ORGANIC REACTIVITY CONTROL BY MEANS OF NEIGHBORING GROUPS AND ORGANOMETALLICS. A PERSONAL ACCOUNT*

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This review summarizes the main topics of our research and covers the period of the last 15 years. The prime interest is focused on various ways of controlling the regio- and stereoselectivity of selected organic reactions, in particular electrophilic additions, cleavage of cyclopropane rings, and allylic substitutions by means of neighboring groups and/or transition and non-transition metals. In the first part, the factors governing the course of electrophilic additions are assessed, culminating in the formulation of selection rules for the reactivity of cyclohexene systems, and in a concise synthesis of the natural cardioactive drug, strophanthidin. These studies also contribute to a better understanding of the mechanisms of electrophilic additions. The second part describes recent developments in the stereo- and regiocontrolled cleavage of cyclopropane rings by non-transition metals (Tl and Hg), and the reactivity and transmetalation (with Pd) of the primary products. This methodology has resulted in novel routes to unique polycyclic structures, and will have synthetic applications in the near future. Evidence for the stereospecific "corner" cleavage of the cyclopropane ring has been provided for the first time for Tl and later for Hg. The third part deals with transition metal-catalyzed allylic substitution. Evidence for a new "*syn*" mechanism for the formation of the intermediate (π-allyl)palladium complex has been provided, which runs counter to the generally accepted "*anti*" mechanism. A novel method for a Pd-catalyzed allylic oxidation has been developed and employed in the synthesis of natural sesquiterpenes. The increasing importance of transition and non-transition metals for synthetic organic chemistry is demonstrated by their unique reactivity in a number of the papers included in this review.

1. INTRODUCTION

An ultimate goal for synthetic organic chemistry is the discovery of novel, efficient routes to biologically significant molecules. The last two decades have brought a plethora of highly selective methods[1], and a general trend towards the increasing application of organotransition metal reagents can be clearly discerned[1,2]. Progress in the constructing stereogeneous elements has been enormous in the last decade, affording new, powerful methods with reactions for which 90% d.e. or e.e. is more a rule than an exception. Some of the methods thus reach the level of stereoselection set by enzymatic catalysis.

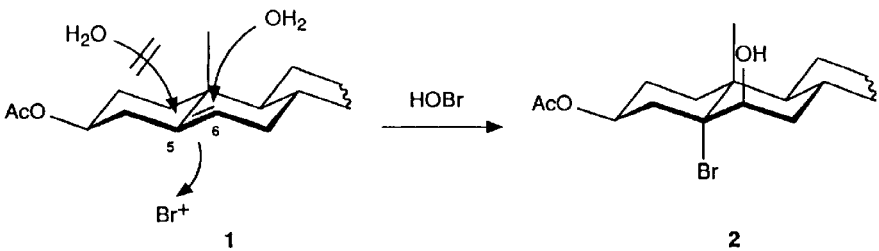
The aim of our work was to design new methods for regio- and stereocontrol of electrophilic additions and related reactions, by means of neighboring groups and to study mechanisms in detail. In recent years we have mostly concentrated on the application of transition and non-transition metals as highly selective reagents. In particular, transition metals have exceptional steric and electronic properties[2,3] so that they hold tremendous promise for effecting highly stereoselective transformations of organic molecules and for achieving goals that cannot be attained by other methodologies.

2. STEREO- AND REGIOCONTROL OF ELECTROPHILIC ADDITIONS TO CYCLOHEXENE SYSTEMS BY NEIGHBORING GROUPS

Conversion of sp^2 to sp^3 carbon atoms employing electrophilic additions is a general and widely used method for building-up vicinal chiral centers. Stereo- and regioselective introduction of hetero-substituents in this way is one of the essential strategic processes for the construction of complex polyfunctional molecules[1,4]. The development of further tools for controlling the stereo- and regioselectivity of electrophilic additions is thus of eminent importance for organic synthesis.

Acyclic, non-symmetrically substituted olefins generally obey Markovnikov rule[5] and react with hypobromous acid and related electrophiles to give the product with the nucleophile usually attached to the most electrophilic center, usually the more substituted carbon[6]. Additions that proceed via cyclic "onium" ions are subject to stringent stereoelectronic control, particularly apparent in cyclohexene systems[7,8] which produce preferentially 1,2-*trans*-diaxial adducts (Fürst–Plattner rule)[9].

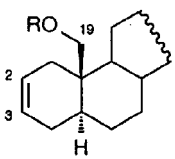
Depending on the olefin structure, the electronic (Markovnikov) and stereoelectronic effects can either be consonant or dissonant[10]. Cholesteryl acetate (**1**) is a typical example of the latter case: although the Markovnikov rule requires that e.g. hypobromous acid be added to form a bromohydrin by cleavage of the corresponding cyclic bromonium ion at the more substituted carbon (C(5)), the reaction is entirely dominated by stereoelectronic effects that favor axial cleavage at the less substituted carbon (C(6)), producing the diaxial bromohydrin **2** (Scheme 1)[7].



SCHEME 1

Neighboring groups have often proved to strongly influence chemical reactivity[11]. It was thus of interest to study the neighboring group effects on the regio- and stereochemistry of electrophilic additions of which little had been known. In particular we were going to address the following questions: how the reaction course (i.e. the stereo- and regioselectivity) will be influenced or controlled by the presence of the neighboring group, its character, orientation, and its distance from the reaction center or potential reaction center. To this end we had originally selected hypobromous acid as a representative electrophilic reagent[12 – 14], where the electrophilic part could easily be dis-

cerned in the product from the nucleophile. Moreover, we intended to use mostly oxygen neighboring groups and to investigate the competition between internal and external nucleophile. Hence, using an external oxygen nucleophile was desirable in order to eliminate or largely suppress the intervention of factors such as different inborn nucleophilicity different atoms. As model compounds we had prepared a series of several dozens of steroidal olefins[12,15] (e.g. Chart I) with double bond in position 1,2-, 2,3-, 3,4-, 4,5-, 5,6-, or 6,7-, and homosteroids unsaturated at positions 6,7- (B-homo) and 19,19a- (19-homo). As neighboring groups we were going to employ hydroxy (OH), ether (OCH_3), ester (RCO_2 and CO_2Me; R = H, Me, C_6H_5, and 4-$MeOC_6H_5$), nitrate (O_2NO), phosphate [$(EtO)_2P(O)O$], carbonate ($EtOCO_2$), and carbamate (H_2NCO_2, $BnNHCO_2$, and Me_2NCO_2), most often located at position 19 and, occasionally, elsewhere (2, 3, 4, 6, 7, 19a, etc.). Another issue to be addressed was the reactivity of bidentate groups and the competition with external nucleophile. We hoped to arrive at practical conclusions and to develop new regio- and stereocontrolled methods for constructing chiral centers from sp^2 carbons.



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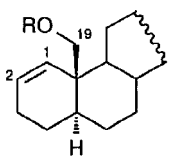
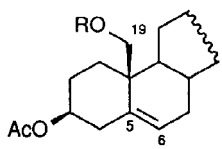
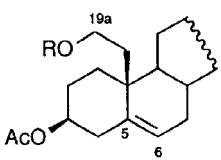
4, R = CH_3
5, R = CH_3CO



6, R = H
7, R = CH_3
8, R = CH_3CO



9, R = H
10, R = CH_3
11, R = CH_3CO
12, R = H_2NCO



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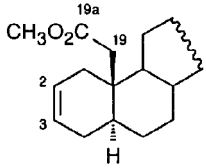
14, R = CH_3



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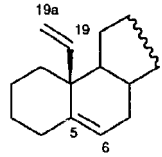

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CHART I

2.1. *Regiocontrol of Hypobromous Acid Addition to Cyclohexene Systems by Neighboring Groups*

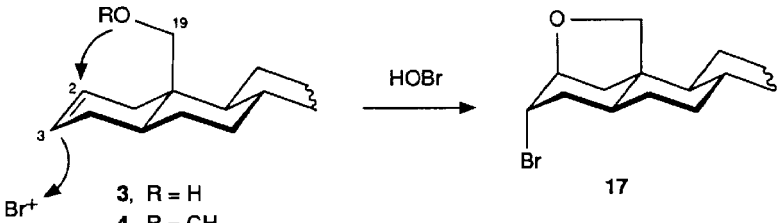
Of numerous studies on HOBr addition carried out in our laboratory, only a few will be dealt with in order to illustrate general principles and to show how some of the conclusions and generalizations have been arrived at.

Initial studies carried out with HOBr have shown that judicious anchoring of a functional group near to the reaction center can, indeed, dramatically affect the course of the addition (Scheme 2). Thus, for instance, addition of HOBr to the hydroxy or methoxy olefin **13** or **14** was found to afford the diequatorial product **22** as the result of an exclusive Markovnikov-type cleavage of the corresponding 5α,6α-bromonium ion[16]. This is in sharp contrast with the addition to cholesteryl acetate[7] (**1**) or its 19-OH (**9**) or 19-OMe (**10**) analogues[12] and the 2,3- and 1,2-unsaturated derivatives **3** – **8** that are dominated by stereoelectronic effect (Scheme 2). Analogous reversal of regioselectivity was observed for esters[10,13,17] (e.g. **11**), carbonates[13], and carbamates[10] (**12**), where it was the carbonyl oxygen that served as an internal nucleophile. The reaction mechanism for the acetate **11** has been verified by isotope labelling[18]: when the reaction was carried out in aqueous dioxane containing $H_2{}^{18}O$, almost quantitative incorporation of the label into the carbonyl of the ester group of the product **20** was detected. This mechanism is also evidenced by the formation of the cyclic carbonate **21** from carbamate **12** (ref.[10]).

At this stage we have introduced notation[13] which would describe the size of the ring to be closed and indicate the nature of the participating atom, e.g. $(O)^n$ or $(O)^{\pi,n}$. Later, we have introduced a merger[10] with the Baldwin notation (*exo-* or *endo-Trig*) in order to take into account the mode of cyclization. Thus the above reactions can be characterized as 5$(O)^n$-*endo-Trig* (**6** – **10**), 5$(O)^n$-*exo-Trig* (**3** – **5**, **13** and **14**), and 6$(O)^{\pi,n}$-*exo-Trig* (**11** and **12**) ring closures (Scheme 2).

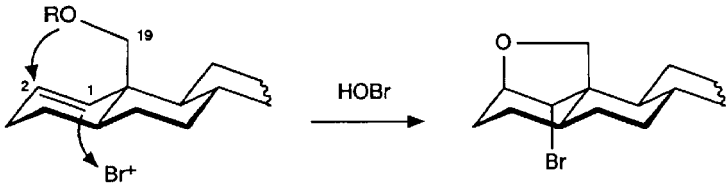
The reversal of the regiochemistry for alcohol **13** and esters **11** was interesting and we explored the structural limits in more detail. For instance, in contrast to 5,6-unsaturated derivatives (**11** – **14**) and their 4,5-olefinic isomers, the 1,2-olefins **6** – **8** turned out to give exclusively diaxial product[19] indicating that in this instance the addition is, again, dominated by stereoelectronic effect.

