Chromyl Chloride Oxidations of Olefins. Possible Role of Organometallic Intermediates in the Oxidations of Olefins by Oxo Transition Metal Species

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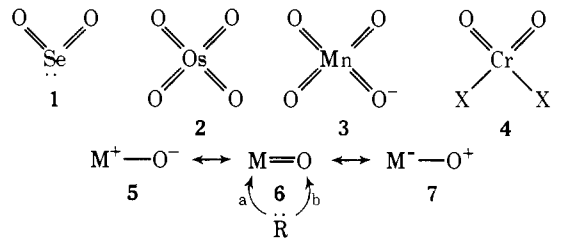
Abstract: Several new aspects of the chromyl chloride oxidation of olefins are presented. By carrying the reactions out at low temperature and by running a variety of control experiments, it is concluded that the three primary products of these oxidations are epoxide, chlorohydrin, and, in some cases, vicinal dichloride. All three of these products result from cis-addition processes. It is argued that these facts are not easily accommodated by any of the literature mechanisms for these oxidations. A new mechanism is proposed whose key feature is the involvement of organometallic intermediates having Cr–C σ bonds. To the best of our knowledge, this is the first time that organometallic species have been suggested as intermediates in the oxidations of olefins by high valent (d°) transition metal reagents. The possibility that organometallic intermediates may play a general role in the reactions of olefins and hydrocarbons with all high valent transition metal oxidants is discussed.

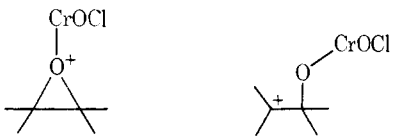
Certain oxo metal compounds (e.g., **1–4**) play a special role in organic synthesis because of their ability to selectively attach oxygen atoms to olefins and other organic substrates. Prior to our work,[1] the proposed mechanisms[2-7] for almost[8]



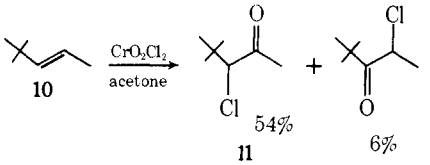
all of these oxygen atom transfer processes involved direct attack of the organic reductant (R̈, path b) on the oxygen end of the oxo moiety **6**, implying polarization of the oxo group as indicated in resonance form **7**. However, the oxo groups in such oxidants are clearly better represented by the dipolar resonance structure **5**, in accordance with dipole moment measurements,[9a,b] ab initio calculations,[9c,d] and recent studies employing photoelectron spectroscopy.[10] The carbonyl group of aldehydes and ketones is surely less polarized toward oxygen than the metal oxides (**1–4**) under consideration; yet nucleophiles react exclusively at the carbon atom of the carbonyl. Also worth pointing out in this context are the numerous examples of coordination compounds between basic ligands (e.g., aromatic amines and solvents such as THF, DMF, and HMPA) and d° oxo transition metal species; in all these complexes (e.g., CrO_3·pyridine$_2$) the basic ligand is coordinated directly to the metal center. Organometallic intermediates are of course ubiquitous in the reactions of olefins with low valent transition metal compounds (e.g., Pd^{II} and Pt^{II}) and with main group metallic species (e.g., Hg^{II} and Tl^{III}). The fact that organic chemists tend to represent the oxo groups of oxo metal compounds in the double bond form (**6**) has probably contributed to the popularity of mechanisms which invoke attack on oxygen.

Thus we felt that these oxidations were more likely initiated by attack of the organic reductant at the metal center (path a) leading by indirect routes, through organometallic intermediates, to the observed products. In support of this hypothesis we have provided good evidence,[1] that organoselenium intermediates are involved in the oxidations of both olefins and carbonyl compounds by the main group oxidant selenium dioxide (**1**). We now report results which suggest that organometallic intermediates may also be involved in the oxidation of olefins by transition metal oxo compounds.

The mechanism of chromyl chloride (**4**, X = Cl) oxidation of olefins was initially suggested[4] to involve an electrophilic attack of $[CrO_2Cl]^+$ on the olefin to give the three-centered intermediate **8** which was then attacked from the backside by



chloride ion. This was based on the observation that cyclohexene gave trans chlorohydrin and that terminal olefins gave anti-Markownikoff addition of the elements of HOCl. However, this picture of the mechanism was complicated by later observations of Stairs and co-workers[3] who found that both cis and trans chlorohydrins are formed from cyclohexene and cyclopentene. These workers suggested that a carbonium ion intermediate (**9**) might account for the observed products. We have reported[11] that oxidation of (*E*)-*tert*-butylmethylethylene (**10**) with chromyl chloride in acetone gives mainly the



chloro ketone **11** and no detectable products of Wagner–Meerwein rearrangement. This result would seem to argue against significant cationic character in the step wherein the carbon–chlorine bond is established and therefore against intermediates such as **8** and especially **9**.

Chromyl chloride oxidations of olefins are known for producing complex mixtures of products.[3,4,7b] However, several years ago[12] we found that when these reactions were performed at low temperature the epoxide and the chlorohydrin became the major product. More importantly the chlorohydrin results from highly stereoselective cis addition of the elements of HOCl across the olefinic linkage (Tables I and III). More recently two other groups[13] have also detected epoxides in these oxidations and Bachelor[6] has reported the exo-cis chlorohydrin as the major product in the reaction of chromyl chloride with norbornene. Since norbornene is well known[14] for its unusual preference for cis additions, the results presented here for simple di- and monosubstituted olefins (Tables I and III) provide more convincing evidence that cis addition is a general

Table I. CrO_2Cl_2 Oxidations of Disubstituted Olefins[a]

Olefin	Epoxide		Halohydrin		Halo ketone
	Z	E	Erythro	Threo	
1. (E)-Cyclododecene	2	20	5	60	8
2. (Z)-Cyclododecene	28	2	25	4	5
3. (E)-5-Decene	1	15	5	55	7
4. (Z)-5-Decene	13	2	35	30	5
5. (Z)-5-Decene[b]	0	0	28[c]	5[c]	35[d]
6. Cyclohexene	5		15	25	5

[a] Unless otherwise noted, all reactions were performed in CH_2Cl_2 at −78 °C using 1.3 equiv of CrO_2Cl_2. After 3 h the reaction mixture was poured into aqueous sodium sulfite at 0 °C. All yields were determined by GLC relative to an internal standard. [b] In this case the oxidation was run in acetone at −78 °C in the presence of excess LiBr. [c] Bromohydrins. [d] Bromo ketone.

phenomenon in the reactions of chromyl chloride with olefins. This fact has led us to question the correctness of earlier proposed mechanisms.

