyclic, allylic alcohols is not surprising since both carbons of the presumed episelenonium ion intermediate, **11**, are both electronically and sterically similar.[6]

By contrast, when allylic acetates such as **13** and **16** are allowed to react with 1, a high degree of regioselectivity (>20:1) is observed (Scheme II). This dramatic increase in the regioselectivity of these additions can be qualitatively understood in terms of the relative charge densities at C_α and C_β in **11** vs. **12**. In **11**, the hydroxyalkyl substituent attached to C_α is expected to be a somewhat weaker inductive donor than the alkyl substituent attached to C_β, resulting in a larger charge density at C_β. In **12** the difference between the relative charge densities at C_β and C_α should be larger, since the acetoxylalkyl substituent represents an even poorer inductive donor than the hydroxyalkyl substituents in **11**. Obviously, the larger the difference between the charge densities at C_β and C_α, the greater should be the observed regioselectivity.

While one can adequately rationalize the regioselectivity observed in additions of 1 to acyclic allylic alcohols and their derivatives using the criteria discussed above, additional factors must be considered for reactions of 1 with cyclic allylic systems. For example, addition of 1 to a chloroform solution of **19** results in the formation of only



19 20 21

(1) Fellow of the Alfred P. Sloan Foundation, 1980-1984. Recipient of a Camille and Henry Dreyfus Teacher-Scholar Fellowship, 1981-1986.

(2) For additions of simple selenium electrophiles to double bonds, see: (a) Liotta, D.; Zima, G. *Tetrahedron Lett.* **1978**, 4977. (b) Sharpless, K. B.; Lauer, R. F. *J. Org. Chem.* **1974**, *39*, 429. (c) Reich, H. J. *Ibid.* (1974) *39*, 428. (d) Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1974**, 100. (e) Raucher, S. *J. Org. Chem.* **1977**, *42*, 2950. (f) Kataev, E. G.; Mannafov, T. G.; Berdnikov, K. A.; Kamarovskaya, O. A. *Zh. Org. Khim* **1973**, *9*, 1983.

(3) For the use of selenium electrophiles in the confunctionalization of double bonds, see: (a) Clive, D. L. J.; Chittattu, G. *J. Chem. Soc., Chem. Commun.* **1977**, 484. (b) Nicolaou, K. C.; Sertz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884.

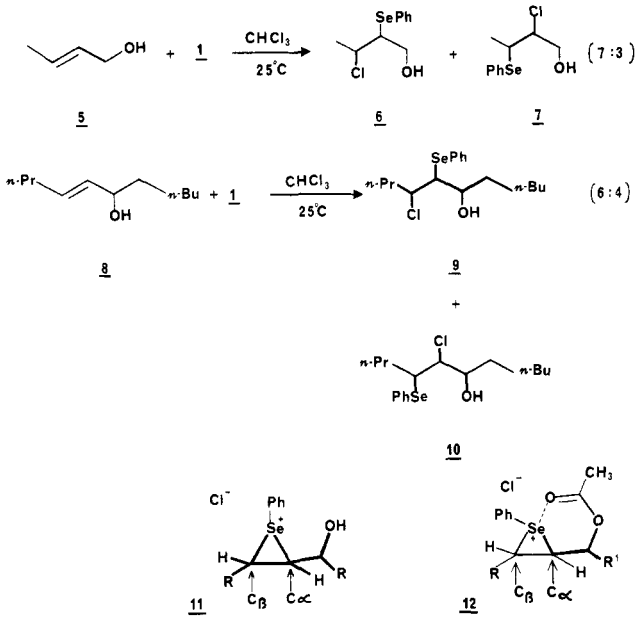
(4) Liotta, D.; Zima, G. *J. Org. Chem.* **1980**, *45*, 2551.

(5) A CHSePh typically appears in the δ 3.0-3.5 region, a CHOH typically appears in the δ 3.5-4.0 region, and a CHCl typically appears in the δ 4.0-4.5 region.

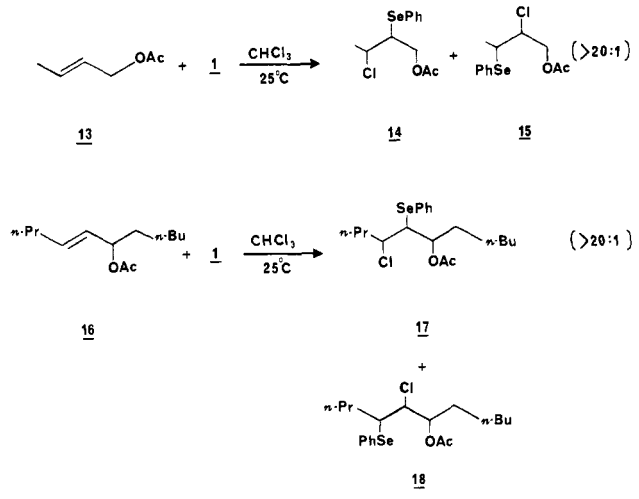
(6) Simple episelenonium ions have been observed spectroscopically. See: Schmid, G. H.; Garratt, D. G. *Tetrahedron Lett.* **1975**, 3991.

0022-3263/82/1947-1258$01.25/0

Scheme I



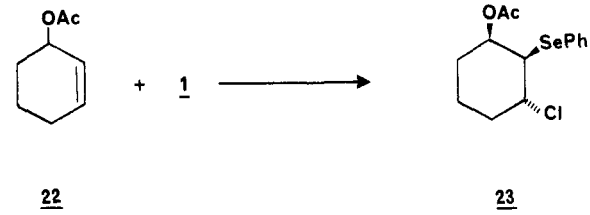
Scheme II



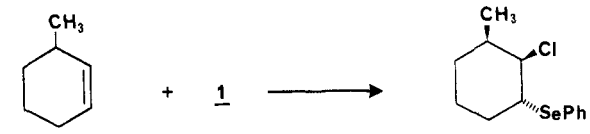
one of the four possible diastereomeric pairs. The stereochemistry of **20** is readily ascertained on the basis of both chemical and spectroscopic data. The fact that **20** undergoes regiospecific oxidative elimination to produce **21** indicates that the phenylseleno group and the chlorine possess a trans relationship.[7] Moreover, in the NMR spectrum of **20** the CH–SePh appears as a doublet of doublets (J = 6 Hz, J' = 3 Hz), suggesting a cis relationship between the hydroxyl and phenylseleno groups.[8]

In order to understand the origins of the regio- and stereospecificity of these additions, we performed a number of preliminary experiments. Reaction of **22** with **1** yields adduct **23**, which possesses the same regio- and stereochemical substitution pattern as adduct **20**. This therefore eliminates from consideration any association between the hydroxyl group of **19** with **1** due to hydrogen bonding.

The fact that addition of **1** to **19** is regiospecific, while additions of **1** to nonterminal acyclic allylic alcohols are generally only regioselective (e.g., **5** + **1**) suggests that the

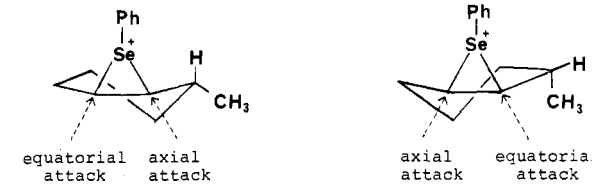


enhanced regioselectivity in cyclic systems is a consequence of conformational rather than electronic factors. In order to probe this, we examined the addition of **1** to **24**.



Compound **24** is a particularly attractive test case because (a) the methyl substituent cannot interact directly with **1**, (b) the methyl substituent exerts a very weak electronic perturbation on the system, effectively leaving the two olefin carbons electronically equivalent, and (c) the methyl group can exert a moderately large conformation bias. Thus, if electronic factors are dominant, the reaction of **24** with **1** should yield a complex mixture of diastereomers. On the other hand, if conformational factors are dominant, the reaction of **24** with **1** should exhibit some selectivity.

In practice, the reaction yields only a single adduct, whose structure has been assigned as **25** on the basis of its NMR spectrum. The simplest rationale for this is that **1** initially reacts with **24** on its less hindered face to yield selenonium ion **26**. Intermediate **26** is then attacked by



chloride ion in an axial fashion to yield **25**.[9] Since **26** is presumably in equilibrium with its other conformer, **27**, some of the products derived from chloride attack on it might also be expected to form. However, these are not observed presumably because axial attack by chloride ion on **27** is hindered by the axial methyl substituent.

The regio- and stereoselectivity observed in the reaction of **19** and **1** can also be readily understood by using this model, if one assumes an initial coordination of **1** with the electron-rich hydroxyl group, followed by an intramolecular "delivery" of the electrophilic selenium species to the double bond (**28** → **29** ⇄ **30**). Ring flip of **29** to its conformationally more stable form, **30**, followed by axial attack of chloride ion would then yield **20**.

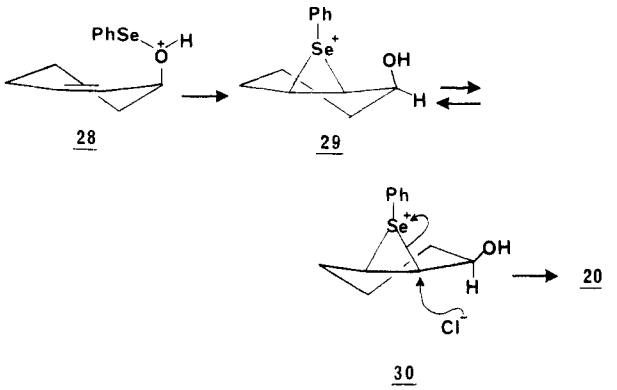
The model presented above involves two basic premises: (a) allylic oxygens direct selenonium ion formation to the syn face of the ring, and (b) axial attack of chloride ion is kinetically favored. Obviously, any perturbations which

(7) Sharpless has previously shown that selenoxide eliminations preferentially occur away from an oxygen substituent. See: Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

(8) There is little doubt that adducts such as **20** are conformationally mobile. Therefore, the observed coupling constants represent a time average of the couplings present in the individual conformers.