These and other examples allowed for the following generalization. Disubstituted olefinic derivatives (such as **3** – **8**) prefer axial approach of the OR groups to the double bond in agreement with the stereoelectronic requirements (path i in Scheme 3), regardless whether the new ring is to be formed by an *exo-Trig* (**3** – **5**) or *endo-Trig* (**6** – **8**) mode[20]. In contrast, trisubstituted olefins such as **11** – **14** react in a different manner, namely by the cleavage of the reactive intermediate at the most electrophilic site, which results in the formation of a diequatorial product (path ii in Scheme 3) in an *exo-Trig* fashion[20]. However, when the spacer between the double bond and the participating



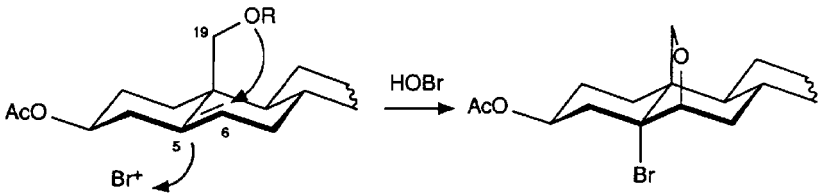
3, R = H
4, R = CH_3
5, R = CH_3CO

17



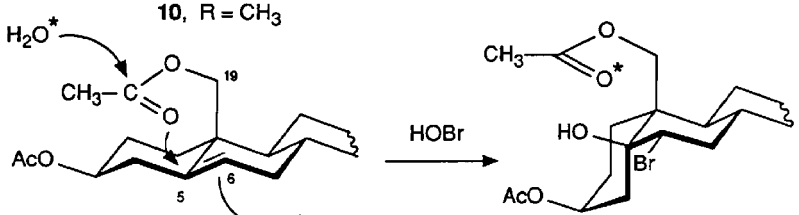
6, R = H
7, R = CH_3
8, R = CH_3CO

18



9, R = H
10, R = CH_3

19



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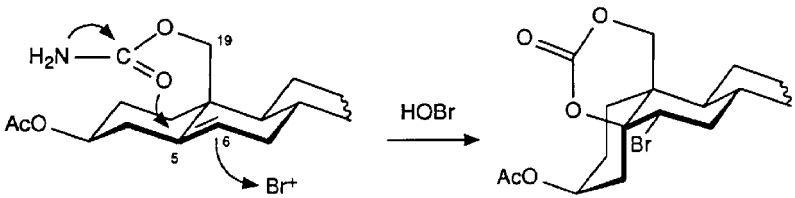

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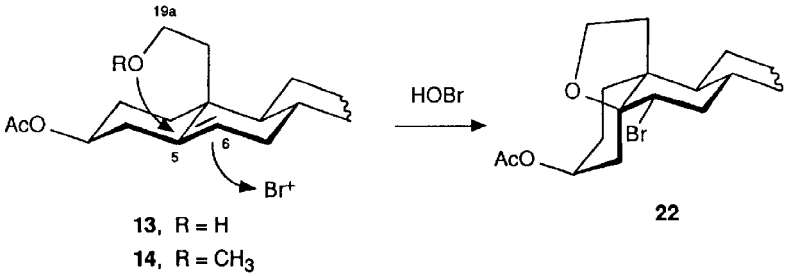
21

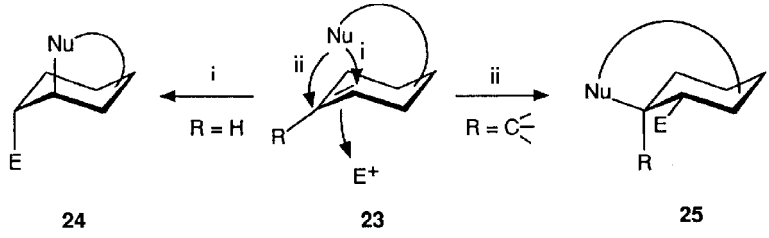


SCHEME 2

group does not allow the closing-up of at least a five-membered ring in this way, the axial cleavage will prevail again, as with **9** and **10** (ref.[10]).

2.2. *Regiocontrol of Other Electrophilic Additions to Cyclohexene Systems by Neighboring Groups and Further Reactivity of the Primary Adducts*

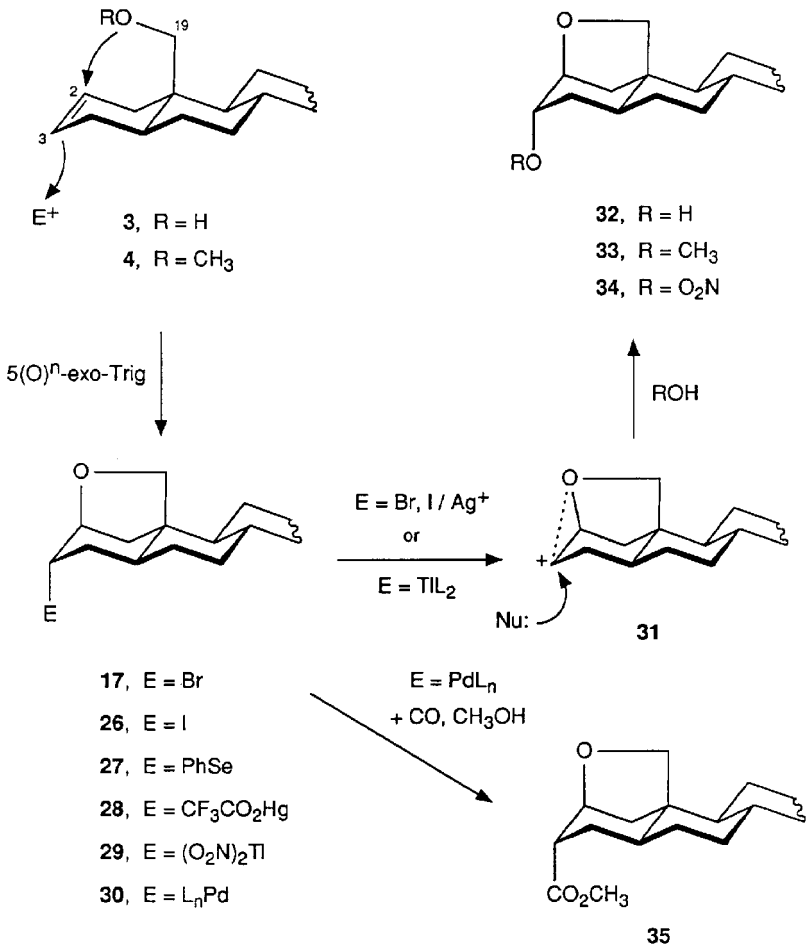
We have shown above[10] significant neighboring group effects upon the HOBr addition. In this chapter we will describe our results obtained with other electrophiles and show that our earlier conclusions derived from the reactivity towards HOBr are of a general character[20]. For these studies we have employed a set of cholestene derivatives with the double bond located in 2,3-, 1,2-, or 5,6- position, respectively, and hydroxy, methoxy, or carbamoyloxy groups attached to C-19 or C-19a (**3** – **14**, Chart I; ref.[20]).



SCHEME 3

2.2.1. Reactivity of 2,3-Unsaturated Derivatives **3** and **4**

As mentioned above, on reaction with HOBr the 2,3-unsaturated alcohol **3** (Scheme 4) readily affords the bromotetrahydrofuran **17** as the result of 5(O)^n-*exo-Trig* cyclization[12a]. Rather surprisingly, **3** was found to be inert to iodine in various solvents (dioxane, THF, DME, $CHCl_3$, and CH_2Cl_2). It turned out, however, that the iodocyclization can be facilitated by thallium(I) (ref.[21]). Thus, when iodine was slowly added to a solution of **3** in the presence of a slight excess of thallium(I) trifluoroacetate (or perchlorate), an almost instantaneous reaction could be observed which resulted in the formation of the iodotetrahydrofuran **26** as the single product.



SCHEME 4

When thallium(I) was replaced by silver(I), again an instantaneous reaction occurred. However, in this instance the process did not stop at the stage of the iodotetrahydrofuran **26**. Instead, the intermediate **26** further reacted with Ag^+ to afford the hydroxy derivative **32** as the product of a stereospecific Koenigs–Knorr-type solvolysis. In methanolic solution, formation of its methoxy congener **33** was observed. The mechanism was verified by the solvolysis of iodotetrahydrofuran **26** upon action of Ag^+ that furnished the same products **32** or **33**, respectively[22, 23] (via **31**). To obtain a good yield of **32** on the silver(I)-mediated iodination, two equivalents of Ag^+ are required. When only one equivalent was used, some of the hydroxy olefin **3** remained unreacted, and formation of both the iodotetrahydrofuran **26** and the hydroxy ether **32** could be detected in ca 5 : 1 ratio. This indicates that the rate of solvolysis of **26** is comparable with the rate of its formation. Other reagents including cerium(IV) sulfate[24], periodic acid, copper(II) chloride, bismuth(III) acetate[25], and potassium iodide were also found to promote iodocyclization, but in a less efficient way. The I_2/KI mixture gives substantial amount of by-products. Methyl ether **4** exhibits the same reactivity pattern as **3**.

Phenylselenenylation of **3** with PhSeCl or PhSeBr afforded the expected cyclic product **27**; Tl^+ was found to accelerate the reaction[26]. Under the same conditions, the unsaturated methoxy derivative **4** was also cyclized to **27**.

Mercuration[27] of **3** produced the intermediary organomercurial **28** (characterized in situ by ^{1}H NMR), which was reduced with alkaline borohydride to furnish the corresponding cyclic ether.

While olefins are generally inert toward Tl^+, they often react with Tl^{3+} yielding various products[4a,4b,28]. It was, therefore, desirable to include thallium(III) into our set of reagents. With **3**, a smooth cyclization was observed on treatment with thallium(III) nitrate, which gave rise to a mixture of the hydroxy ether **32** and its nitrate **34**, presumably via a thallium intermediate **29**. Under the same conditions, the methyl ether **4** did not react and was quantitatively recovered.

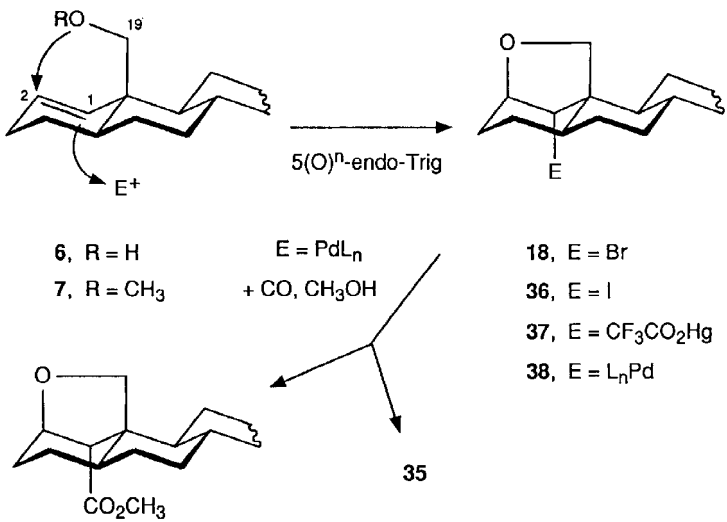
Another reaction of our interest was oxypalladation followed by CO insertion[29] (Scheme 4) for this transformation obviously has the promise of a valuable expansion of the methodology of organic synthesis. As the reported yields are often low[29] and since relatively little is known of the intramolecular version that would involve trapping the transiently formed η^2-palladium complex by a hydroxy group[30], we set out to explore its scope with our model compounds. We were particularly curious whether the η^2-complexes would behave similarly to their classical electrophilic counterparts such as bromonium or iodonium ions[31]. A catalytic amount (10 mol%) of $PdCl_2$ was added to the methanolic solution of **3** containing three equivalents of $CuCl_2$ (to reoxidize Pd) and the mixture was stirred under an atmosphere of CO at room temperature (22 °C) for 48 h. About 30% conversion to the expected product **35** was then observed. However, when the reaction was repeated in the presence of an excess of LiCl (4 equivalents), the isolated yield of **35** climbed up to 63% (ref.[32]). Finally, when copper(I) chloride

(3 equivalents) was added to the latter mixture and the reaction was run in the same manner, almost a quantitative yield of **35** was achieved in 24 h. This result suggests that both the Cu^{2+} and Cu^{+} are required in sufficient concentrations to keep up the cascade of the catalytic cycle[33] involving **30** as an intermediate.