Results and Discussion

The reactions were carried out at −78 °C in methylene chloride except for one instance where carbon tetrachloride was employed at 0 °C. The diastereomeric halohydrins from the disubstituted olefins had different GLC retention times and were thus readily analyzed by this method. We shall first discuss the results obtained for the disubstituted olefins (Table I). At first glance the data in the table would seem to indicate that, although cis addition tends to predominate, substantial trans addition of the elements of HOCl to the olefins has also occurred. However, careful control experiments (Table II) have shown that the chlorohydrin resulting from trans addition could be accounted for by trans opening of the corresponding epoxide by chloride ion under the reaction conditions. (Z)-5-Decene oxide was particularly prone to such opening, which accounts for the especially large amount of threo chlorohydrin formed in this case. Although the control was not run for cyclohexene oxide, it is notorious for the ease with which it undergoes trans-opening reactions. Because the interpretation of these control experiments is crucial to our arguments for cis addition as the primary process in these oxidations, further discussion of them seems merited.

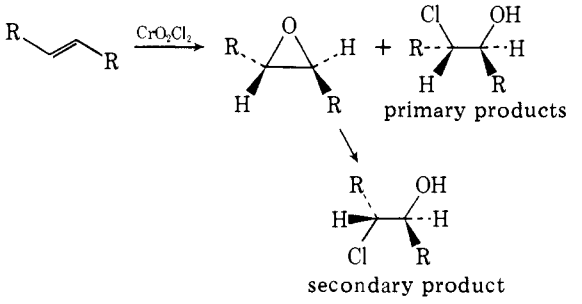
Entries 1 and 2 in Table II reveal that the epoxides are completely stable to the reagent itself (CrO_2Cl_2) under the reaction conditions. However, entries 3–6 indicate that when an epoxide is present in the reaction mixture while another olefin is being oxidized trans opening of the epoxide to the chlorohydrin does occur. In cases 3–6 1 equiv of epoxide was added per equivalent of olefin being oxidized. In a later control with 1-decene oxide (Table IV) only 0.1 equiv of epoxide (amount estimated to be formed during the oxidation of 1-decene by reference to the amount of trans addition of HOCl) was added. It should be obvious that the perfect control experiment is not possible since in an actual oxidation the epoxide, when initially generated, will be coordinated to a chromium species. It would seem that such a coordinated epoxide would be likely to undergo trans opening by chloride with the chromium center playing the role of a Lewis acid. In any case, we feel that the control experiments (Tables II and IV) reveal that epoxides undergo sufficient trans opening to chlorohydrins under the reaction conditions (whether by HCl or by a Lewis acidic chromium species) to completely account for the trans addition of HOCl observed in these oxidations. This leads us to the conclusion shown in Scheme I that epoxide and chlorohydrin, both resulting from cis addition, are the primary products of these oxidations and that the chlorohydrin resulting from trans addition is a secondary product derived by opening of the epoxide.

Table II. Control Experiments

Compd	Conditions[a]	Epoxides		Chlorohydrins		Chloro ketone
		Z	E	Erythro	Threo	
1. (E)-Cyclododecene oxide	I		100			
2. (Z)-Cyclododecene oxide	I	100				
3. (E)-Cyclododecene oxide	II		85	15		
4. (Z)-Cyclododecene oxide	II	82			15	
5. (E)-5-Decene oxide	III	2	55	35	3	5
6. (Z)-5-Decene oxide	III	27	3		43	4
7. *erythro*-2-Chlorocyclododecanol	II			100		

[a] I: The epoxide and 1 equiv of CrO_2Cl_2 were stirred at −78 °C for 2 h. II: The oxidation of (E)-5-decene was carried out in the presence of 1 equiv of the compound to be tested. III: The oxidation of (E)-cyclododecene was carried out in the presence of 1 equiv of the compound to be tested.

Scheme I



The epoxides were formed in yields varying from 5 to 30%. As with other chromyl reagents,[15] these epoxidations are stereospecific giving the epoxide of the same geometry as the starting olefin. In Table I it appears that traces of the isomeric epoxides were also formed but this was due to the fact that all the olefin samples contained some (as much as 5%) of the geometrical isomer as an impurity.

Table III shows the outcome of chromyl chloride oxidation of a stereospecifically deuterated terminal olefin, (E)-1-deuterio-1-decene. Again the chlorohydrins are formed by cis addition and the stereoselectivity is high (>95%) when corrections are made based on the control reaction (Table IV) which was performed to determine the amount and direction of epoxide opening. In this case a substantial amount of vicinal dichloride is also produced (Table III) and it too arises by a process resulting in cis addition (>98% stereoselective). The results shown in Table III were arrived at by analysis of the NMR spectra of the products as will now be discussed.

The NMR data necessary for the analysis of the products formed upon oxidation of (E)-1-deuterio-1-decene (**12**) are given in Table V and the products are shown in Scheme II. The crude reaction mixture was separated into four components by preparative TLC; these consisted of epoxide **13**, 1-hydroxy-2-chlorodecane (**14**), 1-chloro-2-hydroxydecane (**15**), and dichloride **16**. The chlorohydrin regioisomers **14** and **15** were converted by treatment with hydroxide in ethanol to the corresponding epoxides before NMR analysis; this process results in one inversion. The configuration of the epoxide samples thus derived was determined by integration of the

Table III. CrO_2Cl_2 Oxidation of (*E*)-1-Deuterio-1-decene[a]

Solvent (temp, time)	% yields[b,c] 13	14	15	16
1. CH_2Cl_2 (−78 °C, 3 h)	3 (>98:2)	26 (86:14)	6 (58:42)	12 (>98:2)
2. CCl_4 (0 °C, 1 h)	3 (>98:2)	34 (85:15)	12 (67:33)	2 (>98:2)

[a] As a check on these results (*Z*)-1-deuterio-1-decene was also subjected to these oxidations and, as expected, the inverse steriochemical outcome (i.e., erythro products predominating) was observed. [b] These represent the combined yield of threo and erythro product as determined by GLC relative to an internal standard. [c] The ratio of threo product to erythro product is indicated in parentheses.

Table IV. Control Experiment for 1-Decene Oxidations[a]

	% yields Recovered oxide	14	15
1-Decene oxide	10	26	19 (1.4:1)

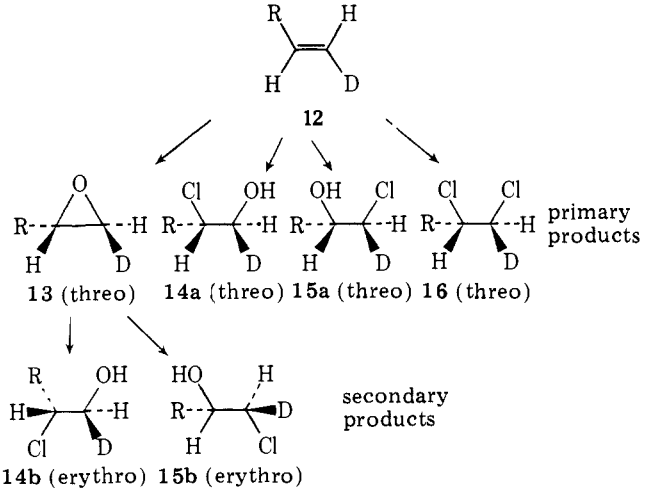
[a] The CrO_2Cl_2 oxidation of 1-hexene was carried out at 0 °C in CCl_4 in the presence of 0.1 equiv of 1-decene oxide.