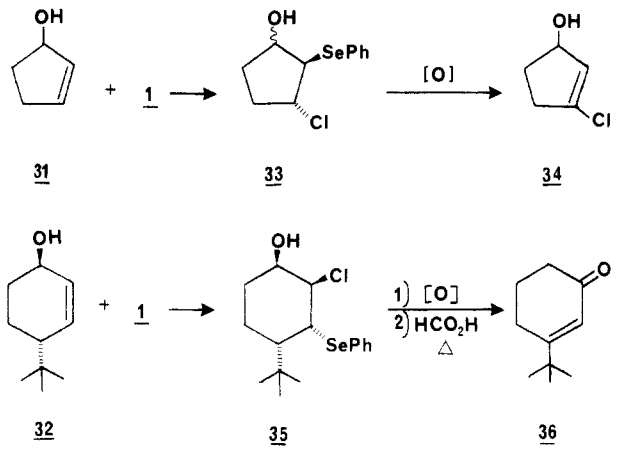
(9) Axial attack is kinetically favored in six-membered ring because it involves a chairlike transition state. Equatorial attack in six-membered rings involves a boatlike transition state and is generally a slower process.

(10) Small amounts (2–4%) of the other regioisomer may have been present and not detected.



28 29 30

significantly interfere with a and b could alter the regio- and/or stereoselectivity of these processes. For example, if one systematically constrains the allylic hydroxyl group to orientation which is increasingly less favorable for directing the selenium electrophile, the relative importance of the model described above should decrease. In order to verify this, we have examined the additions of 1 to both 31 and 32. In 31 the hydroxyl group is "less axial" than in 19, while in 32 the group is actually locked in an equatorial position.

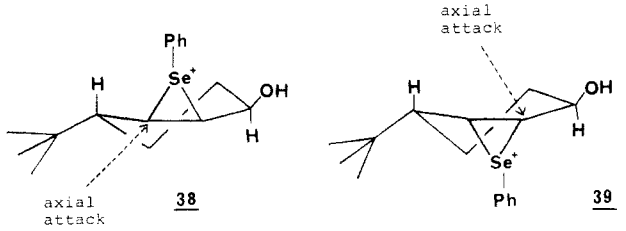


31 33 34

32 35 36

The results of these additions are as shown. The addition of 1 to 31, although regioselective, yields a mixture of stereoisomers. The regiochemical "purity" of 33 was verified by oxidatively eliminating the phenylseleno group, which leads to 34 in excellent yield.[9] In the reaction of 1 with 32 a completely different substituent pattern is produced (see 35). The regio- and stereochemistry of 35 are assigned on the basis of NMR data. The regiochemical assignment is confirmed by converting 35 into 36 via the indicated sequence.

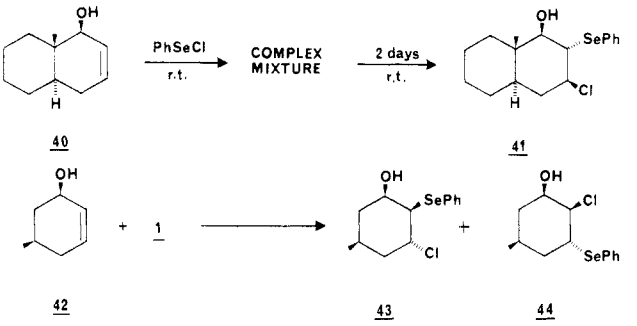
Thus, in the reaction of 31 with 1 the hydroxyl group is not properly oriented to direct the selenium moiety syn to itself, and a mixture of selenonium ions produced. However, both electronic and conformational factors combine to significantly favor α attack by chloride ion. In the reaction of 32 with 1 we assume that selenonium ion formation is not selective, i.e., both 38 and 39 are formed.



38 39

However, models indicate that in 38 axial attack is severely hindered by the adjacent *tert*-butyl group. On the other hand, axial attack in 39 is relatively unhindered and therefore should proceed normally. Since 38 and 39 are undoubtedly in equilibrium, the mixture of intermediates is eventually converted to 35 via 39.

Apparently then, additions of 1 to cyclic allylic alcohols, which result in the regio- and stereochemical pattern present in 20, only occur in systems in which the allylic hydroxyl group can achieve a pseudoaxial orientation. Further support for this hypothesis is obtained from the two reactions shown below. Because of the trans ring

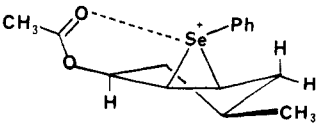


40 41 42 43 44

juncture in 40, the hydroxyl group is locked in an equatorial position and should therefore be unable to direct the incoming selenium electrophile syn to itself. Not surprisingly, addition of 1 to a deuteriochloroform solution of 40 results in the formation of a complex mixture which undoubtedly contains all of the possible adduct regio- and stereoisomers. However, if the mixture is allowed to stand at room temperature for approximately 2 days, it isomerizes almost completely to the diequatorial adduct 41. Thus, addition of 1 to 40 is nonselective kinetically but highly selective thermodynamically.

In 42 the hydroxyl and methyl groups are cis. Therefore, when the hydroxyl group is pseudoaxial, the methyl must also necessarily be pseudoaxial. This arrangement results in relatively severe 1,3-diaxial interactions, not only between the methyl and hydroxyl groups but also between these groups and the incoming selenium electrophile. Consistent with this rationale, the additions of 1 to 42 produces a 7:3 mixture of 43 and 44, respectively.

Since the inability of a pseudoequatorial hydroxyl group to direct an incoming selenium electrophile syn to itself places severe limitations on the synthetic utility of this process, we again focused our attention on reactions involving allylic acetates. In principle these species could induce syn selenonium formation via an initial coordination of the selenium electrophile by the carbonyl oxygen, followed by a subsequent intramolecular delivery to the double bond to form intermediate 45. Axial attack by

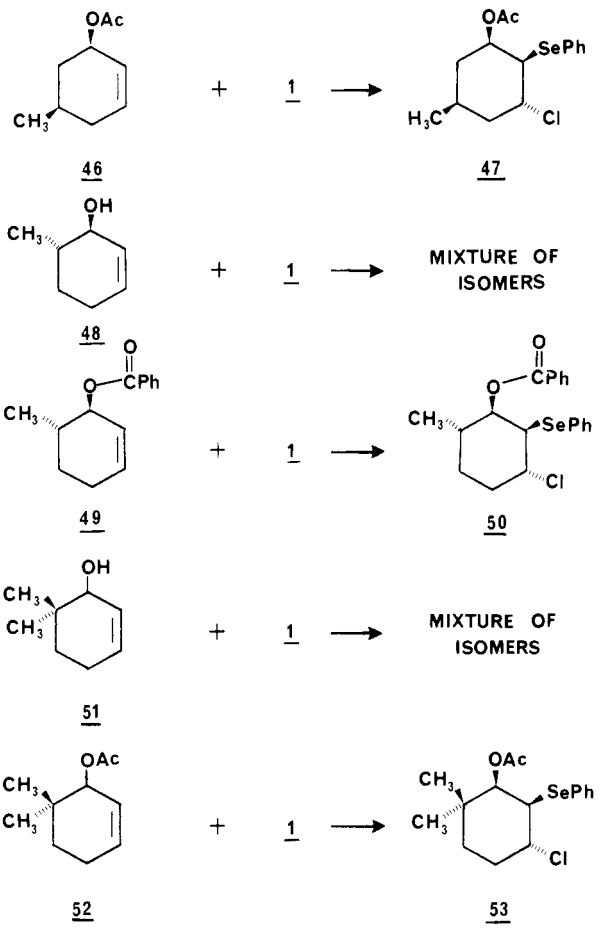


45

chloride should then produce 47. In fact, addition of 1 to 46 results in the formation of 47 as the only observable product (Scheme III). The observation that additions of 1 to cyclic allylic acetates proceed with a higher degree of regio- and stereoselectivity than the additions of 1 to the corresponding allylic alcohols is further substantiated by the other reactions shown in Scheme III.

In summary, we have been able to identify the factors which dictate the mode of addition of 1 to allylic alcohols. As a result of this, we propose the following rules which

Scheme III



have been proven useful for predicting the regio- and stereoselectivity of phenylselenenyl chloride addition to allylic systems: (1) In systems containing "inert" allylic substituents, episelenonium ion formation occurs on the less hindered face of the double bond. (2) When steric parameters on either side of the double bond are similar, a pseudoaxial hydroxyl group will direct episelenonium ion formation syn to itself. (3) An allylic acetate group is capable of directing syn selenation from an equatorial position. [This method is useful when severe diaxial interactions result from an axial hydroxyl group (see rule 2).] In acyclic systems a higher degree of regioselectivity can usually be attained by using allylic acetates in place of allylic alcohols. (4) In the absence of severe steric hindrance, axial attack of chloride occurs on the conformationally preferred episelenonium ion and results in product formation. (5) If axial attack of chloride is too hindered, the observed products may result from either equatorial attack or axial attack on a less stable selenonium ion conformation. (6) In rigid ring systems, diaxial adducts of phenylselenenyl chloride isomerize to the thermodynamically more stable diequatorial adduct. With this information in hand, let us now examine how additions of 1 to allylic alcohols and their derivatives can be used as the key step of a simple 1,3-enone transposition sequence.