Transmetalation of the mercury derivative **28** with $PdCl_2$ in methanol under the CO atmosphere was also attempted, but no more than 10% of the product (**35**) could be detected in the reaction mixture after 72 h. Obviously, direct cyclooxypalladation of **3** is superior to this method[34]. Methoxy derivative **4** was inert towards both the mercuration and cyclooxypalladation.

2.2.2. Reactivity of 1,2-Unsaturated Derivatives **6** and **7**

Both the 1,2-unsaturated alcohol **6** and its methyl ether **7** (Scheme 5) cyclize upon action of HOBr to the bromotetrahydrofuran **18** as the result of 5(O)^n-*endo-Trig* partici-



SCHEME 5

pation[19]. As expected, iodination of **6** and **7** in the presence of Tl^{+} gave analogous iodo derivative **36**. In contrast to **3**, iodination mediated by Ag^{+} stopped at the stage of iodotetrahydrofuran **36**, apparently because the solvolysis assisted by the ring oxygen would create a highly strained intermediate[35] (Chart II). The same iodotetrahydrofuran **36** was also obtained in high yield on the copper(II) and bismuth(III)-mediated iodination.

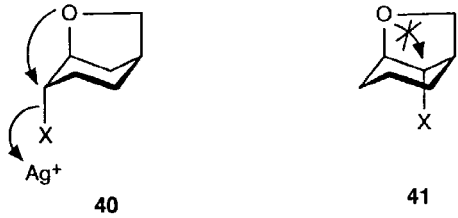


CHART II

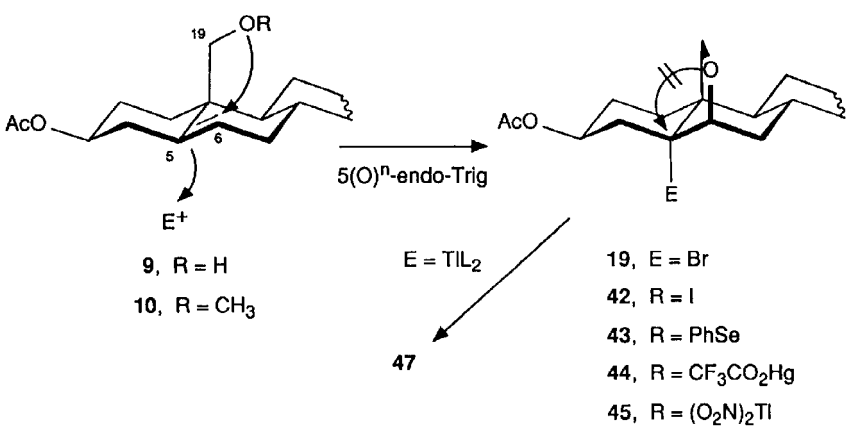
Mercuration of **6** was also found to follow the 5(O)^n-*endo-Trig* pathway giving rise to the intermediate mercurial **37** in quantitative yield. However, subsequent reduction with alkaline $NaBH_4$ afforded a substantial amount of the starting olefinic alcohol **6** (47%) together with the expected cyclic ether (40%).

While no reaction of **6** with $Tl(NO_3)_3$ occurred at room temperature, formation of a complex mixture of polar products was observed at 50 °C.

Palladation of **6** in methanol under an atmosphere of CO was carried out in the presence of CuCl, $CuCl_2$, and LiCl and afforded a mixture of the expected methoxycarbonyl tetrahydrofuran **39** (39%) and its isomer **35** (23%). The former compound is produced via the expected 5(O)^n-*endo-Trig* cyclization, whereas formation of the latter is indicative of a partial isomerization of **6** to **3**, presumably at the stage of η^2-complexes.

2.2.3. Reactivity of 5,6-Unsaturated Derivatives **9** and **10**

The 5,6-unsaturated alcohol **9** exhibits reactivity similar to that of **3** and **6** (Scheme 6). As mentioned before, addition of HOBr results in the formation of bromotetrahydrofuran **19** via the stereoelectronically controlled, anti-Markovnikov 5(O)^n-*endo-Trig* cycli-

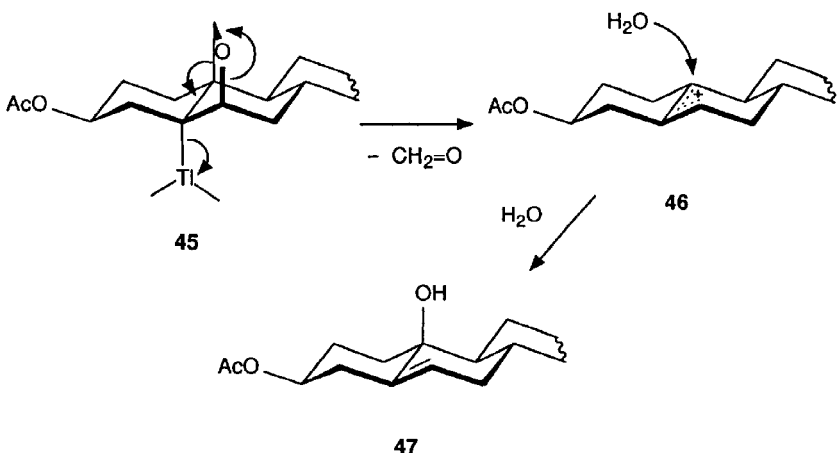


SCHEME 6

zation[12a]. The methyl ether **10** is less prone to the cyclization, producing only 57% of **19** on HOBr addition[12b]. Iodination of **9** carried out in the presence of Tl^+, Ag^+, or other reagents, always stopped at the stage of iodotetrahydrofuran **42** since its subsequent solvolysis is impaired for the same reason as in **36**. Copper(II)- and bismuth(III)-assisted iodinations are much slower, giving 32% and 45% conversion to **42**, respectively, after 24 h at room temperature. No reaction occurs with I_2/KI. In contrast to the smooth iodocyclization of **9** under a variety of conditions, the methyl ether **10** was inert towards I_2/Cu^{2+} and I_2/Bi^{3+}, while a very slow reaction was observed with I_2/Tl^+ (ca 10% conversion over 24 h). Silver(I)-mediated iodination of **10** was completed in 20 min which also contrasts with an instantaneous reaction of **9**.

Thallium(I)-mediated phenylselenenylation of **9** afforded the cyclic ether **43**, whereas the reaction run in the absence of Tl^+ gave the same compound contaminated by a small amount of by-products. Mercuration of **9** by means of $(CF_3CO_2)_2Hg$ or $Hg(NO_3)_2$ was also observed[36] and was the first example of an anti-Markovnikov mercuration[36]. Methyl ether **10** was inert towards both phenylselenenylation and mercuration.

In contrast to **6**, the 5,6-unsaturated alcohol **9** reacted with $Tl(NO_3)_3$ instantaneously, producing essentially a single compound in an 81% isolated yield, identified as the 10β-hydroxy-10-norsteroid **47** by spectroscopic and X-ray methods[20,37]. This unique degradation can be rationalized as follows (Schemes 6 and 7): the 5,6-double bond in **9** first undergoes an electrophilic attack by Tl^{3+}, followed by a stereoelectronically controlled anti-Markovnikov 5(O)^n-*endo*-*Trig* ring closure furnishing a diaxial organothallium intermediate **45**. Then, instead of the bridge-oxygen assisted solvolysis of the C–Tl bond, another competing pathway operates in which a molecule of formaldehyde is lost leaving allylic cation **46**. The latter is then trapped by the solvent to afford the *trans*-annulated product **47**. This fragmentation is obviously boosted by a stereoelectronic effect, since all the bonds involved (C(5)–Tl, C(6)–O, and C(10)–C(19)) are



SCHEME 7

perfectly aligned. Methyl ether **10** and the corresponding acetate were inert under the same conditions[37].

Unlike the hydroxy olefins **3** and **6**, both having a disubstituted double bond, the 5,6-unsaturated alcohol **9** (with a trisubstituted double bond) is inert towards palladation. Attempted transmetalation of the in situ generated organomercurial **44** with $PdCl_2$ in methanol under the CO atmosphere led to the starting olefinic alcohol **9** and partial decomposition.

2.2.4. Reactivity of 5,6-Unsaturated Derivatives **11 – 14**

With homologous alcohol **13** and its methyl ether **14** we have earlier observed reversion of the regioselectivity of HOBr addition in favor of Markovnikov rule[16] (Scheme 8). These reactions resulted in the formation of a diequatorial product **22** rather than the diaxial one. Accordingly, we have found that iodination, phenylselenenylation, and mercuration follow the same pattern and afford the corresponding diequatorial products **48** – **50**, respectively, in excellent yields. No solvolysis of iodo derivative **48** was observed[38] in the presence of Ag(I). In all these cases, competing axial cleavage of the corresponding reactive intermediates at C(6) was not observed. Hence, all the additions are entirely dominated by the electronic (Markovnikov) effects preferring thus the 5(O)^n-*exo-Trig* pathway[39]. Iodination of methyl ether **14** proceeded only in the presence of silver(I), while phenylselenenylation and mercuration did not occur. Palladation of both **13** and **14** as well as an attempted transmetalation of **50** were unsuccessful. Both **13** and **14** were inert to Tl^{3+}.

13, R = H
14, R = CH_3

22, E = Br
48, E = I
49, E = PhSe
50, E = CF_3CO_2Hg

SCHEME 8

Acyloxy and carbamoyloxy groups in position **19** are also capable of the reversion of regiochemistry of the HOBr addition to the 5,6-double bond (Scheme 2). Attempts at phenylselenenylation, mercuration, thalliation and palladation failed[43], but iodination boosted by Tl^+, Ag^+, or Ce^{4+} ions gave fairly good yields of the expected diequatorial

products, as the result of electronically favored 6(O)$^{\pi,n}$-*exo*-*Trig* cyclization[45]. In contrast, no reaction could be observed with I_2/KI, I_2/Cu^{2+}, or I_2/Bi^{3+}.

2.2.5. Discussion

The above results show that all the reagents we have tested share certain characteristic features, although differences in the propensity to react with certain olefins were encountered.

Regioselectivity. The behavior of the olefinic substrates is common for all the electrophilic reagents explored although some differences in reactivity have been observed. In view of these results, the conclusions we have previously inferred from the hypobromous acid addition[10] (see above) can be generalized for a wide range of electrophiles[20].

Iodination. The differences in reactivity of the iodination reagents towards olefinic alcohols are noteworthy. It appears that Ag^+ and Tl^+ salts are the best promoters for iodination[48]. Iodinations mediated by Ce^{4+} are slower (several minutes for **9**) and the mechanism is not clear. Reagents generated in situ by mixing iodine with Bi^{3+} or Cu^{2+} are even less reactive, particularly towards hydroxy olefins with trisubstituted double bonds (24 h or more). Finally, the I_2/KI mixture, often used for iodolactonizations, was found to be inert towards olefinic derivatives having a trisubstituted double bond.

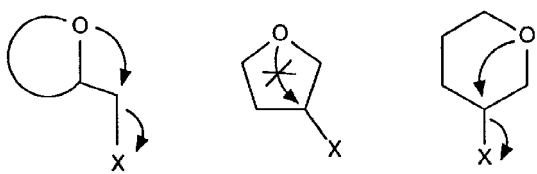
Even more dramatic differences in reactivity were found with methoxy olefins. Again, those having a disubstituted double bond (**4** and **7**) react with NBA, I_2 (in the presence of Ag^+ or Tl^+), and PhSeCl. On the other hand, methoxy olefins containing a trisubstituted double bond (**10** and **14**) are inert to all the reagents except for NBA and I_2/Ag^+. These differences could obviously find application in the selective functionalization of complex molecules, as the neighboring group and/or the reagent can be tailored in order to discriminate between the di- and trisubstituted double bond. It is pertinent to note that this discrimination can be achieved regardless of the mode of the neighboring group participation (*exo*-*Trig* or *endo*-*Trig*). Furthermore, these findings demonstrate the critical importance of the nucleophilic step for the electrophilic addition to occur[43]: the methoxy group is apparently less efficient than hydroxyl which results in th lowered capability of assisting the addition. The behavior of the olefinic esters[10] (e.g. **11**) and carbamates (e.g. **12**) further support this conclusion.