Table V. NMR Data for 1-Decene Adducts[a] (R = C_8H_{17})

δH_A	2.31	3.70	3.41
δH_B	2.58	3.52	3.55
δH_C	2.75	3.92	3.73
J_{AB}	5.4	11	11
J_{AC}	2.5	4.8	7.2
J_{BC}	4.0	8.8	3.5

[a] Shifts are given in parts per million relative to Me_4Si and coupling constants are in hertz. All spectra were run in CCl_4.

Scheme II. CrO_2Cl_2 Oxidation of (*E*)-1-Deuterio-1-decene

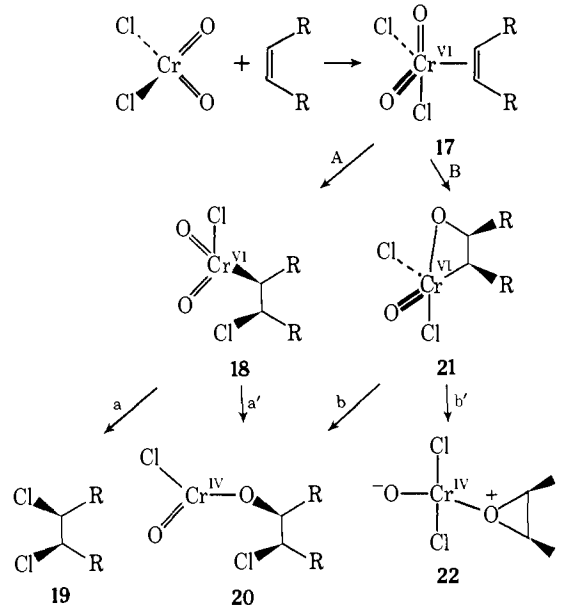


appropriate region (see Table V) of their deuterium decoupled NMR spectra. Assignment of the terminal hydrogens in the epoxide was made by synthesis of the authentic *E* epoxide **13** by peracid (MCPBA) epoxidation of (*E*)-1-deuterio-1-decene (**12**). The monodeuterio chlorohydrin **15** could also be analyzed for its threo/erythro content by direct analysis of its deuterium decoupled NMR. Determination of the configuration of the dichloride **16** was possible owing to the nonequivalence of the terminal hydrogens in 1,2-dichlorodecane (cf. Table V). Assignment of the terminal protons was made using Karplus relations[16] and the fact that vicinal dichlorides prefer a conformation in which the chlorine atoms are anti.[17] This assignment was confirmed by the NMR of the dichloride obtained from cis chlorination[18] of (*Z*)-1-deuterio-1-decene by $MoCl_5$. As an additional check on the results reported in Table III, (*Z*)-1-deuterio-1-decene was also oxidized with chromyl chloride and gave excellent agreement with the outcome reported here for the *E* isomer **12**.

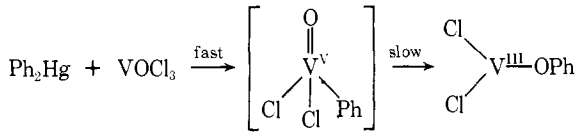
Having indicated how the data in Tables III and IV for the oxidation of (*E*)-1-deuterio-1-decene were obtained, we can now discuss it in light of the reaction sequence proposed in Scheme II. One sees from Table III, entry 2, that the erythro chlorohydrins **14b** and **15b** have been formed in a ratio of 1.3:1. This agrees quite well with the control experiment (Table IV) which indicates that under conditions designed to simulate those of the oxidation 1-decene oxide opens to a 1.4:1 ratio of chlorohydrins **14** and **15**. This conforms with a mechanism in which there are four primary products (**13**, **14a**, **15a**, and **16**) all produced by cis additions in which the erythro chlorohydrins **14b** and **15b** are secondary products formed from epoxide **13** by trans opening with chloride ion. It is interesting to note the high preference for 2-chloro-1-decanol (**14a**) over 1-chloro-2-decanol (**14b**) in CH_2Cl_2 at −78 °C (~6:1) after correction for the ring opening of the epoxide.

Thus, there appear to be three primary products (epoxide, chlorohydrin, and dichloride) formed in these oxidations and each product results from a cis addition. None of these observations, especially cis oxychlorination and cis dichlorination, is readily explained by the previously proposed mechanisms[2-7] for the chromyl chloride oxidation of olefins. Therefore we propose in Scheme III a new mechanism for these oxidations. The initial step is suggested to be formation of a chromyl chloride olefin π complex (**17**). In the case of ligands more basic than an olefin stable complexes related to **17** are of course well known (e.g., CrO_3·pyridine$_2$ and OsO_4·pyridine). In a high valent transition metal complex like **17** insertion of the coordinated olefin into either π or σ metal-ligand bonds would seem a likely process. In the case of chromyl chloride we therefore suggest two possible pathways (A and B) both of which lead to chromium(VI) organometallic intermediates. In path A the olefin inserts into a chlorine–chromium bond (cis chlorometalation) to produce the alkylchromium intermediate **18**. This species could lead to dichloride (**19**) by reductive elimination (path a) or to the chromium derivative of the chlorohydrin (**20**) by migration of the alkyl group from chromium to oxygen (path a′); both of these processes would have to occur with retention of configuration at the carbon center bound to the chromium in **18** in order to result in overall cis addition. Reductive eliminations to form carbon–halogen bonds (i.e., path a) are well known in orgonometallic chemistry and proceed with retention at carbon.[19] The migration or [1,2] shift suggested for path b′, by analogy with the Stevens-type rearrangement,[20] might also be expected to occur with retention at carbon. What appears to be the first transition metal precedent for such a rearrangement has been reported[21] for

Scheme III. Mechanism Involving Organometallic Intermediates



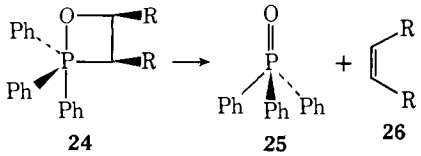
the phenyl oxovanadium species **23**. We have recently provided further evidence for the existence of the organovanadium intermediate **23** beyond that given in ref 21. After removal of all PhHgCl, the solution thought to contain **23** was treated with



bromine and bromobenzene was produced in 85% yield.[22] In light of this vanadium example, we allowed (*n*-decyl)$_2$Hg to react with CrO_2Cl_2 in CH_2Cl_2 at −78 °C. Interestingly 1-chlorodecane and 1-decanol were produced in a ratio of 1:1.4 (59% combined yield). Although in this case the existence of the presumed organometallic intermediate $CH_3(CH_2)_8CH_2CrO_2Cl$ (analogous to **23**) has not yet been established, the apparent decomposition pathways (to give both chloride and alcohol) seem to be consistent with those required of intermediate **18** in Scheme III.