1,3-Enone Transposition Sequence

The regio- and stereospecific of phenylselenenyl chloride additions to allylic alcohols would be of little interest unless one could further elaborate the phenylseleno adducts in a constructive fashion. We have exploited the regiospecificity of these additions to allylic alcohols by using it as the key step to the 1,3-enone transposition shown in Scheme IV.[4,11] IV.[4,11]

Allylic alcohols of type **55** are generated from the corresponding enone **54** either reductively ($LiAlH_4$) or alkylatively (M^+R^-). If electronic and steric parameters are correct (vide supra), **56** will be produced by the addition of **1**. Since oxidative eliminations of phenylseleno groups are *strongly* favored to proceed away from oxygen substituents,[7] chloroallylic alcohols like **57** should be obtained. Hydrolysis of these masked enones will complete the transformation to yield transposed species **58**. As discussed earlier, since phenylselenenyl chloride additions to allylic systems generally produce adducts which possess the desired regiochemistry (e.g., **56**), this transposition sequence should be applicable to a variety of structurally diverse enones. Some specific examples are discussed below.

Reduction of enone **59** with $LiAlH_4$ in ether produces allylic alcohol **60** in 96% yield. Addition of **1** to **60** proceeds rapidly and regiospecifically (Markovnikov addition) at −78 °C. The regiochemistry of the adduct is easily established by NMR, since in 2-(phenylselenenyl)-3-chloro-3-phenylbutan-2-ol the C**H**SePh must appear as a clean doublet of doublets. Although the adduct is easily isolated, for preparative purposes it is more convenient to oxidize and eliminate the resulting selenoxide in situ.[12a] Consistent with the previous findings of Sharpless,[7] the elimination reaction proceeds in a completely regiospecific fashion away from the hydroxyl group to yield **61**. Acetylation[13] and subsequent hydrolysis[14] produces the transposed enone **63** in 65% overall yield from **59**.

Alkylation of **64** with methyllithium in ether at −78 °C proceeds smoothly to produce **2b** in high yield. As mentioned previously, addition of **1** to **2b** yields either **3b** or **4b**, depending upon the conditions employed. If the addition of **1** to **2b** is carried out at −78 °C in CH_2Cl_2, only **3b** is produced; no isomerization of **3b** to **4b** occurs. Oxidative elimination then yields only hydroxyvinyl chloride **65**. **65** is easily converted to transposed enone **66** by using a two-phase hydrolysis (10% $HCl/CHCl_3$). It is important to note that this method of hydrolysis is suitable only for tertiary chloroallylic alcohols, since less substituted chloroallylic alcohols are usually recovered unchanged under these conditions. The overall yield for the conversion of **64** to **66** is 51%.

Reduction of **67** with $LiAlH_4$ produces **8** in good yield. Since the addition of **1** to **8** exhibits poor regioselectivity (vide supra), **8** is first converted to its corresponding acetate **16**. Addition of **1** to **16** and subsequent oxidative elimination results in the formation of **68**. Mercuric acetate catalyzed hydrolysis of **68** gives **69** (41% overall yield from **64**).

Reduction of **70** to **40**, followed by addition of **1** under thermodynamic conditions leads to the formation of **41**. Although the oxidation of **41** to its corresponding selenoxide is readily achieved, the subsequent selenoxide elimination proceeds quite sluggishly, presumably for steric reasons.[12b] Nevertheless, this process ultimately results in the regiospecific formation of **71** in 85% yield.

All attempts to hydrolyze the **71** by using the mercuric acetate procedure previously described result in quanti-

(11) For examples of simple and alkylative 1,3-enone transpositions, see: (a) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615. (b) Wharton, P. S. *Ibid.* **1961**, *26*, 4781. (c) Trost, B. M.; Shanton, J. L. *J. Am. Chem. Soc.* **1975**, *97*, 4018. (d) Trost, B. M.; Hiroi, K.; Holy, N. *Ibid.* **1975**, *97*, 5873.

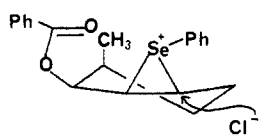
(12) (a) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697. (b) Consistent with ref 12a, selenoxide eliminates involving unactivated cyclohexane rings may take up to 3 days to completely eliminate in refluxing CH_2Cl_2.

(13) Under the experimental conditions, hydrolysis is acetate **62** gave higher yields than with alcohol **61**.

(14) Martin, S. F.; Chow, T. *Tetrahedron Lett.* **1978**, 1943.

tative recovery of the starting material. In fact, this mercuric acetate procedure apparently fails with all cyclic vinyl chlorides.[15] Our rationale of this is that the method basically represents an oxymercuration/dechloromercuration sequence. In cyclic systems this would require a trans oxymercuration followed by a cis dechloromercuration. Since the trans deoxymercuration process is probably much more facile than the cis dechloromercuration process, no net reaction is observed. However, hydrolysis of **71** can be conveniently achieved instead, by using refluxing 90% formic acid.[16]

By use of a similar sequence of reactions, the conversion of **75** to **77** and **78** to **82** are effected in overall yields of 73% and 55%, respectively. In the conversion of **78** to **82** it is noteworthy that the addition of **1** to **80** is apparently regiospecific for both the cis and the trans isomers. In the case of the cis isomer, the most probable modes of addition must therefore involve axial attack of chloride ion on either **86** or **87**. We favor the latter process, since selenonium ion formation syn to an angular methyl group (as in **86**) involves some moderately severe steric interactions.



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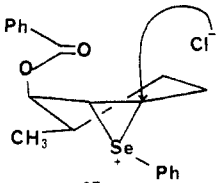

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Some more subtle applications of this transposition methodology are seen in the two remaining reaction sequences shown in Scheme IV. In the first, the chiral, 5-substituted cyclohexanone (−)-**73** is converted into its optical antipode (+)-**73** in good chemical yield and in at least 92% optical purity.[17] In the second we demonstrate that this sequence is also useful for the regiospecific introduction of a deuterium atom into an enone (**83** to **86**, 57% overall yield).

Finally, some general features of this 1,3-enone transposition sequence are noteworthy. First, each of these transpositions can be accomplished by using just two or three reaction flasks, with little or no purification of intermediates being necessary. Second, although the transpositions described in Scheme IV are dependent on the regiochemical outcome of PhSeCl addition, we believe that by using the rules discussed earlier one can successfully predict the regiochemistry of these additions. Moreover, these regiochemistries (and stereochemistries) are easily verified by performing the PhSeCl addition in an NMR tube. Finally, in its current state we are able to use this methodology to effect both simple and alkylative 1,3-enone transpositions on a variety of structurally diverse enones in approximately 40–70% overall yield.

Experimental Section

General Methods. Melting points were determined with a Thomas-Hoover Uni-Melt capillary melting point apparatus. Infrared spectra were determined with Perkin-Elmer Model 257, 457, and 727 spectrophotometers. Nuclear magnetic resonance spectra were recorded by using Varian T-60, EM-360, and EM-390 spectrometers, and chemical shifts are reported in parts per million (δ) relative to an internal tetramethylsilane reference. Normal mass spectra were recorded by using a Finnigan 4000 GC/MS system and a Varian Associates M-66 spectrometer. Precise mass measurements were carried out with the Varian Associates M-66 spectrometer. Optical rotations were determined by using a Perkin-Elmer 241 MC polarimeter. Reagents and solvents were purified by standard methods.

Reduction of 59. A 250-mL, three-necked, round-bottomed flask, fitted with a condenser, a stopper, a septum, and a magnetic stirring bar, was charged with 100 mL of dry ether and 1.00 g (26.3 mmol) of lithium aluminum hydride (under a nitrogen atmosphere). Compound **59** (4.00 g, 27.4 mmol) was added in 25 mL of dry ether dropwise via syringe through the septum at a rate which maintained a gentle reflux. After 15 min the reaction was quenched *very* carefully with water. The resulting white suspension was dried over $MgSO_4$ and filtered through a Celite cake with suction. The solid salts were washed with portions of dry ether (3 × 50 mL). The ether fractions were combined, and the solvent was removed in vacuo, leaving 3.90 g (26.3 mmol) of **60** (96% yield) which was used without further purification: ^{1}H NMR ($CDCl_3$) 7.76–7.87 (m, 5), 6.83–6.04 (m, 2), 4.89–4.26 (m, 1), 2.35 (s, 1), 1.35 (d, J = 6 Hz, 3); IR ($CHCl_3$) 3500 cm^{-1} (br); mass spectrum, m/e 148.

Conversion of 60 to 61. To a 100-mL, three-necked, round-bottomed flask, fitted with a drying tube, a magnetic stirring bar, and two stoppers, were added 50 mL of CH_2Cl_2 and 4.26 g (22.2 mmol) of **1**. After the material dissolved, the stirred solution was cooled to −78 °C, and 3.0 g (20.2 mmol) of **60** was added in 10 mL of CH_2Cl_2 dropwise via syringe. After 5 min one stopper was replaced with a gas dispersion tube, and the mixture was ozonized (Welsbach ozonator). The resulting blue solution was purged with nitrogen until it turned a clear yellow and was then poured directly into 100 mL of refluxing CH_2Cl_2 containing 4.45 g (61 mmol) of diethylamine. After being refluxed for 30 min, the solution was washed with 10% HCl (3 × 25 mL), and saturated $NaHCO_3$ (1 × 25 mL) and dried over $MgSO_4$. After evaporation of the solvent and distillation [bulb-to-bulb, 80 °C (0.5 mm)] 3.60 g (19.7 mmol, 97%) of **61** was isolated: ^{1}H NMR ($CDCl_3$) 7.35–7.20 (m, 5), 6.27 (d, J = 8 Hz, 1), 5.25–4.70 (m, 1), 3.20 (s, 1), 1.37 (d, J = 7 Hz, 3); IR ($CHCl_3$) 3500 cm^{-1} (br); mass spectrum, m/e 182, 184; precise mass calcd for $C_{10}H_{11}O^{37}Cl$ m/e 184.046 89, found 184.047 11.