Phenylselenenylation. Phenylselenenylation carried out in the presence of thallium(I) salts parallels its known[26] silver(I)-mediated analogy, furnishing pure products. Whereas hydroxy olefins react readily irrespective of the degree of substitution on the double bond, methyl ethers, esters, and carbamates with a trisubstituted double bond are inert. This chemoselectivity is also of interest. According to the Clive mechanism[26d,41] of cyclofunctionalization of unsaturated substrates with PhSeCl, the reagent first adds across the double bond to give a β-chloroselenide. The latter intermediate than reacts with an internal nucleophile, presumably via an episeleniranium ion. However, cholesterol, an olefin with trisubstituted double bond, fails to react[26c,49] with

PhSeCl. In the case of its hydroxy congeners **9** and **13** the reaction is apparently facilitated by fast consumption of the intermediate in the final nucleophilic step, shifting thus the equilibrium to the product (**43** and **49**, respectively). Other internal nucleophiles (as in **10** – **12**, and **14**) are probably less prone to serve to serve in the same way.

Mercuration. Mercuration proceeds readily with olefinic alcohols containing disubstituted double bonds and is somewhat slowed down for trisubstituted double bonds. The same control of regioselectivity by neighboring groups has been observed as with other electrophiles. Noteworthy is the 5(O)^n-*endo-Trig* cyclization[50] of **6** and **9**.

Thalliation and Koenigs–Knorr-type solvolysis. Structural effects that control the silver(I)-mediated Koenigs–Knorr-type solvolysis are quite interesting. It appears that this stereospecific, anchimerically assisted reaction occurs readily with the intermediates arising from electrophilic *exo-Trig* ring closure, regardless of the size of the ring initially formed (**51** in Chart III). By contrast, the solvolysis is highly disfavored for the heterocycles formed in a 5-*endo-Trig* fashion, as the corresponding transition state would be too strained. The primary ring-closure product (**52**) is either stable enough to be isolated (X = I), or suffers a different consecutive reaction rather than a simple substitution (X = Tl). However, if a 6-membered heterocycle is being formed as the result of a 6-*endo-Trig* cyclization (**53**), the following solvolysis is possible, at least for



51 **52** **53**

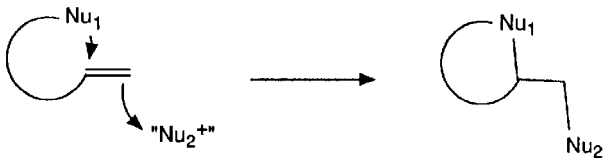
CHART III

the thallium species[28a]. Tetrahydropyran thus appears to be the smallest ring allowing the anchimerically assisted *endo*-type solvolysis. All these facts, as well as the high stereoselectivity of the reaction, clearly show that the anchimeric assistance by the ring heteroatom is of crucial importance for the stereospecific solvolysis to occur. In line with this concept is the readily occurring hydroxy cyclization of **3** on reaction with Tl^{3+} to give **32**, the thallium(III)-mediated fragmentation **9** → **47**, and the reluctance of **6** to react with Tl^{3+} under mild conditions. Moreover, in all the reactive halo ethers the mutual orientation of the leaving halogen and participating ether oxygen must be antiperiplanar. The compounds with gauche disposition (e.g. **48**) are inert. Halolactones are also stable towards Ag^+, presumably as a consequence of the decreased nucleophilicity of their ether oxygen and hence its ability to participate[10,17].

These findings clearly show that the pulling effect of the silver(I) ion and pushing capability of the antiperiplanar ether oxygen work together. This push-pull mechanism appears to be the driving force in Woodward–Prévost reactions, where it promotes the extrusion of iodine[51,52]. The transient ion (e.g. **31**) is highly oxophilic as it instantaneously reacts with oxygen nucleophiles. Attempts to introduce nitrogen and carbon nucleophiles were, thus far, unsuccessful.

Cyclooxypalladation. Finally, the cyclooxypalladation/carbonylation of **6** which gave **39** shows that 5(O)^n-*endo-Trig* cyclization is also possible for η^2-palladium complexes, together with the known[30] 5(O)^n-*exo-Trig* (as, e.g., in **3**) and 6(O)^n-*exo-Trig* processes[53]. However, the concomitant formation of the isomer **35** as a minor product indicates that this reaction course is less favored than its 5(O)^n-*exo-Trig* counterpart. Compounds with trisubstituted double bonds were inert under the same conditions[54].

Synthetic outcome. The synthetic value of these transformations is visualized in Scheme 9. The overall process starting from an unsaturated alcohol and involving *exo-Trig* cyclization can be formally considered as a one-pot electrophilic addition of a nucleophile ("Nu_2^+"), i.e. "RO^+" or "$^+CO_2R$". Other examples of similar methodology, known from the literature, involve "N_3^+" (ref.[47h]) and enol ethers[47i] as "nucleophiles", while the addition is controlled by neighboring hydroxy, amino, and amido groups. S_N2-Displacements of the auxiliary electrophile by, e.g., Ph_3P and stabilized C-nucleophiles have also been reported[47h,55].



SCHEME 9

2.2.6. Conclusions

The regio- and stereochemistry of electrophilic additions to highly discriminating cyclohexene systems can be controlled by neighboring groups. Stringent stereoelectronic effects (resulting normally in the formation of diaxial products) can be suppressed and the regiochemistry of the addition reversed by neighboring groups in those structures, in which the electronic (Markovnikov) effect favors this reaction course. Diequatorial adducts are then formed preferentially (Scheme 3). This appears to be a general behavior for a wide range of electrophiles[60].

Remarkable differences have been observed in the reactivity of iodination reagents generated in different ways (I_2 + Ag^+, Tl^+, Ce^{4+}, Cu^{2+}, Bi^{3+}, or KI). Since most of these reagents can cleanly differentiate between di- and trisubstituted double bonds (depend-

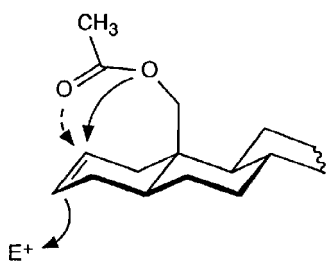
ing on the nature of the participating neighboring group), this cyclofunctionalization methodology could serve as a useful tool for the construction of complex molecules. Similar differentiation has been found for phenylselenenylation, mercuration, and cyclooxypalladation/carbonylation reactions.

Silver(I)-mediated iodocyclization is followed by solvolysis when the departing halogen is exocyclic to the newly formed heterocycle and antiperiplanar to the carbon–heteroatom bond (Chart II). The same effects operate in the thallium(III)-mediated hydroxycyclization. When the ring is to be formed in an *endo-Trig* fashion, the reaction either does not occur, or leads to a novel stereocontrolled fragmentation (Schemes 6 and 7). We believe that our observations on the scope of this tandem transformation could serve as a guide for planning syntheses of complex molecules. In particular, the limits we have found for the thallium(III)-mediated hydroxy cyclization can make this capricious methodology more reliable. Moreover, we are confident that the one-carbon degradation (Scheme 7) will be of general use for a facile synthesis of 19-norsteroids of medicinal importance (see Chapter 6).

An improved procedure for cyclooxypalladation/carbonylation has been developed.

2.3. *Participation by Bidentate Neighboring Groups: Preferred Nucleophilic Centers*

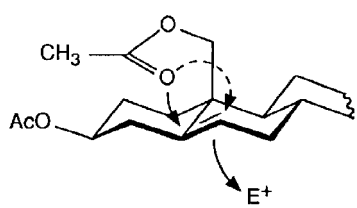
Summarized above was our investigation of participation of mono- and bidentate oxygen groups in electrophilic additions. If the participating group is an acetate, there are, a priori, two different oxygen atoms capable of interaction with the electron-deficient center. For instance, addition to 19-acetoxy-5α-cholest-2-ene (**5**) proceeds with 5(O)^{n}-*exo-Trig* participation of the ether oxygen (Chart IV), while the competing 7(O)$^{\pi,n}$-*exo-Trig* reaction involving carbonyl oxygen is disfavored[10,13,17]. On the other



5

5(O)^{n}-exo-Trig (79%)

7(O)$^{\pi,n}$-exo-Trig (9%)



11

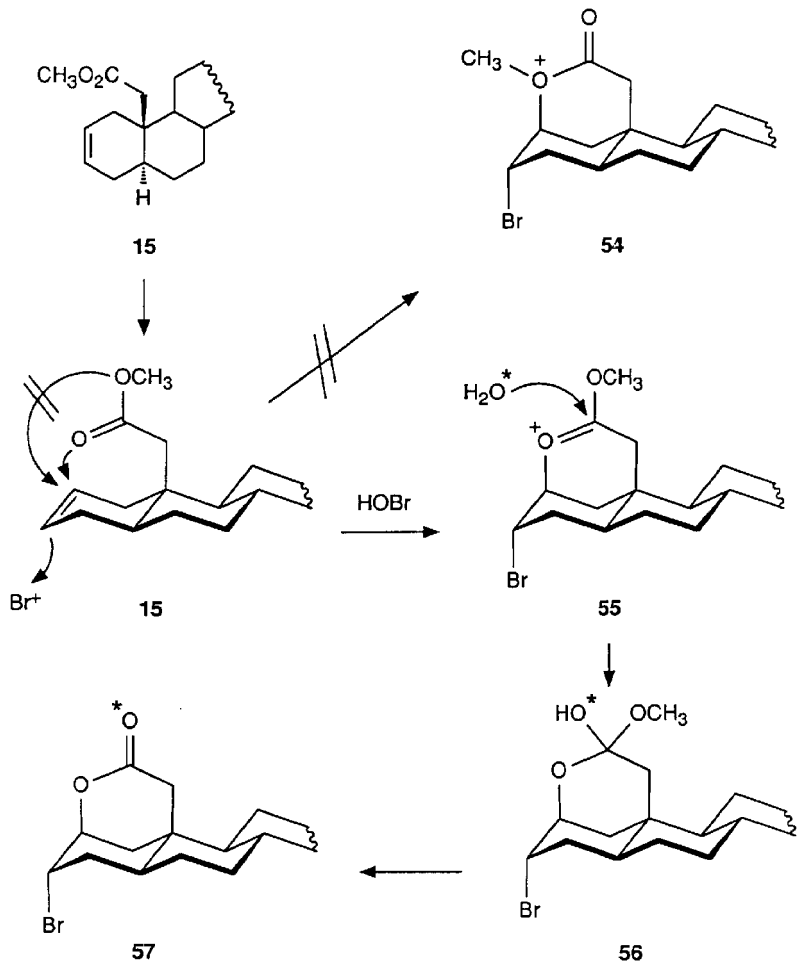
6(O)$^{\pi,n}$-exo-Trig (67%)

7(O)$^{\pi,n}$-endo-Trig (3%)

5(O)^{n}-endo-Trig (0%)

CHART IV

hand, a transposition of the double bond as in 19-acetoxycholest-5-ene (**11**) alters the mechanism in that the participation by the carbonyl is favored over the $5(O)^n$ process[10,13,17]. By contrast, $5(O)^n$-participation is the only reaction with ethers **4** and **7**. The same ring closure is also a major pathway for methyl ether **10** (Scheme 2). In all these cases the reaction course depends on both the participation propensity of the oxygens (such as the electron density, polarizability, and stereoelectronic factors), the ring size in the intermediate (5-, 6-, or 7-membered rings) and the mode of ring closure (*exo-Trig* or *endo-Trig*). In order to eliminate the latter two factors we have synthesized ester **15** as a model compound that would allow to directly study the difference in reactivity of the two oxygens of the ester group (Scheme 10).