A few years ago the proposal of high valent organometallic species such as **18** and **21** in Scheme III, even as intermediates, would have seemed fanciful. But the recent literature abounds with stable high valent organometallic derivatives of vanadium,[21,23] niobium,[24] tantalum,[24] chromium,[25] tungsten,[26] and rhenium.[27] In fact, a complex of tungsten, CH_3WO_2Cl, closely related to the putative organochromium intermediate **18** has been isolated.[26a]

In path B of Scheme III a four-centered intermediate (**21**) is formed via what is formally a [2 + 2] interaction between the olefin and an oxo group on the chromium. This process is essentially the microscopic reverse of the olefin-forming step in the Wittig reaction where a trigonal bipyramidal oxyphosphetane (**24**) decomposes to a tetrahedral phosphine oxide (**25**)



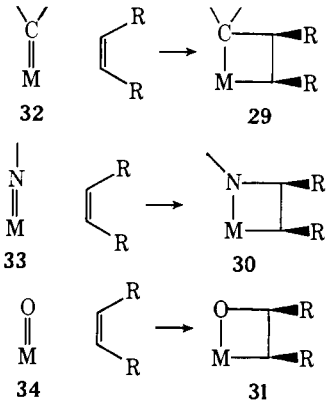
and an olefin (**26**).[28] The main group chalcogen oxo species SO_3 (**27**) has recently been shown to undergo stereospecific [2 + 2] cis addition to (*E*)- and (*Z*)-2-butene to give the corresponding β-sultones.[29] A platinum metallocycle (**28**) with the key structural feature of **21** has been characterized.[30] Returning to Scheme III, the cyclic organochromium intermediate **21** could then yield either the chlorohydrin precursor **20** (path b) or the epoxide precursor **22** (path b) by the appropriate reductive elimination process. We feel that paths A and B are competing processes and the extent of involvement of each varies with the nature of the substrate and with the reaction conditions. The nature of the product mixtures is sensitive to the coordinating ability of the medium. In the presence of polar solvents (e.g., acetone[11]) or good nucleophiles (e.g., chloride ion[12]) the proportion of products with chlorine–carbon bonds increases at the expense of epoxide. It is easy to imagine how additional nucleophiles might play a role in the mechanism shown in Scheme III. For example, coordination of an additional ligand to intermediates **18** or **21** would make them five and six coordinate, respectively, and would very likely change both the rates and modes of their decomposition. In the absence of additional ligands, one might expect intermediate **21** to prefer path b′ leading to coordinated epoxide **22** over path b leading to **20**, since in the former case chromium retains four ligands while in the latter only three are retained. In this connection it is probably also worth mentioning the oxidation of (*Z*)-5-decene with CrO_2Cl_2 in acetone in the presence of excess LiBr (entry 5, Table I). The most dramatic observation is that chlorohydrin and chloro ketone formation is completely suppressed and one obtains instead bromohydrin (again principally cis addition) and bromo ketone. Also, no epoxide is present among the reaction products, a result which is consonant with the aforementioned effect of good nucleophiles on the product distribution. Since there is little threo bromohydrin produced, it seems unlikely that the absence of epoxide can be attributed to its preferential opening by the good nucleophile, bromide ion. Although it is tempting to speculate that the obtention of bromine-containing products in this experiment is evidence that bromide ion coordinates and/or exchanges with the organometallic intermediates **18** or **21** in Scheme III, one can just as well argue that CrO_2Br_2 is formed by exchange with CrO_2Cl_2, and that CrO_2Br_2 then reacts with olefin to give cis addition of HOBr by some other mechanism not involving organometallic intermediates.

Following Scheme III only path A can account for the dichloride (**19**) and only path B for the epoxide. No 1,2-diol could be detected and diol could conceivably arise in path B from intermediate **21** by a [1,2] shift analogous to that postulated in path a′.[31] In this regard it is worth pointing out that we have also found that perrhenyl chloride (ReO_3Cl) reacts with olefins to effect cis addition of HOCl; with three oxo groups it is remarkable that no vicinal diol was detected.[12] We have found too that the monooxo substances $CrOCl_3$[32] and $MnOCl_3$[33] upon reaction with olefins gave no oxygen-containing products, only chlorinated ones.[34]

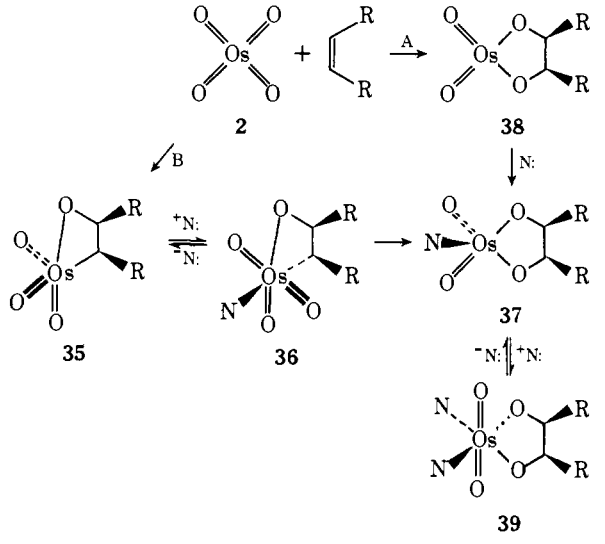
Cis dichlorination of olefins by $MoCl_5$ has recently been reported by two groups.[18] We feel that the mechanism of this reaction is probably similar to that outlined in Scheme III for formation of dichloride **19**. The main group chloride $SbCl_5$ has also been shown to react with olefins to give predominantly the vicinal dichlorides resulting from cis addition.[35]

Oxo transition metal compounds also oxidize nucleophiles other than olefins. Amines (R_3N:), phosphines (R_3P:), and sulfides (R_2S:) are readily transformed by these reagents to

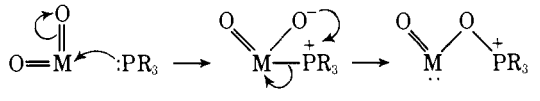
Scheme IV



Scheme V



their corresponding oxides. As in the case of olefins, we favor initial association of the nucleophile with the metal center, followed by migration of the coordinated heteroatom to an oxo group on the metal:



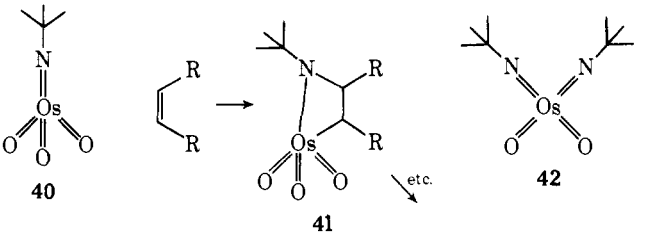
Here too we prefer to avoid mechanisms which invoke direct attack of the nucleophile (e.g., R_3P:) on the oxygen end of an oxo metal moiety.