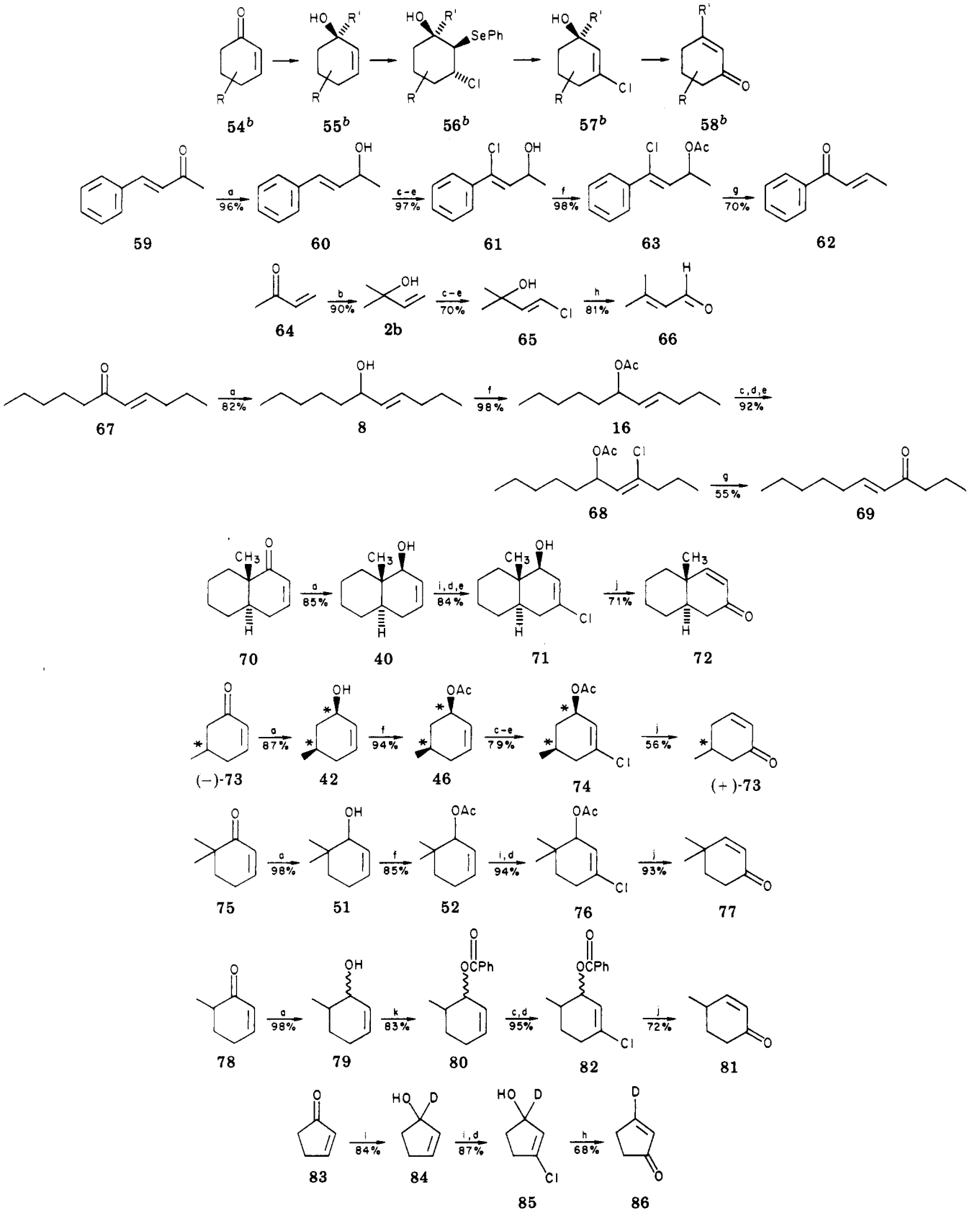
Conversion of 61 to 62. Compound **61** (1.00 g 5.48 mmol) and 0.69 g (8.3 mmol) of pyridine were dissolved in 50 mL of dry ether in a 100-mL, three-necked, round-bottomed flask fitted with a stirring bar, a stopper, a septum and a nitrogen inlet tube. Acetyl chloride (0.65 g, 8.28 mmol) was added via syringe to the stirred solution under nitrogen. The resulting white suspension was allowed to stir overnight. The reaction mixture was washed with 25 mL of 10% HCl and water, (3 × 25 mL), dried over $MgSO_4$, and stripped of its solvent to give 1.21 g (5.39 mmol, 98%) of **62**. The material was used without further purification: ^{1}H NMR ($CDCl_3$) 7.90–7.22 (m, 5), 6.43–5.75 (m, 3), 2.07 (s, 3), 1.42 (d, J = 6 Hz, 3); IR ($CHCl_3$) 1730 cm^{-1}; mass spectrum, m/e 224, 226; precise mass calcd for $C_{12}H_{13}O_2{}^{37}Cl$ m/e 226.057 45, found 226.056 95.

Conversion of 62 to 63. Mercuric acetate (0.596 g, 1.88 mmol) was dissolved in 3 mL of glacial acetic acid in a 10-mL round-bottomed flask equipped with a septum, nitrogen inlet (syringe needle), and a magnetic stirring bar. To the stirred solution under nitrogen was added 0.300 g (1.34 mmol) of **62** in 1 mL of glacial acetic, followed in 5 min by the dropwise addition via syringe of 0.23 mL (0.266 g, 1.88 mmol) of boron trifluoride etherate. After the mixture was stirred at room temperature, the bulk of the acetic acid was removed on a rotary evaporator. The residue was neutralized with saturated $NaHCO_3$ and extracted with ether (4 × 15 mL). After drying of the extract over $MgSO_4$, removal of the solvent, distillation [bulb-to-bulb, 90 °C (0.05 mm)], and chromatography on silica gel was obtained **63** (0.139, 0.94 mmol, 70%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) 8.02–7.03 (m, 7) 2.00 (d, J = 6 Hz, 3); IR ($CHCl_3$) 1665, 1620 cm^{-1}; mass spectrum, m/e 146.

Conversion of 64 to 2b. To a round-bottomed flask containing 1.0 g (14.3 mmol) of freshly distilled methyl vinyl ketone was added 1.6 mL of a 1.5 M solution of methyllithium in ether (40 mL) at −78 °C under a nitrogen atmosphere. After the mixture was stirred for 10 min, the reaction was quenched with 10 mL

(15) Martin, S. F., personal communication, University Texas, Austin.
(16) Lansbury, P. T. *Acc. Chem. Res.* **1972**, *5*, 311.
(17) Optical rotations were determined on the tosylhydrazone of **73** (see Experimental Section).

Scheme IV[a]



[a] (a) $LiAlH_4$, Et_2O; (b) CH_3Li, Et_2O, −78 °C; (c) PhSeCl, CH_2Cl_2, −78 °C; (d) O_3, CH_2Cl_2; (e) Et_2NH, CH_2Cl_2, Δ; (f) CH_3COCl, py, Et_2O; (g) $Hg(OAc)_2$, CF_3COOH; (h) 10% HCl/$CHCl_3$; (i) PhSeCl, CH_2Cl_2, 25 °C; (j) 90% HCOOH; (k) PhCOCl, py, Et_2O; (l) $LiAlD_4$, Et_2O. [b] R = alkyl and R¹ = H or alkyl.

of saturated NH_4Cl solution. After separation of the layers, the aqueous layer was extracted with ether (3 × 25 mL), and the combined organic layers were then dried over anhydrous Na_2SO_4. After filtration and solvent evaporation, 1.11 g (90% yield) of **2b** was isolated: ^1H NMR ($CDCl_3$) 6.05–4.61 (ABX pattern, 3), 2.35 (s, 1), 1.23 (s, 6); IR ($CHCl_3$) 3400 cm^{-1}.

Conversion of 2b to 65. To a 100-mL, three-necked, round-bottomed flask fitted with a drying with tube, a magnetic stirring

bar, and two stoppers were added 50 mL of CH_2Cl_2 and 8.00 g (41.8 mmol) of **1**. After the material dissolved, the stirred solution was cooled to −78 °C, and 3.00 g (34.9 mmol) of **2b** was added to 10 mL of CH_2Cl_2 dropwise via syringe. After 5 min one stopper was replaced with a gas dispersion tube, and the mixture was ozonized (Welsbach ozonator). The resulting blue solution was purged with nitrogen until the solution was clear yellow and was then poured directly into 100 mL of refluxing CH_2Cl_2 containing 5.6 g (77 mmol) of diethylamine. After 1 h at reflux the dark solution was washed with 10% HCl (2 × 25 mL), and saturated $NaHCO_3$ (1 × 25 mL) and dried over $MgSO_4$. After removal of the solvent and column chromatography on silica gel (eluted with pentane until the eluent was colorless, follow with ether) afforded 2.9 g (24.5 mmol, 70%) of **65** as a yellow oil: ^1H NMR ($CDCl_3$) 6.28 (AB pattern, J = 14 Hz, 2), 1.35 (s, 6 + 1 exchangeable H); IR ($CHCl_3$) 3450 cm^{-1}; mass spectrum, m/e 120, 122; precise mass calcd for $C_5H_9O^{37}Cl$ m/e 122.031 24, found 122.031 65.