SCHEME 10

The unsaturated ester **15** was reacted with HOBr (generated in situ from NBA and $HClO_4$) in dioxane containing water enriched in ^{18}O by 25% and afforded the corresponding lactone (Scheme 10). The lactonization could proceed, a priori, in three pathways: (a) carbonyl participation, (b) ether oxygen participation, and (c) reaction with water as external nucleophile followed by lactonization. Spectral analysis of the product (MS, IR, and ^{13}C NMR) unequivocally demonstrated that only path (a) was operating, giving solely the carbonyl-labelled lactone **57** via intermediates **55** and **56** (ref.[40]).

The observed preferential reactivity of the carbonyl oxygen can be in part ascribed to a greater polarizability of the ester π-orbitals when compared with the p_z orbital of the ether oxygen. This polarization of ester group that increases the net charge at the carbonyl oxygen[63] favors the interaction of the latter with the carbon electron-deficient center. It should be noted that stereoelectronic factors such as the distance and angle of approach[10,12] of the oxygen orbitals are favorable for both types of participation due to relative flexibility of the 6-membered ring in the corresponding intermediates.

2.4. *Stereocontrol by Neighboring Groups*

It has been shown on numerous examples that steroid skeleton has a strong preference for the attack by reagents from the bottom side[7]. It was therefore of interest to explore whether or not a suitably located functional group could reverse this inherent bias. Model 5-cholestenes with an acetoxy group at position 3α or 7α were therefore examined[64,65].

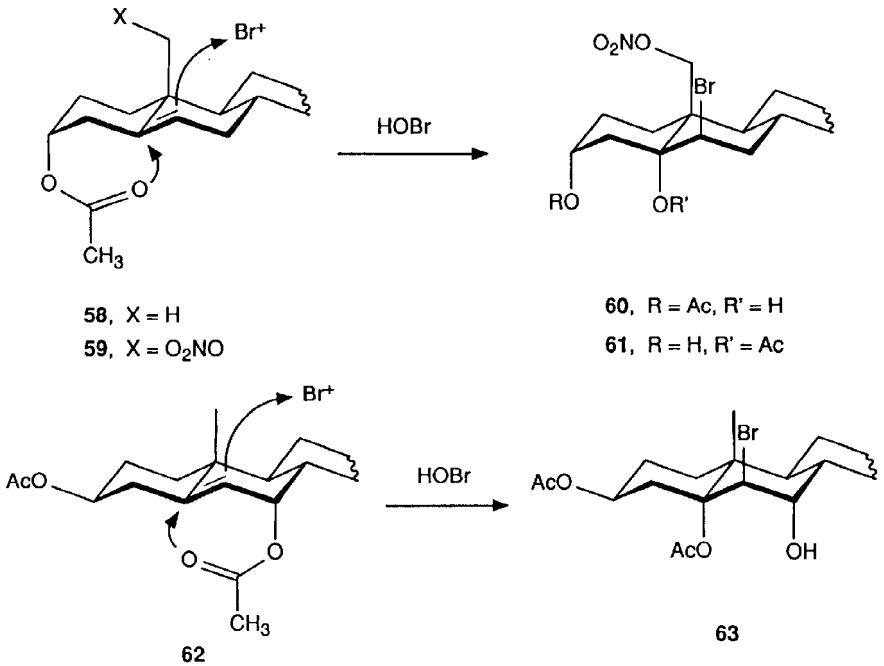
The reaction of 19-unsubstituted 3α-acetoxy derivative **58** with HOBr gave a complex mixture of products which could not be isolated for their instability. We therefore turned our attention to the 19-nitrate **59** as equivalent of the 19-unsubstituted derivative since we have shown earlier that the 19-nitrate group does not participate in the course of addition to the 5,6-double bond[17]. When treated with HOBr, the nitrate **59** afforded two major products (Scheme 11): the diaxial bromohydrin **61** and the 5α,6α-epoxide. The latter compound is presumably arising from the less stable bromohydrin **60** (ref.[65]).

Similar results have been obtained with 3α-acetoxy–cholest-4-ene (ref.[64]) and with 7α-acetoxy derivative **62** where diaxial bromohydrin **63** was found to be the only product[65].

The products arising from olefins **59** and **62** are apparently formed from the corresponding β-bromonium ions. This clearly indicates that the reversal of the "ordinary" stereochemistry must be due to the presence of the neighboring groups.

Although the approach from the top face is assumed to be more hindered (by the angular methyl), it seems to be more effective with olefins **59** and **62**. One can, of course, argue that introduction of a substituent on the originally more accessible α-face of the skeleton could alter the relative steric hindrance, which itself might result in reversal of the overall stereochemistry. However, this is certainly not the case with the

5-unsaturated 7α-acetoxy derivative **62**, since **62** is known to be oxidized with peroxy acids preferentially from the α-side[66].



SCHEME 11

Reversal of the stereochemistry of the addition can be rationalized as follows (Chart V and Scheme 12). Better accessibility from the bottom face of the double bond leads to a higher concentration of the corresponding intermediate in the first, reversible step[67]. If the quenching of this intermediate is fast enough ($k_1 \geq k_2$) the reaction follows the usual way dominated by α-attack[68] (path **64**). However, if the less populated diastereoisomeric intermediate is consumed faster ($k_1 < k_2$, or, better, $k_1 << k_2$) the reaction

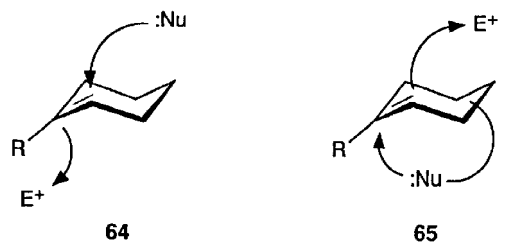
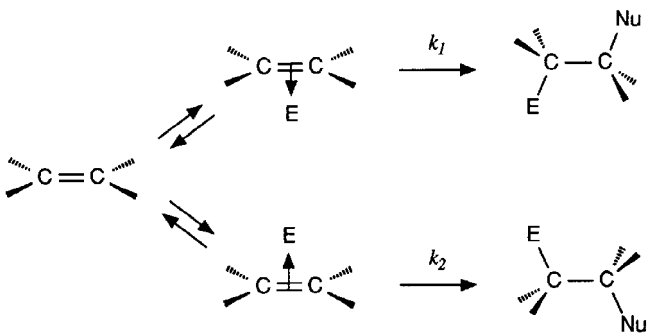


CHART V

can switch to the pathway **65**. Note that in **65** the second step is boosted by consonant electronic and stereoelectronic effects. Hence, the second step in **65** should be faster than that in **64** where these effects are dissonant. However, $k_1 << k_2$ only when the second step is intramolecular[69]. Therefore, without intervention of a neighboring group, the reaction usually follows path **64**. However, an extremely bulky external nucleophile can also alter the reaction stereochemistry in favor of **65** even in the absence of the neighboring group[70]. This can be rationalized by slowing down the nucleophilic step in path **64** ($k_1 < k_2$); when the electrophile is less sterically demanding than the nucleophile, path **65** can become kinetically preferred.



SCHEME 12

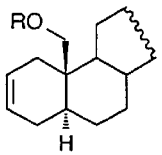
Our observations lead to the conclusion that the judicious introduction of a neighboring group can control the stereochemical course of electrophilic additions not only to aliphatic compounds[4] but also to highly biased and fastidious cyclohexene systems. Careful evaluation of the relative importance of the factors governing the addition can lead to a reliable prediction of the favored and disfavored pathway. Such an analysis may be useful for driving the addition in the desired direction and for designing syntheses of complex polysubstituted molecules[60].

2.5. *Reactivity of Various Neighboring Groups*

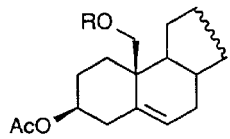
Neighboring group participation is an established tool for controlling regio- and stereoselectivity of electrophilic additions and for masking a double bond as shown in the literature and above. On the other hand, it sometimes may become desirable to suppress the participation[71] or, in case of competition of several neighboring groups, to favor one at the expense of the other group[65,66]. We reasoned that it would be valuable to assess the ability of various neighboring group (with different distribution of electron density and different steric requirements) to participate in electrophilic additions.

We have shown that bidentate groups were capable of $5(O)^n$, $6(O)^n$, $5(O)^{\pi,n}$, and $6(O)^{\pi,n}$ participation, while $7(O)^{\pi,n}$ process was observed to operate only to a minor

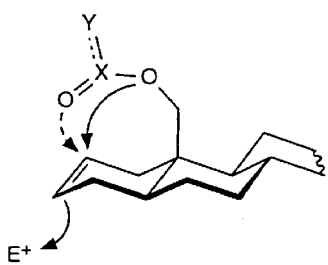
extent and 4(O) participation was not recorded with our systems[10,20]. For testing the participation propensity of various groups we have prepared representative model compounds having ether, ester, carbamate, phosphate, sulfonate, or nitrate groups and with bishomoallylic double bond (**5**, **66 – 72**) for which reactivity pattern **A** can be expected (Chart VI) or those with homoallylic arrangement (**11**, **12**, **73** – **78**) where type **B** reactivity was assumed.



5, R = CH_3CO
66, R = H_2NCO
67, R = PhCO
68, R = p-MeO-C_6H_4CO
69, R = $(EtO)_2P(O)$
70, R = CF_3CO
71, R = CH_3SO_2
72, R = O_2N

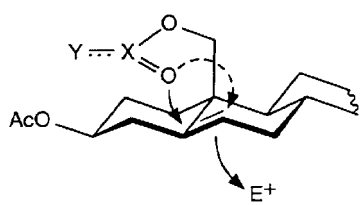


11, R = CH_3CO
12, R = H_2NCO
73, R = PhCO
74, R = p-MeO-C_6H_4CO
75, R = $(EtO)_2P(O)$
76, R = CF_3CO
77, R = CH_3SO_2
78, R = O_2N



A

5(O)^{n}-exo-Trig
7(O)$^{\pi,n}$-exo-Trig



B

6(O)$^{\pi,n}$-exo-Trig
7(O)$^{\pi,n}$-endo-Trig
5(O)^{n}-endo-Trig

CHART VI

The model compounds were successively treated with HOBr in aqueous dioxane and the product analysis was used for the assessment[17]. Isotope labelling ($H_2{}^{18}O$) was used to differentiate 7(O)$^{\pi,n}$ participation from external attack[10,18]. Product analysis shows dramatic differences between the functional groups. For carbamate, esters, and phos-

phate, the nucleophilic participation is dominating with both representative models **A** and **B**. By contrast, nitrate and sulfonate group still display some tendency to $5(O)^n$ ring closure, whereas $(O)^{\pi,n}$ participation is largely suppressed. Finally, trifluoroacetate is an inert group and the reaction is dominated by external attack[10,17].

The different reactivity of the neighboring groups can be qualitatively correlated with the effective nucleophilicity of the participating carbonyl or ether oxygen. Thus, for instance, the corresponding 2α,3α-bromonium ion derived from the acetate **5** is preferentially cleaved by the ether oxygen of the acetoxy group, i.e. by a $5(O)^n$-*exo-Trig* process (path a). The corresponding bromohydrin arising from **5** mainly by $7(O)^{\pi,n}$-*exo-Trig* participation (path b) is formed in a yield as low as 9%. On the other hand, benzoyloxy (**67**, **73**) and *p*-methoxybenzoyloxy (**68**, **74**) groups display a relative decrease of the $(O)^n$ nucleophilicity, while the reactivity of the carbonyl oxygen dominates, particularly with **68** and **74**. In contrast, the CF_3CO_2 group in **70** and **76** does not participate at all by either oxygen which can be attributed to the electron-withdrawing effect by fluorine atoms. Hence, the latter group can be used for the protection from nucleophilic participation. Similarly, nitrate (**72**, **78**) will protect from $(O)^{\pi,n}$ ring closure.