A general class of atom transfer reactions is emerging in which a high valent MX species (e.g., X is Cl,[36] =O,[36] =NR,[37] or $=CR_2$[38]) transfers its X group to an olefin. We feel that involvement of what is formally a [2 + 2] addition ($[2\sigma + 2\pi]$ or $[2\pi + 2\pi]$) is a likely first event in the transfer process. In the case of multiply bound X atoms (C, N, and O) this produces four-membered metallocyclic intermediates (analogous to **21** in Scheme III) as shown in Scheme IV. The ultimate fate of these initially formed intermediates (**29**, **30**, and **31**) would then be determined by the nature of the central metal and its other ligands. When M is a main group element, especially sulfur, species related to **29**,[39] **30**,[40] and **31**[29] can sometimes be isolated. In the case of transition metals such four-membered organometallic species have never been detected in the reactions of ylides (**32**), alkylimido compounds (**33**), or oxo species (**34**) with olefins. However, the evidence supporting involvement of metallocyclobutanes (**29**) in olefin metathesis continues to mount,[41] and the first examples of stable d^0 transition metal ylides (**32**) have been reported by Schrock.[42]

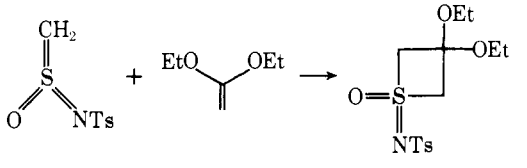
We now briefly consider the possible significance of these new mechanistic concepts for oxidants other than chromyl chloride. Having four identical oxo groups, osmium tetroxide (**2**) provides a classic example of an oxo transition metal species. Its well-known reaction with olefins has long been accepted to proceed by a [3 + 2] cycloaddition process (path A, Scheme V).[43] In path B of Scheme V we propose an alternative mechanism which involves a four-membered organoosmium intermediate (**35**) analogous to **21** proposed in Scheme III for CrO_2Cl_2 oxidiations of olefins. Coordination of a ligand (e.g., pyridine) to **35** would produce the octahedral complex **36** and trigger reductive insertion of the Os–C bond into an oxo group yielding the osmium(VI) ester **37**. In this regard it is perhaps significant that reaction of OsO_4 with olefins in the presence of acetyl chloride results in cis addition of the elements of ClOAc across the olefinic unit.[44]

At first glance the simplicity of path A leading to intermediate **38** is deceptively appealing. Although octahedral osmate esters such as **39** are stable and isolable, there would be severe angle strain in the initial tetrahedral metallocycle **38** due to the long (ca. 2.2 Å) osmium–oxygen bonds.[45] By contrast, the four-membered intermediate **35** of path B should be substantially less strained since the long Os–C and Os–O bonds would have the effect of relieving the angle strain in the four-membered ring. Of course it must be pointed out that these objections to the [3 + 2] mechanism are removed if one invokes prior coordination of the nucleophile (N:) to OsO_4;[46] in this case [3 + 2] cycloaddition could proceed directly to the five coordinate ester **37**.

We have recently found that aza analogues of OsO_4 such as the *tert*-butyl imido species **40** react with olefins to produce β-amino alcohols.[37] Again we feel that a reaction path involving a four-membered intermediate (**41**) is a likely alter-



native to direct [3 + 2] cycloaddition. Accepting for the moment that a four-membered intermediate may be involved, then there is some reason for believing that the initial association is with the imido group (i.e., leading to **41**) rather than one of the three oxo groups. We have just found that the diimido analogue **42** reacts with olefins to give preferentially and in some cases exclusively the 1,2-diamines.[37d] It is remarkable that these reagents exhibit such a strong preference for delivery of the nitrogen to one of the olefinic carbons. This mode of reaction would appear to be very disfavored by the steric bulk in the vicinity of the nitrogen produced by the tertiary alkyl substituents. There is precedent for this selection of nitrogen over oxygen in the reactions of related sulfur species with olefins. The most impressive example is that of Johnson in which an iminosulfene reacts with an enol ether to give a [2 + 2] adduct:[39]

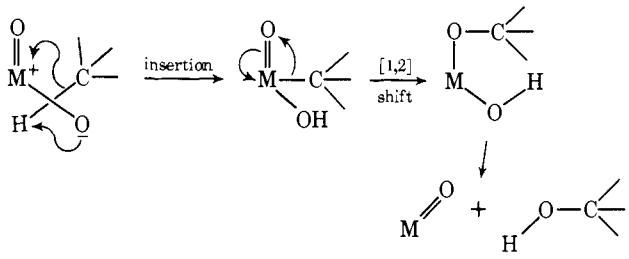


In this case the olefin has a choice of three first-row elements (C, N, and O) and it chooses the element furthest to the left. This rule of selection (C > N > O) appears to hold for all known [2 + 2] and [2 + 4] additions of other similar sulfur

compounds with olefins and dienes.[40] From our experience with oxo- and azaosmium species,[37] it appears that it may also have validity for elements other than sulfur.

Although this discussion has been limited to olefins, oxo transition metal reagents also hydroxylate saturated C–H bonds with retention of configuration (see ref 7a and 15). To the best of our knowledge none of the mechanisms proposed to rationalize these hydroxylations has invoked organometallic intermediates. We feel that the sequence shown in Scheme VI

Scheme VI



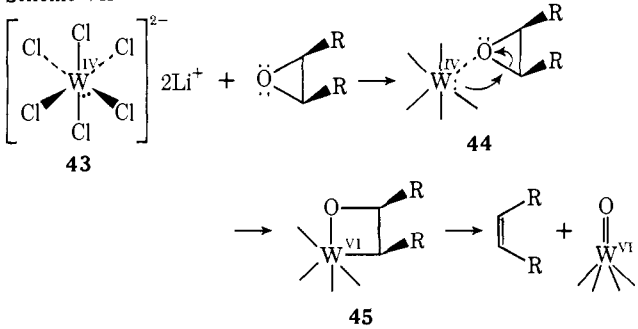
where an organometallic intermediate results from insertion of an oxo group into the C–H bond would provide an attractive means of explaining the unusual stereochemical features of these oxidations.

Several years ago we provided evidence[15] that an oxo iron species (i.e., Fe=O) was a likely candidate for the active oxidant in P_{450} dependent mixed-function oxygenases; in light of the mechanism proposed in Scheme VI we further suggest that an iron organometallic species (Fe–C) be considered as a possible intermediate in these enzymic hydroxylations.

The key step in Scheme VI involves direct attack by a highly electrophilic metal center on a saturated C–H bond. This process may not be as unprecedented as it first seems. Certain nickel and platinum systems are able to accomplish this end.[47] Also, Barton and co-workers have recently reported that molecular fluorine fluorinates methine C–H bonds in steroids with retention.[48] In general, we feel that an electrophilic path, such as that in Scheme VI, is more likely to lead to retention than the radical mechanisms previously[49] proposed.