Conversion of 65 to 66. Compound **65** (0.25 g, 2.07 mmol) was stirred in a two-phase system consisting of 2 mL of 10% HCl and 8 mL of $CDCl_3$. The progress of the reaction was followed by decanting the organic phase and observing its NMR. After 7 days the reaction was complete. The layers were separated, and the aqueous phase was extracted with ether (2 × 5 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was carefully evaporated. After distillation [bulb-to-bulb, 60 °C (0.5 mm)] 0.140 g (1.67 mmol, 81%) of **66** was obtained: ^1H NMR ($CDCl_3$) 9.92 (d, J = 8 Hz, 1), 5.95 (dm, J = 8 Hz, 1), 2.11 (s, 3), 2.02 (s, 3); IR ($CHCl_3$) 3475 cm^{-1}; mass spectrum, m/e 84.

Reduction of 67. A 50-mL, three-necked, round-bottom flask, fitted with a condenser, a stopper, a septum, and a magnetic stirring bar, was charged with 25 mL of dry ether and 0.23 g (6.1 mmol) of lithium aluminum hydride (under a nitrogen atmosphere). Compound **67** (0.96 g, 5.70 mmol) was added in 5 mL of dry ether dropwise via syringe through the septum. The reaction mixture was stirred at a rate which maintained a gentle reflux. After 15 min the reaction was quenched *very* carefully with water. The resulting white suspension was dried over $MgSO_4$ and filtered through a Celite cake with suction. The solid salts were washed with portions (3 × 25 mL) of dry ether. The ether fractions were combined, and the solvent was removed in vacuo, leaving 0.80 g (4.59 mmol, 82%) of **8** which was used without further purification: ^1H NMR ($CDCl_3$) 5.71–5.24 (m, 2), 4.21–3.81 (m, 1), 2.22–1.05 (m, 12), 1.05–0.65 (m, 6); IR ($CHCl_3$) 3460 cm^{-1}; mass spectrum, m/e 170.

Conversion of 8 to 16. Compound **8** (0.70 g, 4.1 mmol) and 0.65 g (8.2 mmol) of pyridine were dissolved in 50 mL of dry ether in a 100-mL, three-necked, round-bottomed flask fitted with a stirring bar, a stopper, a septum, and a nitrogen inlet tube. Acetyl chloride (0.5 g, 7.4 mmol) was added dropwise via syringe to the stirred solution under nitrogen. The resulting white suspension was allowed to stir overnight. The reaction mixture was washed with 25 mL of 10% HCl and water (3 × 25 mL) and dried over $MgSO_4$. The solvent was removed in vacuo. Compound **16** (0.85 g, 4.0 mmol, 98%) was obtained. The material was used without further purification: ^1H NMR ($CDCl_3$) 5.66–4.90 (m, 3), 2.12 (s, 3), 2.25–1.06 (m, 12), 1.06–0.64 (m, 6); IR ($CHCl_3$) 1730 cm^{-1}; mass spectrum, m/e 212.

Conversion of 16 to 68. Compound **16** (0.7500 g, 3.55 mmol) was dissolved in 25 mL of methylene chloride a 60-mL separatory funnel. Phenylselenenyl chloride (0.71 g, 3.7 mmol) was added with rapid decoloration of the red solid. After the reaction was complete, the orange solution was washed once with 10 mL of water and filtered through an anhydrous sodium sulfate bed directly into an ozonolysis reactor. The reactor consisted of a 50-mL, three-necked, round-bottomed flask fitted with a drying tube, a gas dispension tube, and a stopper. The mixture was ozonized at −78 °C (Welsbach ozonator) until the solution turned blue and then was purged with nitrogen until colorless. The contents of the flask were poured directly into 25 mL of refluxing methylene chloride containing 0.50 g (6.8 mmol) of diethylamine. After 2 h at reflux, the mixture was cooled, washed with 10% HCl (2 × 20 mL) and 20 mL of water, and dried over $MgSO_4$. After removal of the solvent and distillation [bulb-to-bulb, 100 °C (0.15 torr)], 0.8074 g (3.28 mmol, 92%) of **68** was isolated as a light yellow oil: ^1H NMR ($CDCl_3$) 5.76–5.16 (m, 2), 2.48–2.10 (m, 2), 2.00 (s, 3), 1.86–1.05 (m, 10), 1.00–0.72 (m, 6); IR ($CHCl_3$) 1735 cm^{-1}; mass spectrum, m/e 246, 248; precise mass calcd for $C_{13}H_{23}O_2{}^{37}Cl$ m/e 248.135 72, found 248.135 29.

Conversion of 68 to 69. Mercuric acetate (0.466 g, 1.46 mmol) was dissolved in 5 mL of glacial acetic acid in a 10-mL round-bottomed flask equipped with a septum, nitrogen inlet (syringe needle), and a magnetic stirring bar. To the stirred solution under nitrogen was added 0.2400 g (0.976 mmol) of **68** in 1 mL of glacial acetic acid, followed in 5 min by the dropwise addition via syringe of 0.18 mL (0.21 g, 1.5 mmol) of boron trifluoride etherate. GLC analysis (OV-17, 125 °C) indicated complete reaction after the mixture was stirred for 2 h at room temperature. The bulk of the acetic acid was removed on a rotary evaporator. The residue was neutralized with saturated $NaHCO_3$, saturated with NaCl, and extracted with ether (4 × 15 mL). After drying of the extract over $MgSO_4$, evaporation of the solvent, and distillation [bulb-to-bulb, 90 °C (0.15 mm)] there was obtained **69** (0.0900 g, 0.534 mmol, 55%) as a colorless liquid: ^1H NMR ($CDCl_3$) 6.83 (dt, J = 16, 7 Hz, 1), 6.07 (dt, J = 16, 1.5 Hz, 1) 2.48 (t, J = 7 Hz, 2), 2.33–1.96 (m, 2), 1.96–1.09 (m, 8), 1.09–0.75 (m, 6); IR ($CHCl_3$) 1670, 1630 cm^{-1}; mass spectrum, m/e 168; precise mass calcd for $C_{11}H_{20}O$ m/e 168.151 41, found 168.136 25.

Reduction of 70. A 25-mL, three-necked, round-bottomed flask, fitted with a condenser, a stopper, a septum, and a magnetic stirring bar, was charged with 10 mL of dry ether and 0.1 g (4.73 mmol) of lithium aluminum hydride (under a nitrogen atmosphere). Compound **70** (0.127 g, 0.481 mmol) was added in 2 mL of dry ether dropwise via syringe through the septum with stirring at a rate which maintained a gentle reflux. After 15 min the reaction was quenched *very* carefully with water. The resulting white suspension was dried over $MgSO_4$ and filtered through a Celite cake with suction. The solid salts were washed with portions (3 × 10 mL) of dry ether. The ether fractions were combined, and the solvent was removed in vacuo, leaving 0.10 g (0.402 mmol, 85%) of **40**. The material was used without further purification: ^1H NMR ($CDCl_3$) 5.91–5.27 (m, 2), 3.98–3.72 (m, 1), 2.44–0.84 (m, 1 + 1 exchangeable H), 0.75 (s, 3); IR ($CHCl_3$) 3400 cm^{-1}; mass spectrum, m/e 266.

Conversion of 40 to 71. Compound **40** (0.100 g, 0.376 mmol) was dissolved in an NMR tube in 0.5 mL of $CDCl_3$. Compound **1** (0.86 g, 0.45 mmol) was added. After 2 days isomerization was complete, and the solution was diluted to 10 mL with CH_2Cl_2, washed with water, and filtered through an anhydrous sodium sulfate bed directly into the ozonolysis reactor. The reactor consisted of a 25-mL, three-necked, round-bottomed flask equipped with a drying tube, a gas dispersion tube, and a stopper. The mixture was ozonized at −78 °C (Welsbach ozonator) until the solution turned blue and then was purged with nitrogen until colorless. The contents of the flask were poured directly into 15 mL of refluxing methylene chloride containing 3 drops of diethylamine. After 3 days at reflux the mixture was cooled, washed with 10% HCl (2 × 10 mL) and 10 mL of water, and dried over $MgSO_4$. The solvent was removed, and the residue was chromatographed on silica gel (hexanes, then ether), affording 0.956 g (0.317 mmol, 84%) of **71** as a light yellow oil: ^1H NMR ($CDCl_3$) 5.73–5.56 (m, 1), 3.97–3.79 (m, 1), 2.55–0.97 (m, 11 + 1 exchangeable H), 0.80 (s, 3); IR ($CHCl_3$) 3450 cm^{-1}; mass spectrum, m/e 200, 202; precise mass calcd for $C_{11}H_{17}O^{37}Cl$ m/e 202.093 84, found 202.094 01.

Conversion of 71 to 72. Compound **71** (0.072 g, 0.239 mmol) was refluxed in 2 mL of formic acid for 5 min. The cooled mixture was poured into 10 mL of water, and 40 mL of ether was added. The organic phase was separated, washed with water (2 × 10 mL), neutralized with saturated $NaHCO_3$, and dried over $MgSO_4$. After evaporation of the solvent and distillation [~120 °C (3 mm)], 0.045 g (0.170 mmol, 71%) of **72** was isolated: ^1H NMR ($CDCl_3$) 6.73 (d, J = 10 Hz, 1), 5.83 (d, J = 10 Hz, 1), 2.50–1.22 (m, 11), 1.02 (s, 3); IR ($CHCl_3$) 1665, 1630 cm^{-1}; mass spectrum, m/e 264.

Reduction of (−)-73. A 50-mL, three-necked, round-bottomed flask, fitted with a condenser, a stopper, a septum, and a magnetic stirring bar, was charged with 25 mL of dry ether and 0.15 g (3.9 mmol) of lithium aluminum hydride (under a nitrogen atmosphere). Compound (−)-**73** (0.420 g, 3.81 mmol) was added in 5 mL of dry ether dropwise via syringe through the septum with stirring at a rate which maintained a gentle reflux. After 15 min the reaction quenched *very* carefully with water. The resulting white suspension was dried over $MgSO_4$ and filtered through a

Celite cake with suction. The solid salts were washed with portions (3 × 10 mL) of dry ether. The ether fractions were combined, and the solvent was removed in vacuo, leaving 0.373 g (3.32 mmol, 87%) of **42** which was used without further purification: ^{1}H NMR ($CDCl_3$) 6.05–5.14 (m, 3), 2.04 (s, 3), 2.02–0.82 (m, 8); IR ($CHCl_3$) 1735 cm^{-1}; mass spectrum, *m/e* 154.