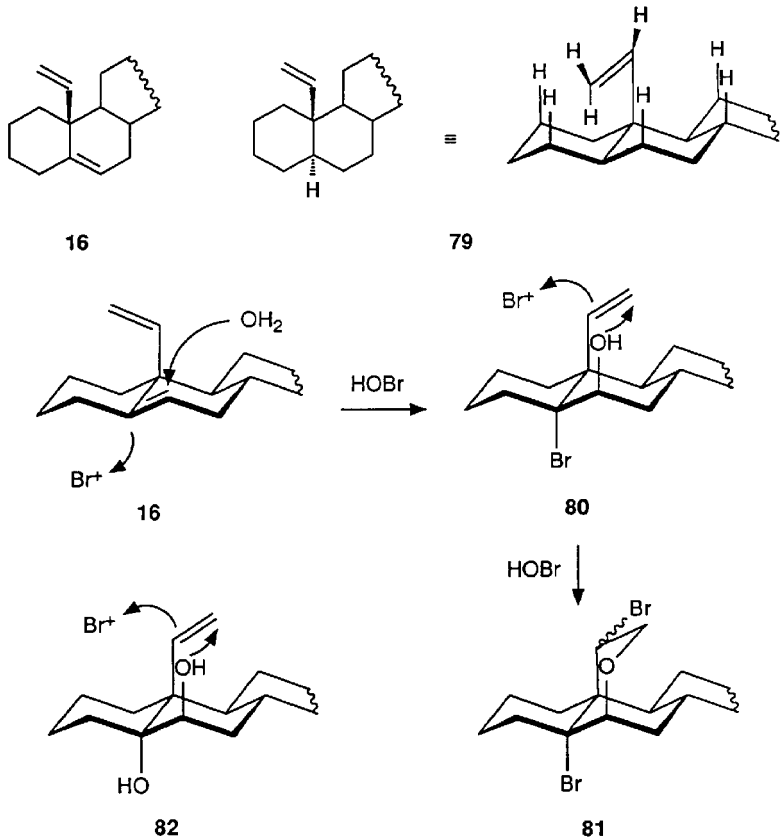
2.6. *Reactivity of 10*β*-Vinyl Steroids Towards Electrophilic Reagents*

Due to the donating properties of the bonding π-orbital, a suitably oriented carbon–carbon double bond can serve as a participating group in electrophilic addition to another double bond forming a new C–C bond[72]. Thus, for instance, the vinylic double bond in diene **16** might be considered as a $(C)^\pi$ analogue of some of the above described neighboring group. However, in this case the C–C bond formation would be disfavored due to the orthogonal arrangements of the two π-systems. Nevertheless, diene **16** represents an interesting structure: while the 5,6-double bond, as well as other skeletal double bonds, readily reacts with wide range of electrophiles[73,74], the vinyl group alone was known to be inert, e.g., towards peroxy acids[75]. Later, we have found that vinyl derivative **79** was inert to other strongly electrophilic reagents, such as Br_2, HOBr, $Hg(NO_3)_2$, and I_2/Ag^+. It was thus of interest to explore the reactivity of the diene **16** and its congeners[73,74] (Scheme 13).

On treatment with two equivalents of HOBr, diene **16** afforded the tetrahydropyran derivative **81** (as an 83 : 17 mixture of two epimers)[73]. In view of the known behavior of cholesteryl acetate (**1**) and the monoolefin **79**, the following mechanism can be suggested to rationalize this outcome: 5,6-double bond first adds HOBr to give diaxial bromohydrin **80** which then reacts with the second equivalent of HOBr. Diol **82**, prepared from the 5α, 6α-epoxide, reacted similarly to give the corresponding bromotetrahydropyran (again as a mixture of epimers).

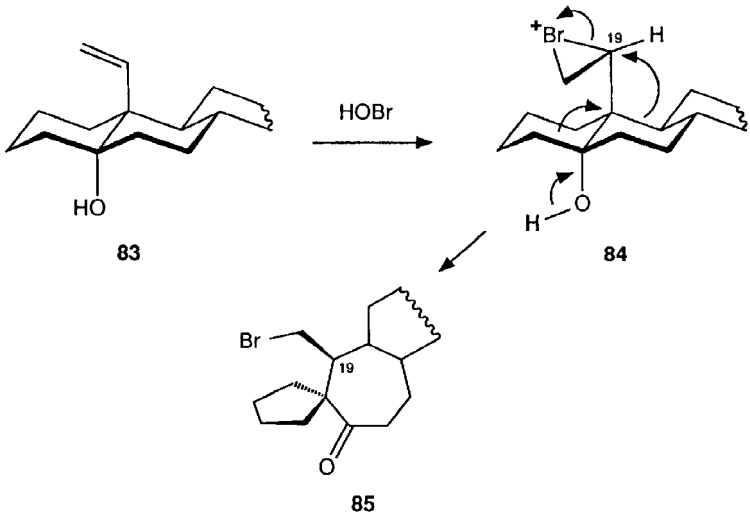
Surprisingly, when diene **16** was treated with only one equivalent of HOBr, the bromohydrin **80** could not be isolated or detected[73]. Instead, the reaction mixture yielded unreacted starting material (45%) and tetrahydropyran **81** (ca 40%). This behavior

clearly shows that the presence of a neighboring group (OH) facilitates addition to the vinylic bond. In the absence of such a substituent (as in **79**), 10β-vinyl is totally unreactive. This points to the reversibility of the first step of electrophilic additions (which has recently been shown to be a general phenomenon[67]). Since we have seen the 10β-vinyl reacting with an electrophile (in **16**), this double bond must be capable of interacting with the electrophile. Further reactivity of the complex thus formed will depend on the nucleophile counterpart. If the access of the nucleophile is impaired as in **79** (due to the axial hydrogen atoms), the complex dissociates back to the starting materials. However, the suitably placed neighboring group can trap this intermediate and drive the addition into completion (**80** or **82**)[74].

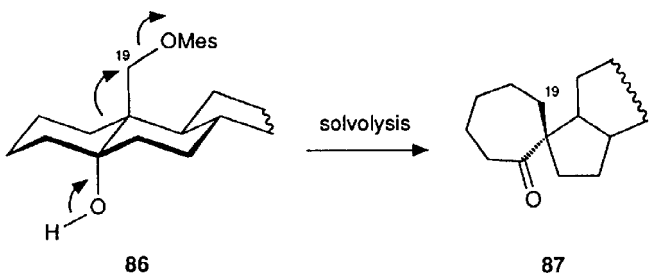


SCHEME 13

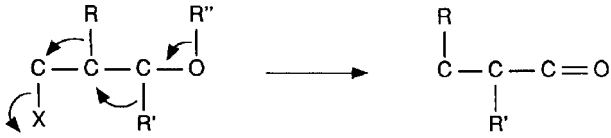
It is noteworthy that the required participation can also be exerted by a suitably oriented and reactive C–C single bond as documented by a unique Wagner–Meerwein rearrangement in 10β-vinyl-5α-hydroxy derivative **83** giving spirocyclic ketone[74] **85** (Scheme 14). We have later found this stereoelectronically controlled rearrangement to be a general reaction pattern for 19-electrondeficient species[76], as the solvolysis of mesylate **86** resulted in the formation of the analogous spirocycle **87** (Scheme 15). The latter reaction can be viewed as a double pinacol rearrangement[76] (Scheme 16). In similar conformationally locked systems it might find synthetic applications in the stereospecific construction of spirocycles from easily accessible decalins.



SCHEME 14



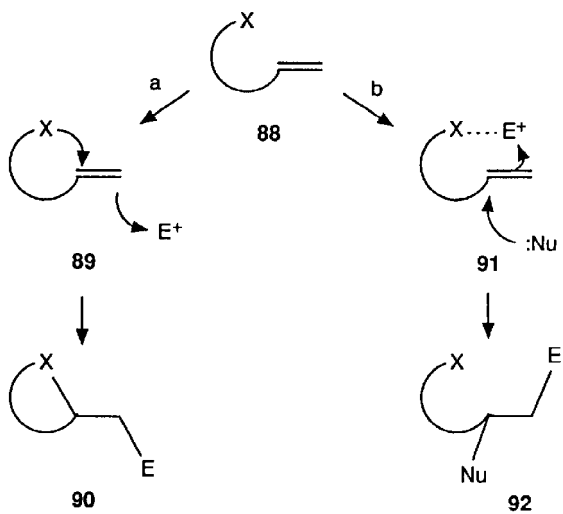
SCHEME 15



SCHEME 16

2.7. *Steric Control of Epoxidation by Carbamate and Amide Groups*

Neighboring groups can control addition to a double bond in two conceptually different ways (Scheme 17). Described thus far was the mechanism according to which the electrophile was first attacking the double bond (**88** → **89**) and the internal nucleophile facilitated its fast consumption (**89** → **90**). Since the diastereofacial isomer of **89** could only react with an external nucleophile (i.e. in a slower process), facial diastereoselection is thus achieved and can be characterized as an "indirect" way of stereocontrol[1].

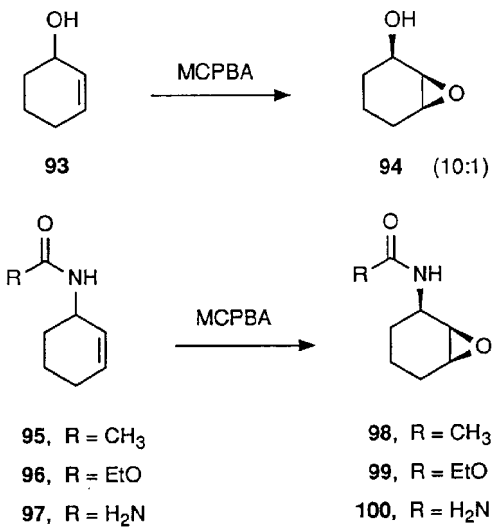


SCHEME 17

Another possible mechanism would involve a primary coordination of the electrophile to the nucleophilic neighboring group (**88** → **91**) followed by intramolecular *syn* delivery to the double bond and stabilizing of the intermediate (**91** → **92**). In contrast to the former mechanism, the latter can be considered as a "direct" stereocontrol[1].

While halolactonization and other reactions described above are typical examples for the former pathway (a), the latter mechanism (b) can be exemplified by epoxidation controlled by hydroxyl[1,77] and other groups[1].

The hydroxyl-directed epoxidation of allylic alcohols (e.g. of **93**) has evolved into a reliable and highly stereoselective method for the construction of vicinal chiral centers[77,78] (Scheme 18). A similar *syn*-directing effect has been found for amido (**95**), urethano (**96**), and ureido (**97**) olefins and for unsaturated acetals, sulfones, and sulfoxides both in aliphatic and alicyclic series[79]. In contrast, epoxidation of esters[7,77,81] and carbonates[14,82] of allylic alcohols proceeds either nonstereoselectively or produces predominantly *trans*-epoxides, while β,γ-unsaturated carboxylic acids afford mixtures of both *cis*- and *trans*-products[83].