The reactions so far considered have involved transfer of atoms (usually oxygen) from the metal to the carbon compound. Some time ago, employing lower valent tungsten halides, we discovered that the direction of these reactions could be reversed.[50] For example, both 1,2-diols[50a] and epoxides[50b,50c,51] could be deoxygenated to olefins. We believe that these deoxygenations occur by mechanisms which are essentially the microscopic reverse of the forward processes (Schemes III and V). Such a mechanism is illustrated in Scheme VII for the stereoselective reduction of epoxides to

Scheme VII



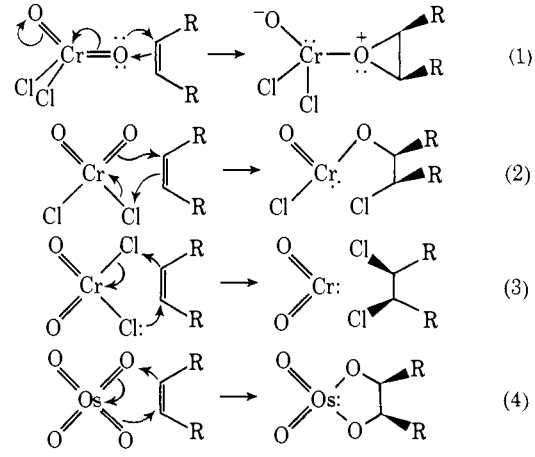
olefins by dilithium hexachlorotungstate (**43**, Li_2WCl_6).[52] Notice the similarity of intermediates **44** and **45** in Scheme VII to intermediates **22** and **21** in Scheme III and also the essential identity of the mechanistic steps which connect them. In both the oxygenation process (chromyl reagents) and the deoxygenation process (tungsten(IV) reagents) the stereochemistry of the olefin or epoxide is retained.

Conclusions

Most all organic oxidizing agents are ultimately based on highly electronegative elements, especially oxygen and the halogens. A common outcome in such oxidations is for the electronegative oxygen or halogen atom to insert into a C–H bond or add to the π bond of an alkene. Because oxygen (O_2) and the halogens (X_2) are vigorous oxidants and often nonselective in their reactions with olefins and hydrocarbons, the organic chemist has come to appreciate the remarkably selective oxidants which arise when oxygen or halogen combine with certain metallic elements (e.g., chromium, osmium, and selenium). Reagents such as CrO_2Cl_2, OsO_4, and SeO_2 react in unique ways with olefins to transfer their oxygen and halogen atoms to the organic reductant. Since the organic chemist has tended to think of these atom transfer reagents as sources of oxygen and halogen atoms, it is perhaps not surprising that the mechanisms proposed for getting the atom transferred from the metal center to the organic substrate involved direct assault on the atom itself. The possibility of indirect mechanisms involving initial attack at the metal center were not considered.[64]

In this paper we have proposed and tried to defend an entirely new approach to the mechanism of oxidation of olefins by oxo transition metal compounds. In this approach we believe that the olefin, albeit a weak nucleophile, always interacts initially with the metal itself leading to the formation of d° organometallic intermediates. We would be the first to admit that the arguments presented here in favor of carbon–metal bonded intermediates in these olefin oxidations are inconclusive. In fact, as we have tried to emphasize throughout, we have as yet no evidence which cannot also be rationalized by direct attack of the olefin on the ligands. Perhaps the single most impressive fact about these oxidations is that the original geometry of the olefin is always maintained in the products (i.e., cis addition is the rule). Although our organometallic mechanisms readily account for cis addition, so do some mechanism involving direct interaction with the ligands. The principal cis-addition products discussed above are epoxide, 1,2-chlorohydrin, 1,2-dichloride, and 1,2-diol. In Scheme VIII are

Scheme VIII. Mechanisms Involving Direct Attack on the Heteroatom Ligands[53]



shown conceivable direct modes of reaction of an olefin with CrO_2Cl_2 and OsO_4 which would produce such products. Although we have already discussed a number of considerations which we feel make mechanisms such as depicted in Scheme VIII unattractive,[53] we cannot exclude any of them at this time.

Since the main group element selenium exhibits certain metallic properties, the course of oxidation of olefins by SeO_2 is perhaps relevant to the mechanisms of olefin oxidation by transition metal oxo compounds. We have provided strong evidence that species bearing a Se-C bond are key intermediates in the oxidations of olefins by SeO_2. This was accomplished both by synthesizing and by trapping the putative organoselenium intermediate. Although similar attempts to prepare or trap the proposed organometallic intermediates in the reactions of oxo transition metal species with olefins have so far failed, we feel that this approach is still worth pursuing. Since a number of important industrial processes for oxidation of hydrocarbons rely on heterogeneous transition metal oxides as catalysts, better understanding of the mechanisms of oxidation by these homogeneous oxo species is of more than academic interest.

The concept that organometallic intermediates may be involved in these oxidations has motivated much of our research for the past 5 years. In spite of the inconclusive results at present, we have decided that our new hypothesis should be published since it offers an important alternative to those already in the literature. Should these new mechanistic concepts prove correct, then there is a whole class of reactions involving organometallic intermediates which had not been appreciated previously.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 237 or 257 spectrophotometer. NMR spectra were obtained with a Varian T-60 or a Hitachi Perkin-Elmer R22 (90 MHz) spectrometer. GLC analyses were performed on 6 ft × 0.125 in. glass columns packed with 3% OV-17 on Gas Chrom Q (100–120 mesh). All olefins were obtained from Chemical Samples Co.

Reagent grade methylene chloride was purified by stirring over portions of concentrated sulfuric acid until the acid layer remained colorless. The CH_2Cl_2 layer was washed with 10% aqueous $NaHCO_3$, water, and brine and was dried ($MgSO_4$). Distillation from calcium hydride afforded dry, olefin-free CM_2Cl_2, which was stored over 4A molecular sieves. Reagent grade carbon tetrachloride was dried by passing it through activity I neutral alumina and storing it over 4A molecular sieves.

We routinely prepare chromyl chloride on a 1.5-mol scale (150 g of CrO_3) as described in ref 62; the preparation in ref 62 is for 1/3 this scale.

The 1-deuteriodecenes were prepared by hydroalumination[63] of the appropriate terminal acetylene.[37c] The *E* isomer derived from hydroalumination of 1-decyne followed by D_2O quench, and the *Z* isomer by hydroalumination of 1-deuterio-1-decyne followed by H_2O quench.