Conversion of 46 to 74. Compound **46** (0.4178 g, 2.69 mmol) was dissolved in 25 mL of methylene chloride in a 60-mL separatory funnel. Phenylselenenyl chloride (0.541 g, 2.82 mmol) was added with rapid decoloration of the red solid. After the reaction was complete, the orange solution was washed once with 10 mL of water and filtered through an anhydrous sodium sulfate bed directly into the ozonolysis reactor. The reactor consisted of a 50-mL, three-necked, round-bottomed flask equipped with a drying tube, a gas dispersion tube, and a stopper. The mixture was ozonized at −78 °C (Welsbach ozonator) until the solution turned blue and then was purged with nitrogen until colorless. The contents of the flask were poured directly into 25 mL of refluxing methylene chloride containing 0.40 g (5.50 mmol) of diethylamine. After 4 days at reflux, the mixture was cooled, washed with water (2 × 20 mL), and dried over $MgSO_4$. After removal of the solvent, the residue was distilled [bulb-to-bulb 100 °C (0.15 torr)], affording 0.4025 g (2.12 mmol, 79%) of **74** as a light yellow oil: ^{1}H NMR ($CDCl_3$) 5.84–5.73 (m, 1), 5.53–5.25 (m, 1), 2.01 (s, 3), 2.4–1.80 (m, 5), 1.02 (d, J = 5 Hz, 3); IR ($CHCl_3$) 1730 cm^{-1}; mass spectrum, *m/e* 188,190; precise mass calcd for $C_9H_{13}O_2{}^{37}Cl$ *m/e* 190.057 45, found 190.056 46.

Conversion of 74 to (+)-73. Compound **74** (0.200 g, 105 mmol) was refluxed in 2 mL of formic acid for 5 min. The cooled reaction mixture was poured into 10 mL of water, and 40 mL ether was added. The organic phase was separated, washed with water (2 × 10 mL), neutralized with saturated $NaHCO_3$, and dried over $MgSO_4$, and the solvent was removed. After distillation [∼100 °C (0.5 mm)], 0.0652 g (0.592 mmol, 56%) of (+)-**73** was obtained. Its NMR spectrum was identical with that of (−)-**73**: ^{1}H NMR ($CDCl_3$) 7.07–6.81 (dm, J = 10 Hz, 1), 5.98 (dm, J = 10 Hz, 1), 2.65–1.80 (m, 5), 1.07 (d, J = 5 Hz, 3); IR ($CHCl_3$) cm^{-1}; mass spectrum, *m/e* 110; 2,4-DNP derivative, $[\alpha]_D$ (DME) +179.5 ± 1.75°.

Reduction of 4-*tert*-Butylcyclohexenone (88). A 50-mL, three-necked, round-bottomed flask, fitted with a condenser, a stopper, a septum, a magnetic stirring bar, was charged with 25 mL of dry ether and 0.29 g (7.6 mmol) of lithium aluminum hydride (under a nitrogen atmosphere). Compound **88** (1.15 g, 7.54 mmol) was added in 10 mL of dry ether dropwise via syringe through the septum with stirring at a rate which maintained a gentle reflux. After 15 min the reaction was quenched *very* carefully with water. The resulting white suspension was dried over $MgSO_4$ and filtered through a Celite cake with suction. The solid salts were washed with portions (3 × 25 mL) of dry ether. The ether fractions were combined, and the solvent was removed in vacuo, leaving 1.03 g (6.67 mmol, 88%) of **32** which was used without purification: ^{1}H NMR ($CDCl_3$) 5.85–5.73 (m, 2), 4.44–4.05 (m, 1), 2.53–1.00 (m, 5 + 1 exchangeable H), 0.88 (s, 9); IR ($CHCl_3$) 3400 cm^{-1}; mass spectrum, *m/e* 154.

Conversion of 32 to 4-*tert*-Butyl-3-chlorocyclohex-2-en-1-ol (89). Compound **32**, (0.200 g, 1.31 mmol) was dissolved in 10 mL of methylene chloride in a 30-mL separatory funnel. Phenylselenenyl chloride (0.280 g, 1.46 mmol) was added with rapid decoloration of the red solid. After the reaction was complete, the orange solution was washed once with 2 mL of water and filtered through an anhydrous sodium sulfate bed directly into the ozonolysis reactor. The reactor consisted of a 25-mL, three-necked, round-bottomed flask equipped with a drying tube, a gas dispersion tube, and a stopper. The mixture was ozonized at −78 °C (Welsbach ozonator) until the solution turned blue and then was purged with nitrogen until colorless. The contents of the flask were poured directly into 15 mL of refluxing methylene chloride containing 0.28 g (3.8 mmol) diethylamine. After 4 days at reflux, the mixture was cooled, washed with 10% HCl (2 × 10 mL) and 10 mL of water, and dried over $MgSO_4$. The solvent was removed, and the residue was distilled [bulb-to-bulb, 100 °C (0.15 torr)], affording 0.230 g (1.23 mmol, 94%) of **89** as a light yellow oil: ^{1}H NMR ($CDCl_3$) 6.11–5.96 (m, 1), 4.46–4.03 (m, 1), 265 (s, 1), 2.54–0.99 (m, 5), 0.90 (s, 9); IR ($CHCl_3$) 3450 cm^{-1}; mass spectrum, *m/e* 188, 190.

Conversion of 89 to 36. Compound **89** (0.29 g) was refluxed in 3 mL of formic acid for 5 min. The cooled reaction mixture was poured into 10 mL of water, and 50 mL of ether was added. The organic phase was separated, washed with water (2 × 15 mL), neutralized with saturated $NaHCO_3$, and dried over $MgSO_4$, and the solvent was removed. After distillation [∼110 °C (0.5 mm)], 0.150 g (0.987 mmol, 63%) of **36** was obtained: ^{1}H NMR ($CDCl_3$) 6.13–5.96 (m, 1), 2.60–1.48 (m, 6), 1.13 (s, 9); IR ($CHCl_3$) 1670 cm^{-1}; mass spectrum, *m/e* 152.

Reduction of 75. A 250-mL, three-necked, round-bottomed flask, fitted with a condenser, a stopper, a septum, and a magnetic stirring bar, was charged with 100 mL of dry ether and 1.3 g (34.2 mmol) of lithium aluminum hydride (under a nitrogen atmosphere). Compound **75** (3.0 g, 24.2 mmol) was added in 15 mL of dry ether dropwise via syringe through the septum with stirring at a rate which maintained a gentle reflux. After 15 min the reaction was quenched *very* carefully with water. The resulting white suspension was dried over $MgSO_4$ and filtered through a Celite cake with suction. The solid salts were washed with portions (3 × 25 mL) of dry ether. The ether fractions were combined, and the solvent was removed in vacuo, leaving 3.0 g (23.8 mmol, 98%) of **51**. The material was used without further purification: ^{1}H NMR ($CDCl_3$) 5.91–5.55 (m, 2), 3.85–3.70 (m, 1), 2.19–1.88 (m, 2), 1.67–1.20 (m, 2 + 1 exchangeable H), 0.96 (s, 3), 0.92 (s, 3); IR ($CHCl_3$) 3450 cm^{-1}; mass spectrum, *m/e* 126.

Conversion of 51 to 52. Compound **51** (3.0 g, 23.8 mmol) and 3.0 g (38.0 mmol) of pyridine were dissolved in 50 mL of dry ether in a 100-mL, three-necked, round-bottomed flask fitted with a stirring bar, a stopper, a septum, and a nitrogen inlet tube. Acetyl chloride (3.0 g, 38.3 mmol) was added dropwise via syringe to the stirred solution under nitrogen. The resulting white suspension was allowed to stir overnight. The reaction mixture was washed with 25 mL of 10% HCl and water (3 × 25 mL) and dried over $MgSO_4$. The solvent was evaporated, and the residue was distilled [bulb-to-bulb, 65 °C (0.1 torr)], affording 3.4 g (85%) of **52**: ^{1}H NMR ($CDCl_3$) 5.87 (dt, J = 10, 3.5 Hz, 1), 5.58 (dq, J = 10, 2 Hz, 1), 5.10–4.95 (m, 1), 2.03 (s, 3), 2.18–1.96 (m, 2), 1.50 (q, J = 6 Hz, 2), 0.92 (s, 6); IR ($CHCl_3$) 1735 cm^{-1}; mass spectrum, *m/e* 168.

Conversion of 52 to 76. Compound **52** (1.7 g, 10.1 mmol) was dissolved in 30 mL of methylene chloride in a 60-mL separatory funnel. Phenylselenenyl chloride (2.1 g, 11.1 mmol) was added with rapid decoloration of the red solid. After the reaction was complete, the orange solution was washed once with 10 mL of water and filtered through an anhydrous sodium sulfate bed directly into the ozonolysis reactor. The reactor consisted of a 50-mL, three-necked, round-bottomed flask fitted with a drying tube, a gas dispersion tube, and a stopper. The mixture was ozonized at −78 °C (Welsbach ozonator) until the solution turned blue and then was purged with nitrogen until colorless. The contents of the flask were poured directly into 25 mL of refluxing methylene chloride containing 1.46 g (20 mmol) of diethylamine. After 3 days at reflux, the mixture was cooled, washed with 10% HCl (2 × 20 mL) and 20 mL of water, and dried over $MgSO_4$. The solvent was removed, and the residue was distilled [bulb-tobulb, 120–125 °C (2 torr)], affording 1.93 g (9.5 mmol, 94%) of **76** as a light yellow oil: ^{1}H NMR ($CDCl_3$) 5.80 (dt, J = 5, 1.5 Hz, 1), 5.00 (br d, J = 5 Hz, 1), 2.47–2.22 (m, 2), 2.05 (s, 3), 1.85–1.30 (m, 2), 0.95 (s, 6); IR ($CHCl_3$) 1735 cm^{-1}; mass spectrum, *m/e* 202, 204; precise mass calcd for $C_{10}H_{15}O_2{}^{37}Cl$ *m/e* 204.073 10, found 204.072 75.