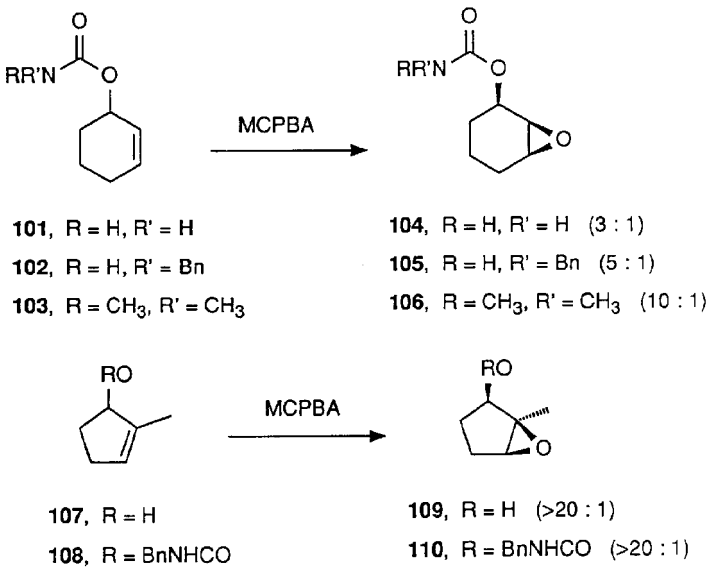
SCHEME 18

We have found that carbamates **101** – **103**, and **108** derived from allylic alcohols **93** and **107** are predominantly oxidized with *m*-chloroperoxybenzoic acid (MCPBA) in noncoordinating solvents (CH_2Cl_2 or $CHCl_3$) from the *syn*-side[80] (Scheme 19), in analogy with the parent epoxides. It turned out that this effect is strong enough to override the steric bias of the steroid skeleton, whose α-side is usually less hindered[80] and to drive the epoxidation to occur predominantly from the β-face (Scheme 20).

This steric control appears not to be confined to allylic carbamates, but can be observed with some homoallylic derivatives (Scheme 21). Thus 19-carbamoyloxy groups in **119** – **121** and other model compounds also steer the epoxidation from the β-side. Some of the carbamates (**119** and **120**) furnished even a slightly higher *cis*/*trans* ratio

than does the parent alcohol[80]. By contrast, benzoate **118** affords mostly the 5α,6α-diastereoisomer[80].

These findings show that the carbamate group can serve as an alternative to the hydroxyl in steric control of epoxidation. This behavior raised the question as to the



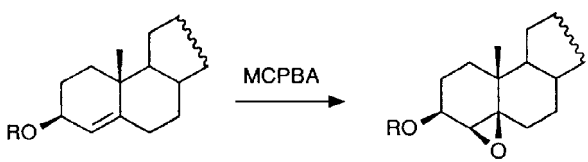
101, R = H, R' = H
102, R = H, R' = Bn
103, R = CH_3, R' = CH_3

104, R = H, R' = H (3 : 1)
105, R = H, R' = Bn (5 : 1)
106, R = CH_3, R' = CH_3 (10 : 1)

107, R = H
108, R = BnNHCO

109, R = H (>20 : 1)
110, R = BnNHCO (>20 : 1)

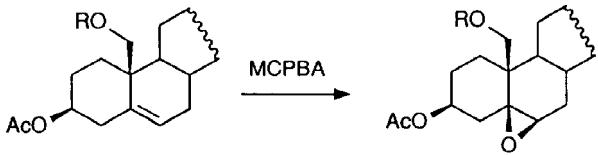
SCHEME 19



111, R = H
112, R = BnNHCO
113, R = Me_2NCO

114, R = H
115, R = BnNHCO (>20 : 1)
116, R = Me_2NCO (>20 : 1)

SCHEME 20



117, R = H
118, R = PhCO
119, R = H_2NCO
120, R = BnNHCO
121, R = Me_2NCO

122, R = H (5 : 1)
123, R = PhCO (1 : 10)
124, R = H_2NCO (6 : 1)
125, R = BnNHCO (>10 : 1)
126, R = Me_2NCO (1 : 1)

SCHEME 21

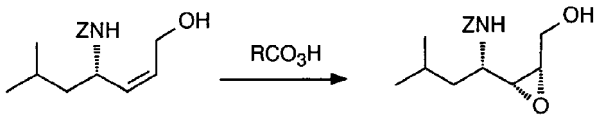
mechanism. The steering effect of hydroxy group was attributed by Henbest to the hydrogen bonding between OH and the reagent[77] (**127** in Chart VII) employing O(2) of peroxy acid as the acceptor. Since then this mechanism has been widely accepted[1,78,79]. Later, Whitham[81] suggested alternative OH bonding to the carbonyl oxygen, i.e. to O(3). Finally, detailed analysis of stereoelectronic effects led Sharpless[84] to the formulation of a mechanism, according to which the allylic OH is coordinated to O(1), whose remaining lone pair becomes thus favorably aligned with the π-system of the double bond (**128**).

Roush[85] has rationalized the *syn*-epoxidation of allylic amides[85,86] by analogous NH bonding (**129**). In light of the Sharpless mechanism **128** we feel that the Roush scheme can be modified as indicated in **130**. Our carbamates, however, represent a rather different class of allylic compounds. Although NH bonding to the reagent can still be assumed for N-unsubstituted (**101** and **119**) and N-benzyl (**102**, **108**, **112**, and **120**) derivatives, the (*N*,*N*-dimethylcarbamoyl)oxy group in **103**, **113**, and **121** cannot offer any OH or NH. In spite of that the latter group is also capable of controlling the epoxidation in *syn*-fashion. To account for this behavior an alternative mechanism can be proposed. We can speculate on the hydrogen bonding in a reversed way, i.e. from the reagent (MCPBA) to the carbamate group of the substrate. In view of its ambident character, both the ether (**131**) and the carbonyl oxygen (**132**) of the carbamoyloxy group can be considered as the acceptor for the hydrogen bonding. Neither the former nor the latter way of steering is unprecedented (with other groups). Thus, examples have been reported on epoxidation directed by alkoxy groups[19,87] and ketone carbonyl[88]. Furthermore, cooperative effect[89] of a carbonyl group was postulated by Kogen and Nishi[90] to account for the high diastereoselectivity of epoxidation

TABLE I
THP derivatives of prostaglandin $F_{2\alpha}$ *VIIIa,b – XIa,b*

Product	Starting material/ phosphonium salt	Yield, % in procedure A/B	Infrared spectra, cm^{-1}	^1H NMR spectra				
				CH_3/OCH_3	H-13, H-14	H-5, H-6	aromatic H	hetero-aromatic H
VIIIa	*IIIa*	75	3 610 w, 3 520 m, 3 020 s,	0.87 t	5.37 m,	6.28 d,		6.25 d,
	IV	88	2 950 s, 2 860 s, 1 740	3.87 s	5.54 m	6.44 m		7.12 d
VIIIb	*IIIb*	91	3 600 w, 3 500 w, 3 010 s,		5.53 m,	6.22 d,	6.78 m, 7.17 m,	6.20 d ,
	IV	93	2 950 s, 2 870 s, 1 720 s	3.84 s	5.71 m	6.46 m	6.91 m, 2 H	7.12 d
IXa	*IIIa*	47	3 600w, 3 420 m, 3 020 s,	0.88 t	5.36 m,	6.20 –		6.32 d,
	V	72	2 940 s, 2 880 s, 1 725 s	3.82 s	5.38 m	– 6.51 m		7.20 d
IXb	*IIIb*	51	3 600 w, 3 480 w, 3 020 s,		5.42 –	6.18 –	6.75 m, 7.16 m,	6.35 d,
	V	75	2 960 s, 2 880 s, 1 720 s	3.80 s	– 5.75 m	– 6.42 m	6.89 m, 2 H	7.22 d
Xa	*IIIa*	75	3 600 w, 3 400 m, 3 010 s,	0.88 t	5.33 m,	6.21 –		6.83 d,
	VI	79	2 940 s, 2 870 s, 1 710 s	3.88 s	5.52 m	– 6.51 m		7.62 d
Xb	*IIIb*	82	3 600 w, 3 400 m, 3 010 s,		5.53 m,	6.28 m,	6.79 m, 7.18 m,	6.76 d,
	VI	89	2 940 s, 2 870 s, 1 710 s	3.85 s	5.75 m	6.50 d	6.90 m, 2 H	7.64 d
XIa	*IIIa*	56	3 600 w, 3 380 w, 3 010 s,	0.88 t	5.38 –	5.98 m,		7.22 d,
	VII	84	2 940 s, 2 870 s, 1 710 s		– 5.68 m	6.41 d		7.59 d
XIb	*IIIb*	79	3 600 w, 3 500 w, 3 010 s		5.30 –	5.98 m,	6.73 m, 7.20 m,	7.08 d,
	VII	89	2 950 s, 2 870 s, 1 710 s		– 5.63 m	6.33 m	6.90 m, 2 H	7.38 d

of the unsaturated hydroxy carbamate **133** (Scheme 22). It was therefore desirable to bring further experimental material in order to address the question as to which of the two oxygen centers in the carbamoyloxy group acts as the proton acceptor and steers the approach of peroxy acid. Coordination to nitrogen would be unlikely; for detailed rationalization, see our original paper[80].

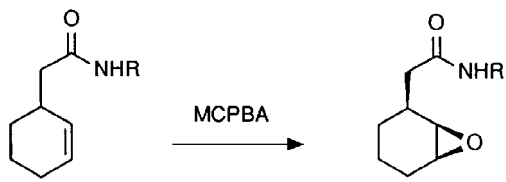


133 **134**

Z = $PhCH_2NCO$

SCHEME 22

Amide **135** that can be considered as the "carba" analogue for the carbamate **102** was expected to provide the desired evidence[80]. If the carbonyl oxygen in **102** were responsible for the steering effect (**132**), amide **135** should also afford the *cis*-epoxide as the major product. On the other hand, if the steering in **102** were due to the ether oxygen (**131**), we could anticipate predominant formation of a *trans*-epoxide in this case or a nonstereoselective reaction. On treatment with MCPBA the amide **135** furnished the *cis*-epoxide **137** (Scheme 23) as the major product[80] (12 : 1). When this work was in progress a paper by Mohamadi[91] appeared, dealing with the stereochemistry of the closely related isopropyl amide **136**. In consonance with our findings, the *syn*-epoxidation was also observed as the dominating pathway (> 20 : 1).



135, R = Bn
136, R = Pr^i

137, R = Bn
138, R = Pr^i

SCHEME 23

These observations strongly support the mechanism **132** according to which the carbonyl oxygen of the carbamoyloxy and amido group serves as the acceptor for bonding the molecule of peroxy acid and is thus responsible for the pronounced *syn*-steering. It

appears that the increased coordination capability of the carbonyl oxygen in carbamates and amides (compared to esters) stems from the strong donation by nitrogen, as reflected in general increase of the nucleophilicity of carbamate vs ester group in other reactions, as cited[10] in Chapter 5. There are two possible acceptor sites at the carbonyl oxygen for hydrogen bonding, namely π-electrons and 2*p* orbital. In view of the fact that, e.g., IR spectra of hydroxy carbonyl compounds indicate higher basicity of the 2*p* orbital[92], we believe that the latter is responsible for coordination of the molecule of peroxy acid.

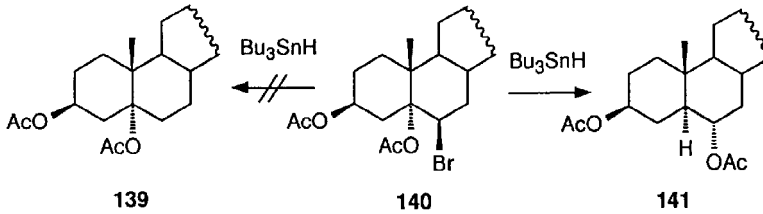
Additional support for operating of the carbonyl steering of the peroxy acid approach can be found by analyzing the literature data; for details, see the original paper[80].