(*E*)-Cyclododecene oxide was a commercial sample (Aldrich). (*Z*)-Cyclododecene oxide,[54] (*E*)- and (*Z*)-5-decene oxide,[55] and 1-decene oxide[56] were prepared by reaction of the appropriate olefin with *m*-chloroperbenzoic acid in CH_2Cl_2. 1,2-Dichlorodecane was prepared[57] from 1-decene and sulfuryl chloride. 2-Chlorocyclododecanone and 6-chloro-5-decanone were prepared by reaction of the olefins with CrO_2Cl_2 in acetone.[11]

The yields reported in Tables I–IV are absolute yields and were determined by GLC using *n*-saturated hydrocarbons as internal standards. The internal standards were added at the completion of the workup since CrO_2Cl_2 is known to attack even saturated hydrocarbons. During a GLC yield analysis both the response factor mixture and the reaction mixture were analyzed at least three times each. Averages of these runs were used in the calculations. Response factors (RF) were calculated by the following equation:

$$RF = \frac{\text{mmol (standard)}}{\text{mmol (compound)}} \times \frac{\text{area (compound)}}{\text{area (standard)}}$$

Preparation of Authentic Halohydrins. Chlorohydrins. According to the procedure described by House,[58] a solution of the epoxide (5 mmol) in dry ether (10 mL) was saturated with dry HCl gas at 0 °C. The solution was stirred for 1 h at 0 °C, then poured into ice-water (10 mL). The aqueous layer was extracted with ether, and the organic phases combined, washed with $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated.

***erythro*-2-Chlorocyclododecanol:** mp 78–79 °C (lit.[59] 79–80 °C); NMR (CCl_4) δ 4.17 (1, m, CHCl), 3.87 (1, m, C*H*OH).

***threo*-2-Chlorocyclododecanol:**[60] NMR (CCl_4) δ 4.03 (1, m, CHCl), 3.80 (1, m, C*H*OH).

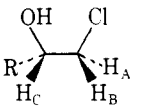
***erythro*-6-Chloro-5-decanol:**[61] bp 60 °C (1 mm); IR (neat) 3700–3100 (OH), 1120 (C-O), 740 cm^{-1} (C-Cl).

Anal. Calcd for $C_{10}H_{21}ClO$: C, 62.32; H, 10.98. Found: C, 62.10; H, 10.90.

***threo*-6-Chloro-5-decanol:**[61] bp 60 °C (1 mm); IR (neat) 3580, 3520–3300 (OH), 1450, 1380, and 1060 cm^{-1} (C-O).

2-Chloro-1-decanol[61] and **1-chloro-2-decanol**[61] was obtained as a mixture (3.4:1) from ring opening of 1-decene oxide. They were separated on silica gel by preparative TLC (hexane–ethyl acetate, 9:1), 2-chloro-1-decanol being the more polar regioisomer.

1-Chloro-2-decanol: NMR (CCl_4, 90 MHz). Analysis of the spectra gave δ_A 3.41, δ_B 3.55, δ_C 3.73.



$J_{AC} = 7.2$, $J_{BC} = 3.5$, $J_{AB} = 11$ Hz

Bromohydrins. *threo*-6-Bromo-5-decanol. To 2.0 mL of 48% hydrobromic acid was added dropwise at 25 °C 1.56 g (10 mmol) of (*Z*)-5-decene oxide. The two-phase mixture was stirred for 5 h at 25 °C, then poured into cold aqueous $NaHCO_3$ and extracted twice with 20 mL of ethyl acetate. The organic phases were washed with H_2O, dried, filtered, concentrated, and bulb-to-bulb distilled (Kugelrohr) at 80–90 °C (~1 mm) to yield 2.01 g (84%) of *threo*-6-bromo-5-decanol as a pale yellow liquid: IR (neat) 3600–3200 (OH), 790 cm^{-1} (C-Br); NMR (CCl_4) δ 4.00 (1, m, CHBr), 3.60 (1, m, C*H*OH), 2.60 (1, broad s, OH).

Anal. Calcd for $C_{10}H_{21}BrO$: C, 50.63; H, 8.92. Found: C, 50.38; H, 8.88.

***erythro*-6-Bromo-5-decanol.** The same procedure described above for preparation of the threo isomer was applied to 1.56 g (10 mmol) of (*E*)-5-decene oxide to yield 2.10 g (87%) of *erythro*-6-bromo-5-decanol as a pale yellow liquid: IR (neat) 3600–3200 (OH), 790 cm^{-1} (C-Br); NMR (CCl_4) δ 4.00 (1, m, CHBr), 3.60 (1, m, C*H*OH), 2.60 (1, broad s, OH).

Upon GLC analysis (OV-17 at 105 °C) the threo and erythro bromohydrin isomers had retention times of 14 and 15 min, respectively. The chlorohydrin diastereomers derived from 5-decene and cyclododecene exhibited this same GLC (OV-17) behavior (i.e., the threo isomer having a shorter retention time than the erythro isomer).

Preparation of Authentic 1-Deuterio-1,2-dichlorodecanes. Erythro Diastereomer. Generally following San Filippo's procedure,[18b] a solution of (*Z*)-1-deuterio-1-decene (337 mg, 2.4 mmol) in CH_2Cl_2 (1 mL) was added over a 5-min period to a stirred solution of $MoCl_5$ (655 mg, 2.4 mmol) in CH_2Cl_2 (5 mL) at −78 °C under an atmosphere of dry nitrogen. The resulting mixture was allowed to warm to room temperature and aqueous $Na_2S_2O_3$ (0.1 g in 2 mL) was added. The mixture was stirred for 5 min, then extracted with CH_2Cl_2. The combined organic phases were washed with $NaHCO_3$ solution, water, and brine, dried (Na_2SO_4), and concentrated to give an oil. This crude product mixture was subjected to two successive purifications by preparative TLC which afforded 40 mg (8%) of relatively pure *erythro*-1-deuterio-1,2-dichlorodecane: deuterium decoupled NMR (CCl_4) δ 3.92 (1, m, -C*H*ClCHDCl), 3.52 (1, d, J = 8.8 Hz, -C*H*DCl).

***Threoo* Diastereomer.** Following exactly the same procedure just described for synthesis of the erythro isomer, but replacing the *Z* olefin with (*E*)-1-deuterio-1-decene, *threo*-1-deuterio-1,2-dichlorodecane was obtained: deuterium decoupled NMR (CCl_4) δ 3.92 (1, m, -C*H*ClCHDCl), 3.70 (1, d, J = 4.8 Hz, -C*H*DCl).

General Procedure for the Oxidation of Olefins with CrO_2Cl_2 at −78 °C. To a solution of the olefin (6 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added dropwise with stirring CrO_2Cl_2 (8 mmol). The dark red-brown solution was stirred at −78 °C for 3 h, then was added to 50 mL of a cold aqueous solution of $NaHSO_3$. The green mixture was stirred for 15 min, then extracted with CH_2Cl_2. The organic phase was washed with $NaHCO_3$ solution, water, and brine and dried (Na_2SO_4). The solution was either analyzed by GLC (in which case the appropriate *n*-saturated hydrocarbon was added as an internal

standard) or concentrated, and the products isolated for characterization by preparative TLC.

Oxidation of 1-Deuterio-1-decene with CrO_2Cl_2 at 0 °C in CCl_4. Following the procedure of Stairs,[3] 1-deuterio-1-decene (*Z* or *E*) (0.336 g, 2.4 mmol) was added to chromyl chloride (0.38 g, 2.4 mmol) in CCl_4 (5 mL) at 0 °C while stirring. The mixture was stirred for 1 h at 0 °C, then hydrolyzed by adding 3 mL of a solution of sodium metabisulfite (0.15 g) in ice-cold water. The mixture was stirred for 15 min and worked up as described above for the oxidation in CH_2Cl_2.