Conversion of 76 to 77. Compound **76** (1.9 g, 9.5 mmol) was refluxed in 2 mL of formic acid for 5 min. The cooled mixture was poured into 10 mL of water, and 40 mL of ether was added. The organic phase was separated, washed with water (2 × 10 mL), neutralized with saturated $NaHCO_3$, and dried over $MgSO_4$. The solvent was removed, and the residue was distilled [bulb-to-bulb, 65 °C (2 torr)], affording 1.1 g (8.8 mmol, 93%) of **77**: ^{1}H NMR ($CDCl_3$) 6.73 (d, J = 11 Hz, 1), 5.89 (d, J = 11 Hz, 1), 2.49 (t, J = 7 Hz, 2), 1.89 (t, J = 7 Hz, 2), 1.18 (s, 6); IR ($CHCl_3$) 1680 cm^{-1}; mass spectrum, *m/e* 124.

Reduction of 78. A 100-mL, three-necked, round-bottomed flask, fitted with a condenser, a stopper, a septum, and a magnetic stirring bar, was charged with 50 mL of dry ether and 0.4 g (10.5 mmol) of lithium aluminum hydride (under a nitrogen atmosphere). Compound **78** (1.0 g, 9.1 mmol) was added in 5 mL of dry ether dropwise via syringe through the septum with stirring

at a rate which maintained a gentle reflux. After 15 min the reaction was quenched *very* carefully with water. The resulting white suspension was dried over $MgSO_4$ and filtered through a Celite cake with suction. The solid salts were washed with portions (3 × 25 mL) of dry ether. The ether fractions were combined, and the solvent was removed in vacuo, leaving 1.0 g (8.9 mmol, 98%) of **79** which was used without further purification: ^1H NMR ($CDCl_3$, mixture of isomers) 5.91–5.52 (m, 2), 4.05–3.70 (m, 1), 2.19–1.90 (m, 3), 1.88–1.30 (m, 2), 1.12–0.98 (2 overlapping d, 3); IR ($CHCl_3$) 3400 cm^{-1}; mass spectrum, *m/e* 112.

Conversion of 79 to 80. Compound **79** (0.56 g, 5.0 mmol) and 0.5 g (6.3 mmol) of pyridine were dissolved in 50 mL of dry ether in a 100-mL, three-necked round-bottomed flask fitted with a stirring bar, a stopper, a septum, and a nitrogen inlet tube. Benzoyl chloride (0.8 g, 5.7 mmol) was added dropwise via syringe to the stirred solution under nitrogen. The resulting white suspension was allowed to stir overnight. The reaction mixture was washed with 25 mL of 10% HCl and water (3 × 25 mL) and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was chromatographed on silica gel to give 0.9 g (4.2 mmol, 83%) of **80**: ^1H NMR ($CDCl_3$) 8.25–8.05 (m, 2) 7.70–7.20 (m, 3), 6.06–5.21 (m, 3), 2.34–1.30 (m, 5), 1.02 (d, J = 6 Hz, 3); IR ($CHCl_3$) 1705 cm^{-1}; mass spectrum, *m/e* 216.

Conversion of 80 to 81. Compound **80** (1.0 g, 4.6 mmol) was dissolved in 25 mL of methylene chloride in a 60-mL separatory funnel. Phenylselenenyl chloride (1.0 g, 5.3 mmol) was added with rapid decoloration of the red solid. After the reaction was complete, the orange solution was washed once with 10 mL of water and filtered through an anhydrous sodium sulfate bed directly into the ozonolysis reactor. The reactor consisted of a 50-mL, three-necked, round-bottomed flask fitted with a drying tube, a gas dispersion tube, and a stopper. The mixture was ozonozied at −78 °C (Welsbach ozonator) until the solution turned blue and was purged with nitrogen until colorless. The contents of the flask were poured directly into 25 mL of refluxing methylene chloride containing 0.73 g (10 mmol) of diethylamine. After 2 days at reflux, the mixture was cooled, washed with 10% HCl (2 × 20 mL) and 20 mL of water, and dried over $MgSO_4$. The solvent was removed, and the residue was distilled [bulb-to-bulb, 120–130 °C (2 torr)], affording 1.1 g (4.4 mmol, 95%) of **81** as a light yellow oil: ^1H NMR ($CDCl_3$) 8.20–7.16 (m, 5), 6.15–5.71 (m, 1), 5.35–5.18 (m, 1), 2.54–2.29 (m, 2), 2.25–1.31 (m, 3), 1.03 (d, J = 7 Hz, 3); IR (CH_3Cl_3) 1705 cm^{-1}; mass spectrum, *m/e* 250, 252; precise mass calcd for $C_{14}H_{15}O_2{}^{37}Cl$ *m/e* 252.073 10, found 252.072 78.

Conversion of 81 to 82. Compound **81** (1.1 g, 4.4 mmol) was refluxed in 2 mL of formic acid for 5 min. The cooled mixture was poured into 10 mL of water, and 40 mL of ether was added. The organic phase was separated, washed with water (2 × 10 mL), neutralized with saturated $NaHCO_3$, and dried over $MgSO_4$. The solvent was removed, and the residue was distilled [bulb-to-bulb, 30–40 °C (2 torr)] to give 0.35 g (3.2 mmol, 72%) of **82**: ^1H NMR ($CDCl_3$) 6.81 (ddd, J = 11, 2 Hz, 1), 5.98 (dd, J = 11, 3 Hz, 1), 2.75–1.32 (m, 5), 1.11 (d, J = 7 Hz, 3); IR ($CHCl_3$) 1675 cm^{-1}; mass spectrum, *m/e* 110.

Reduction of 83. A 50-mL, three-necked, round-bottomed flask, fitted with a condenser, a stopper, a septum, and a magnetic stirring bar, was charged with 25 mL of dry ether and 0.25 g (6.0 mmol) of lithium aluminum deuteride (under a nitrogen atmosphere). Compound **83** (1.0 g, 12.2 mmol) was added in 5 mL of dry ether dropwise via syringe through the septum with stirring at a rate which maintained a gentle reflux. After 15 min the reaction was quenched *very* carefully with water. The resulting white suspension was dried over $MgSO_4$ and filtered through a Celite cake with suction. The solid salts were washed with portions (3 × 25 mL) of dry ether. The ether fractions were combined, and the solvent was removed. The residue was distilled [bulb-to-bulb, 50–60 °C (2 torr)], affording 0.86 g (10.1 mmol, 84% of **84**: ^1H NMR ($CDCl_3$) 6.03–5.70 (m, 2), 2.63–1.55 (m, 5); IR ($CHCl_3$) 3450 cm^{-1}; mass spectrum, *m/e* 85.

Conversion of 84 to 85. Compound **84** (0.86 g, 10.1 mmol) was dissolved in 25 mL of methylene chloride in a 60-mL separatory funnel. Phenylselenenyl chloride (2.1 g, 11.1 mmol) was added with rapid decoloration of the red solid. After the reaction was complete, the orange solution was washed once with 10 mL of water and filtered through an anhydrous sodium sulfate bed directly into the ozonolysis reactor. The reactor consisted of a 50-mL, three-necked, round-bottomed flask fitted with a drying tube, a gas dispersion tube, and a stopper. The mixture was ozonized at −78 °C (Welsbach ozonator) until the solution turned blue and then was purged with nitrogen until colorless. The contents of the flask were poured directly into 25 mL of refluxing methylene chloride containing 1.46 g (20.0 mmol) of diethylamine. After 2 h at reflux, the mixture was cooled, washed with 10% HCl (2 × 20 mL) and 20 mL of water, and dried over $MgSO_4$. After the solvent was removed, there remained 1.05 g (8.8 mmol, 87%) of **85** which was used without purification: ^1H NMR ($CDCl_3$) 5.95–5.70 (m, 1), 2.79–1.70 (m, 5); IR ($CHCl_3$) 3450 cm^{-1}; mass spectrum, *m/e* 119, 121; precise mass calcd for $C_6H_5DO^{37}Cl$ *m/e* 121.021 85, found 121.021 47.

Conversion of 85 to 86. Compound **85** (1.05 g, 8.8 mmol) was stirred in a two-phase system consisting of 2 mL of 10% HCl and 8 mL of $CDCl_3$. The progress of the reaction was followed by decanting the organic phase and observing its NMR. After 7 days the reaction was completed. The layers were separated, and the aqueous phase was extracted with ether (2 × 5 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was carefully evaporated. After distillation [bulb-to-bulb, 60 °C (2 torr)], 0.5 g (6.0 mmol, 68%) of **86** was obtained: ^1H NMR ($CDCl_3$) 6.30–6.10 (m, 1), 2.95–2.21 (m, 4), IR ($CHCl_3$) 1725 cm^{-1}; mass spectrum, *m/e* 83.

3b: ^1H NMR ($CDCl_3$) 7.36–6.76 (m, 5), 3.57 (s, 2), 3.46 (s, 2), 2.32 (s, 1 exchangeable H), 1.83 (q, J = 7 Hz, 2), 0.89 (t, J = 7 Hz, 3).

4a: ^1H NMR ($CDCl_3$) 7.40–6.71 (m, 5), 3.53 (d, J = 5.5 Hz, 2), 3.04 (d, J = 5.5 Hz, 1), 2.29 (s, 1 exchangeable H), 1.21 (s, 3).

4b: ^1H NMR ($CDCl_3$) 7.24–6.75 (m, 5), 3.76 (dd, J = 9, 3 Hz, 1), 3.07 (ddd, J = 12, 9, 3 Hz, 2), 2.17 (s, 1 exchangeable H), 1.21 (s, 6).

Mixture of 6 and 7: ^1H NMR ($CDCl_3$) 7.98–7.28 (m, 5), 4.85–3.20 (m, 4), 2.60 (s, 1 exchangeable H), 1.96–1.23 (2 overlapping d, 3).

14: ^1H NMR ($CDCl_3$) 7.83–7.22 (m, 5), 4.63–4.04 (m, 3), 3.56–3.25 (m, 1), 2.02 (s, 3), 1.66 (d, J = 7 Hz, 3).

17: ^1H NMR ($CDCl_3$) 7.71–6.96 (m, 5), 5.50 (dt, J = 7, 2 Hz, 1), 4.07 (dt, J = 9, 3 Hz, 1), 3.29 (dd, J = 9, 2 Hz, 1), 2.03 (s, 3), 1.83–0.65 (m, 18).

20: ^1H NMR ($CDCl_3$) 7.66–6.97 (m, 5), 4.65–4.31 (m, 1), 4.31–3.80 (m, 1), 3.80–3.41 (dd, J = 6, 3 Hz, 1), 2.50–1.40 (m, 6 + 1 exchangeable H).

23: ^1H NMR ($CDCl_3$) 7.61–6.95 (m, 5), 5.43–5.00 (m, 1), 4.60–4.20 (m, 1), 3.83–3.52 (dd, J = 6, 4 Hz, 1), 2.41–1.46 (m, 9).

25: ^1H NMR ($CDCl_3$) 7.56–6.97 (m, 5), 4.69–4.47 (dd, J = 7 Hz, 3).

33: ^1H NMR ($CDCl_3$) 8.07–7.30 (m, 5), 4.65–4.02 (m, 2), 4.00–3.40 (m, 1) 2.83 (s, 1 exchangeable H), 2.57–1.47 (m, 4).

35: ^1H NMR ($CDCl_3$) 7.94–7.25 (m, 5), 5.04–4.45 (m, 2), 4.00–3.88 (m, 1), 2.81 (s, 1 exchangeable H), 2.30–1.50 (m, 5), 1.07 (s, 9).

41: ^1H NMR ($CDCl_3$) 7.90–6.95 (m, 5), 3.92–2.90 (m, 3), 4.10–3.21 (m, 2), 3.14 (dd, J = 12, 10 Hz, 1), 2.14–1.10 (m, 11 + 1 exchangeable H), 0.86 (s, 3).

47: ^1H NMR ($CDCl_3$) 8.06–7.18 (m, 5), 5.47 (dt, J = 12, 4 Hz, 1), 4.70 (dt, J = 4, 3 Hz, 1), 4.14–4.00 (m, 1), 2.02 (s, 3), 2.28–1.23 (m, 5), 1.00 (d, J = 6 Hz, 3).

50: ^1H NMR ($CDCl_3$) 8.30–7.10 (m, 10), 5.66 (dd, J = 10, 4 Hz, 1), 4.75–4.60 (m, 1), 4.30–4.16 (m, 1), 2.70–1.50 (m, 5), 1.08 (d, J = 6 Hz, 3).

53: ^1H NMR ($CDCl_3$) 5.46–5.81 (m, 1), 4.87–4.25 (m, 1), 3.80–1.70 (m, 5).

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80663-70-3; **49**, 80663-71-4; **50**, 80663-72-5; **51**, 38313-10-9; **52**, 80663-73-6; **53**, 80663-74-7; **59**, 122-57-6; **60**, 17488-65-2; **61**, 80663-75-8; **62**, 80663-76-9; **63**, 495-41-0; **64**, 78-94-4; **65**, 53977-97-2; **66**, 107-86-8; **67**, 32064-74-7; **68**, 80663-77-0; **69**, 56312-55-1; **70**, 73587-69-6; **71**, 73587-71-0; **72**, 22844-34-4; (+)-**73**, 15466-88-3; (−)-**73**, 54307-74-3; **74**, 80734-37-8; **75**, 6553-64-6; **76**, 80663-78-1; **77**, 1073-13-8; **78**, 6610-21-5; **79**, 3718-56-7; **80**, 80663-79-2; **81**, 80663-80-5; **82**, 5515-76-4; **83**, 930-30-3; **84**, 20826-91-9; **85**, 80663-81-6; **86**, 75308-19-9; **88**, 937-07-5; **89**, 80663-82-7; (+)-5-methylcyclohex-2-en-1-one 2,4-DNP derivative, 80663-83-8.

Palladium-Catalyzed Reactions of Vinylic Bromides with Allylic Alcohol and Amine Derivatives

Lien-Chung Kao, F. Gregory Stakem, Babu A. Patel, and Richard F. Heck*

Department of Chemistry, University of Delaware, Newark, Delaware 19711

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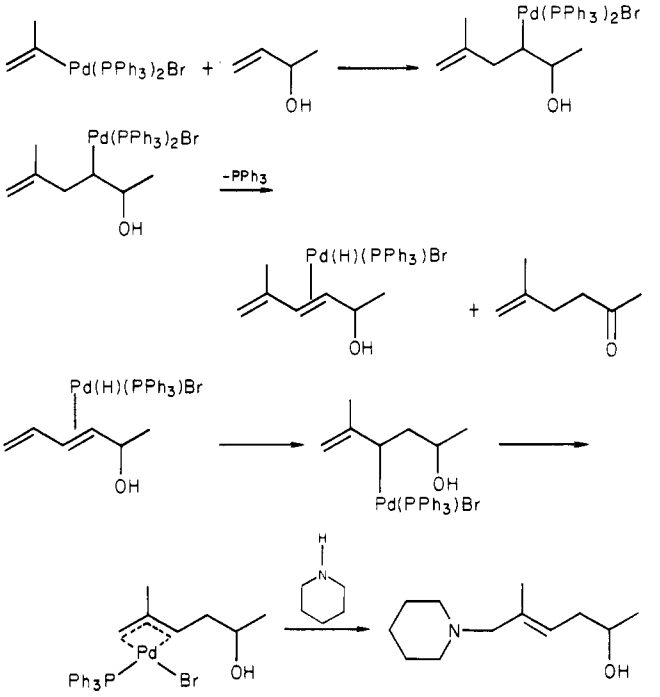
Allylic alcohols, amines, tetrahydropyranyl ethers, *N*-allylphthalimide, and tetraallyl silicate have been reacted with various vinylic bromides and, in some cases, bromobenzene by using a palladium catalyst with an amine as an acid acceptor. Of the allylic alcohols, methallyl alcohol was the most useful synthetically. It produced 4-enals in modest yields in many examples without formation of the regioisomers which are a problem in other cases. Secondary allylic alcohols reacted regioselectively to form mixtures of 4-enals and amino alcohols. Some nonallylic alcohols gave good yields of amino alcohols, also. Allylic tertiary amines reacted more selectively in some instances than allylic alcohols, producing 4-enals after hydrolysis of the enamine products. The allylic tetrahydropyranyl ethers, in general, formed mixtures of dienyl ethers and amino alkenyl ethers. The *N*-allylphthalimide–vinylic bromide reactions were the most selective we found. The products were *N*-(2,4-dienyl) phthalimides, formed in fair to good yields. The reactions of tetraallyl silicate were of limited value. The reaction was selective with bromobenzene, forming after hydrolysis only cinnamyl alcohol, but it was not selective with vinylic halides, and conversions were always low due to facile reduction and inactivation of the catalyst under the reaction conditions.

The palladium-catalyzed reaction of vinylic bromides or iodides with alkenes and an amine has been shown to be a useful method for the synthesis of conjugated dienes[1] and/or allylic amines.[2] The tolerance of the reaction for a variety of functional groups makes it of value for preparing polyfunctional compounds often without the need of employing "protecting groups".[3] We now report applications of the reaction to allylic alcohol and amine derivatives as further examples of its usefulness in the preparation of polyfunctional molecules with relative ease.

Results and Discussion

In the initial experiment, it was observed that 2-bromopropene and 3-buten-2-ol failed to react under conditions where bromobenzene reacted easily.[2] Since the palladium remained in solution, it appeared that a stable organopalladium complex had been formed. Several attempts to isolate this complex from the reaction mixture were unsuccessful. However, we observed that the use of piperidine instead of triethylamine as the acid acceptor caused a rapid catalytic reaction to occur, with, however, formation of the desired ketone 5-methyl-5-hexen-2-one and also 5-methyl-6-piperidino-4-hexen-2-ol. The last product was likely formed by nucleophilic attack of the piperidine upon an intermediate π-allylic complex. It had previously been reported, in one case, that a secondary amine reacted with a π-allylic palladium chloride complex to form an allylic amine,[4] and we had already suspected that π-allylic palladium complexes were intermediates in the reactions of vinylic halides with, at least, some alkenes.[1] Larock more recently isolated π-allylic complexes from related stoichiometric reactions.[5] Therefore, in retrospect, the formation of the relatively stable π-allylic complexes in the allylic alcohol reactions with vinylic halides could have been expected. It appears that the vinylic halide reactions follow the mechanism shown in Scheme I.

Scheme I. Mechanism of the 2-Propenylation of 3-Buten-2-ol



We have now looked at reactions of vinylic bromides with a variety of other allylic alcohols, allylic amines, allylic

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