CrO_2Cl_2 Oxidation of (*Z*)-5-Decene in Acetone in the Presence of Lithium Bromide. This oxidation was performed as described in the general procedure for oxidation of olefins with CrO_2Cl_2 in CH_2Cl_2 at −78 °C with the exceptions that acetone was the solvent and 2 equiv of lithium bromide was dissolved in it before cooling to −78 °C. Normal workup and analytical procedures were employed.

Dehydrohalogenation of 1-Deuterio-1-chloro-2-decanol and 1-Deuterio-2-chloro-1-decanol. The chlorodecanol (50 mg, 0.26 mmol) was treated with 32 mg (0.8 mmol) of NaOH in 4 mL of 50% aqueous ethanol (0.2 N NaOH) for 20 min at room temperature with stirring. Ether (10 mL) and water (5 mL) were added and the aqueous phase was extracted with ether. The organic phase was dried ($MgSO_4$) and concentrated to give 1-deuterio-1,2-epoxydecane (37 mg) which was analyzed by NMR without any further purification to give the ratio of cis and trans isomers $(H_1)_{cis}$ 2.58, $(H_1)_{trans}$ 2.31 ppm (CCl_4).

Control Experiments. Chromyl Chloride Oxidation of an Olefin in the Presence of an Epoxide. In a representative experiment chromyl chloride (0.31 g, 2 mmol) was added to a mixture of (*Z*)-5-decene oxide (0.154 g, 1 mmol) and (*E*)-cyclododecene (0.174 g, 1 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The reddish-brown solution was stirred at −78 °C for 3 h, then worked up and analyzed as above for the regular chromyl chloride oxidations. The olefins used in these control experiments were chosen so that none of the oxidation products derived from them interfered with GLC analysis of the products derived from the epoxides.

Reaction of 1-Decene Oxide with Chromyl Chloride in the Presence of 1-Hexene. Chromyl chloride (0.38 g, 2.4 mmol) and 1-hexene (0.2 g, 2.4 mmol) were mixed in CCl_4 (5 mL) at 0 °C. 1-Decene oxide (37.4 mg, 0.24 mmol) was added dropwise during 5 min and the resulting mixture was stirred for 1 h. The mixture was hydrolyzed by adding sodium metabisulfite (0.15 g) in ice-cold water (3 mL) and worked up as described above. GLC analysis showed that 1-chloro-2-decanol and 2-chloro-1-decanol had been formed in a ratio of 1:1.4 in a combined yield of 45%.

Reaction of 1,2-Dihydroxydecane with CrO_2Cl_2 in the Presence of 1-Hexene. To a freshly prepared mixture of chromyl chloride (1.2 mmol) and 1-hexene (101 mg, 1.2 mmol) in CCl_4 (2.5 mL) at 0 °C was added the decanediol (10.5 mg, 0.06 mmol). The mixture was stirred for 1 h and then worked up in the usual manner. GLC showed that all of the diol had been consumed.

Attempted Preparation of $CH_3(CH_2)_8CH_2CrO_2Cl_2$. Reaction of (n-decyl)$_2$Hg with CrO_2Cl_2. To a solution of 77 mg (0.5 mmol) of CrO_2Cl_2 in 3 mL of CH_2Cl_2 was added dropwise, while stirring at −78 °C, 120.6 mg (0.25 mmol) of (*n*-decyl)$_2$Hg dissolved in 0.5 mL of CH_2Cl_2. The deep red solution turned dark immediately upon addition of the mercurial; stirring was continued for 1.5 h at −78 °C. The temperature of the reaction mixture was raised to 0 °C, and after 15 min reductive hydrolysis was accomplished by adding 1.5 mL of an ice-cold aqueous $NaHSO_3$ (110 mg) solution. This mixture was stirred for another 15 min at 0 °C, then the organic phase was separated. The aqueous phase was washed several times with CH_2Cl_2, and the combined organic phases were washed with brine. At this point *n*-eicosane was added as an internal standard and the yields of 1-decanol (35%), 1-chlorodecane (24%), and 1-decanal (6%) were determined by GLC (yields are based on (*n*-decyl)$_2$Hg). In a separate experiment the identity of the three products was established by isolation from preparative GLC and spectral (IR and NMR) comparison with authentic samples.

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(53) The mechanisms shown in Scheme VIII all involve direct attack of the olefin on the heteroatom ligands. They are the type of mechanism favored in the literature (ref 2–7) and are shown here for comparison with the alternative approaches which we have been espousing. Actually the cis dichlorination of olefins by these reagents (i.e., CrO_2Cl_2 in this work and $MoCl_5$[18a,18b]) is a rather new observation and a mechanism analogous to entry 3 in Scheme VIII has, to the best of our knowledge, not yet appeared in the literature. The mechanism shown in entry 3 is what we imagine those (ref 2–7) who support direct ligand attack processes would favor to explain the cis addition aspect of this new transformation.
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Near-Ultraviolet-Excited Raman Spectroscopy of Lysozyme and the Lysozyme–Glucose Complex

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Abstract: A study is reported of the Raman spectrum of lysozyme excited by the near-UV argon ion laser line at 363.8 nm. Compared to the Raman spectrum excited by visible lines, the spectrum is simplified due to a strong preresonance enhancement of the Raman spectrum of tryptophan. This preresonance Raman enhancement by the UV excitation is approximately as expected from the simple theory, but not all normal Raman lines of lysozyme are affected the same way. The tryptophan spectrum is strongly enhanced, with the vibrations of the indole ring of tryptophan enhanced greatly in the UV-excited Raman spectrum. The net effect of the UV excitation is a simplification from the normal Raman spectrum of lysozyme, permitting easier study of the changes in the Raman spectrum of tryptophan in lysozyme when it interacts with a substrate. The procedure is illustrated by a study of both visible and UV-excited Raman spectra of the weak lysozyme–glucose complex.

The Raman spectrum of proteins is normally complicated by the presence of a large number of bands, due both to the amide backbone and to the amino acids that compose the protein.[1,2]

We expect that the Raman bands of a molecule will be enhanced when the frequency of the exciting line is near one of the allowed electronic absorption regions of the molecule, due to the preresonance Raman effect.[3] Three of the common amino acids in proteins (tryptophan, tyrosine, and phenylalanine) absorb in the near-UV region of the spectrum (250–300 nm), so we might expect the Raman lines from these three species in the protein to be selectively enhanced by use of a near-UV excitation line.[4,5] If the enhancement is sufficient we might expect to see Raman bands from only these three residues (or perhaps from only one of these three) when we study the Raman spectrum of a protein such as lysozyme using a UV exciting line. Since tryptophan absorbs more strongly at lower frequencies than do either tyrosine or phenylalanine, we expect that the Raman spectrum of most proteins excited by a line longer than 300 nm would contain, for the most part, only