Another mechanism can involve Coulombic interaction of the electrophile with the nucleophilic allylic center, where the negative electrostatic potential in the most reactive conformation[87] is created by the π-system of the double bond and the carbonyl oxygen.

Regardless of the detailed mechanism of the above epoxidation, carbamoyloxy epoxides in general are useful intermediates for organic synthesis, both in aliphatic and alicyclic series[85,90,93]. In principle, they can be prepared in a reversed way, i.e. by epoxidation of allylic or homoallylic alcohols followed by derivatization with the corresponding isocyanates. Although this method seems reasonably reliable and has found numerous applications to the synthesis of natural products, there are examples where it fails, as some epoxy alcohols do not cleanly react with isocyanates (particularly **114**). Furthermore, preparation of (*N*,*N*-dimethylcarbamoyl)oxy epoxides from the corresponding epoxy alcohols would require drastic conditions[80,94] (Me_2NCOCl + BuLi) that are not compatible with this sensitive functionality. Our stereoselective epoxidation of carbamates thus seems to be a useful alternative to the classical approach. Since the carbamate groups have been frequently employed to control opening of the oxirane ring[1,93] this stereocontrolled epoxidation could also find synthetic application. On the top of it, the carbonyl-directed epoxidation of amides of γ,δ-unsaturated carboxylic acids seems particularly promising.

2.8. *Stereospecific Radical Rearrangement of Esters of Certain Vicinal Bromohydrins*

Reductive removal of halogens by means of Bu_3SnH is an established, mild, and reliable method which tolerates various functional groups in the substrate molecule[97]. We have used this radical reduction in a number of instances both for the structure elucidation and synthetic purposes and we have always obtained good yields of the expected products[73,74,98]. During the structure elucidation of one of the products of HOBr addition[65] we have observed a stereospecific rearrangement of the bromohydrin acetate **140** which afforded **141**, rather then giving the expected product **139** (Scheme 24).



SCHEME 24

This type of rearrangement is not unprecedented in the literature[99]. However, only little was known of its structural requirements and more information was therefore desirable[100]. Hence, we undertook a brief study of a series of several related bromohydrins and their derivatives (for details, see the original paper)[101]. From their behavior we concluded that the rearrangement has some specific requirements: (i) Only esters of vicinal bromohydrins can rearrange. (ii) The mutual orientation of AcO and Br must be antiperiplanar (a reactive conformation), e.g. diaxial in cyclohexene ring. (iii) The ester group can only migrate from tertiary to secondary carbon. The driving force for the rearrangement to occur thus appears to comprise two factors: (1) The stereoelectronic effect (alignment of Br and AcO) and (2) the stabilization of the secondary radical by migration of the ester group to yield more stable tertiary radical, which is subsequently quenched to give the product.

The bidentate character of the migrating group raised the question of the detailed mechanism (Chart VIII), i.e. whether the rearrangement proceeds as an unprecedented 1,2-shift involving the ether oxygen (**142**) or as a 2,3-shift[99,102] with intervention of the carbonyl oxygen (**143**). The actual role of the two potential pathways was elucidated by a labelling experiment: the ^{18}O-labelled acetoxy bromide **144** was reduced with Bu_3SnH and the resulting product analyzed by ^{13}C NMR spectroscopy[103]. The analysis

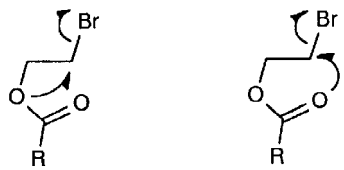
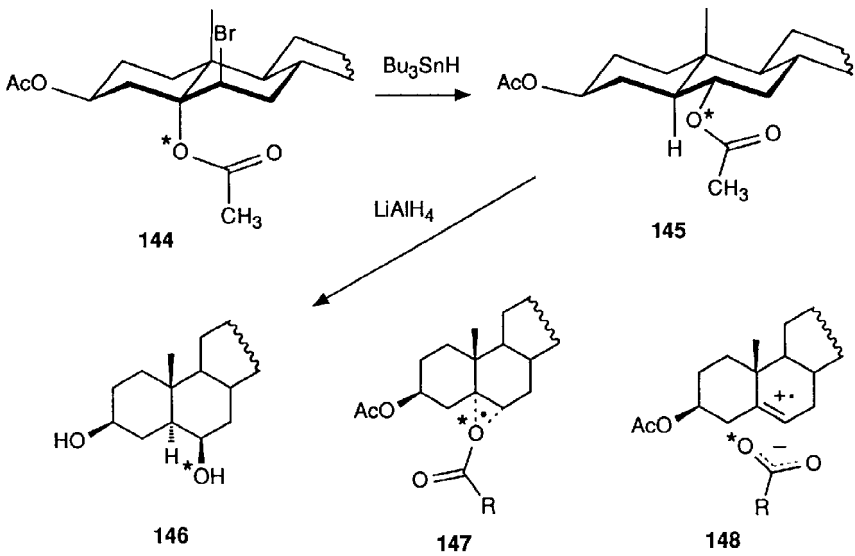


CHART VIII

showed that the label remained in the ether oxygen (Scheme 25). This qualitative information was supplemented by quantitative determination of the content of ^{18}O by mass spectrometry using the alcohol **146** (obtained from the $LiAlH_4$ reduction of acetate **145**), which revealed that at least 77% of the label remained in the ether oxygen of the migrating acetoxy group. This was in conflict with the observation of Beckwith[102] who found, though with a different (aliphatic) substrate, a 2,3-shift of an ester group. We have attributed this difference to the rigid character of our model compound and to a strict *anti*-disposition of both the leaving Br and the migrating AcO group[101].



SCHEME 25

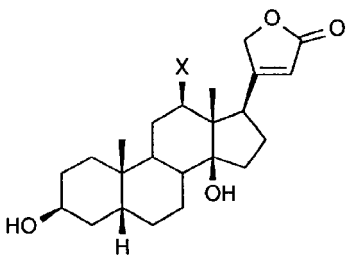
Our results, summarized in a preliminary communication[101], were soon challenged by Beckwith[104], who had synthesized the ^{18}O-labelled butyrate analogous to our acetate **144** and submitted it to the Bu_3SnH reduction. He had to admit that in this particular case, the rearrangement did occur preferentially via a formal 1,2-shift as his mass-spectrometric analysis of the product confirmed our results. Kinetic measurements showed that the rate constant is by more than three orders of magnitude greater[104] for **140** than that previously reported for the acyclic model[102] compounds. This led Beckwith to the conclusion that the rearrangement of the steroid-derived radical proceeded by a different mechanism[104]. The 1,2-shift (**147**) seemed to him unprecedented and he proposed an alternative mechanism involving the intermediacy of an anion–radical cation ion pair **148** which would be sufficiently tight to prevent complete randomization of the

ether and carbonyl oxygen atoms, or migration of the acyloxy group to the β-face of the molecule.

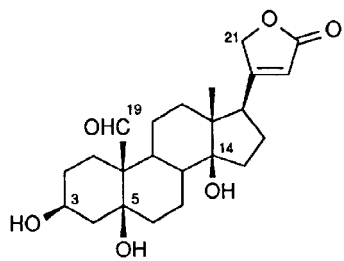
In summary, there are two mechanisms for the rearrangement of β-(acyloxy)alkyl radicals. Simple acyclic systems undergo slow rearrangement through a five-membered transition structure. The steroid radical, presumably because of the steric compression and a perfect alignment of the reactive groups, rearranges more rapidly, either through a three-membered cyclic transition structure **147** suggested by us (ref.[101]), or via a tight anion–radical cation ion pair **148** proposed by Beckwith[104].

2.9. *Practical Application: Synthesis of Strophanthidin*

Steroidal cardiotonic glycosides are indispensable drugs for treatment heart insufficiency. Aglycones of the most common compounds (Chart IX) possessing this unique activity are digitoxigenin (**149**), digoxigenin (**150**) and strophanthidin (**151**)[105]. Although **149** has been synthesized more than dozen times[106], there was only one synthesis of **151** described in the literature[107,108] which represents a 24-step sequence. We believed we could find a shorter route to **151** based on our methodology[10,13] of the stereo- and regiocontrol of electrophilic additions by neighboring groups that would allow a selective hydroxylation in position 5β.



149, X = H
150, X = OH



151

CHART IX

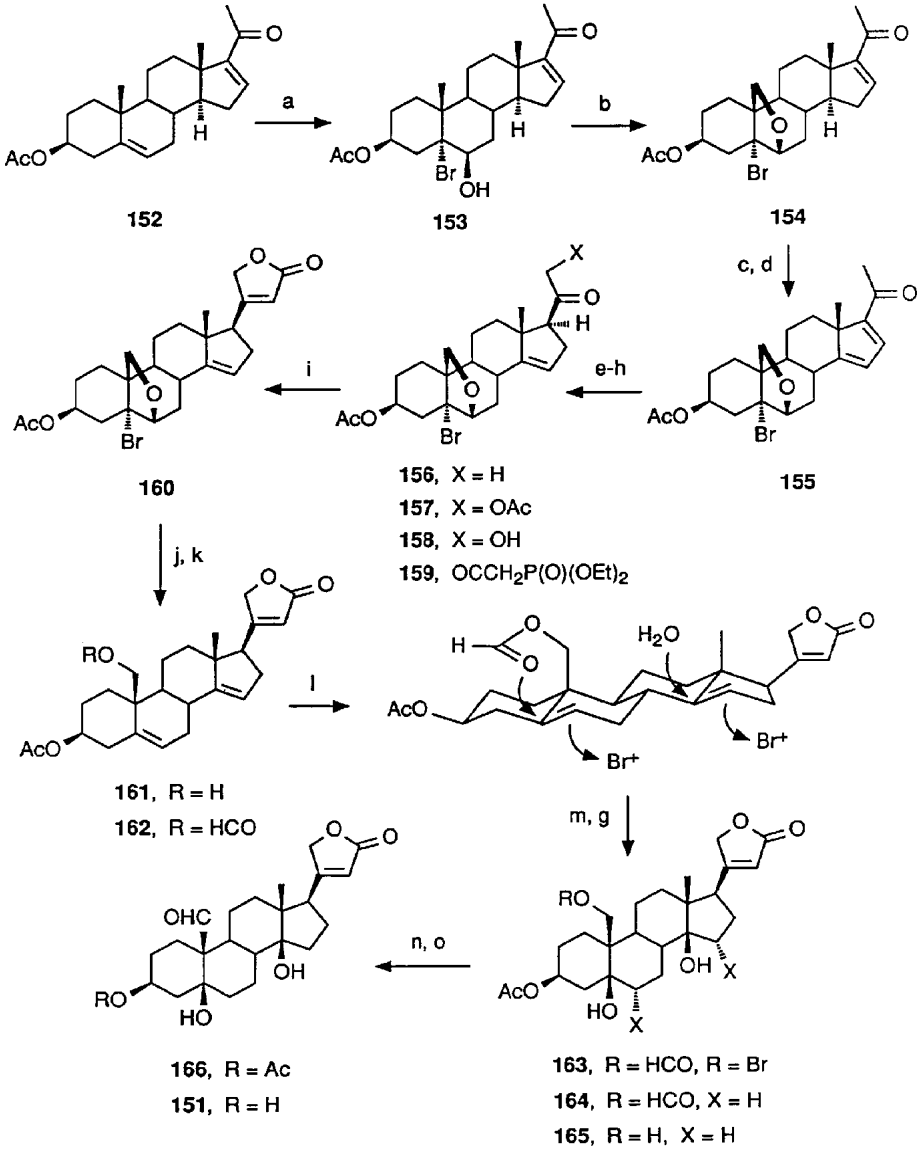
Retrosynthetic analysis suggested 5,16-pregnadien-3β-yl-20-one acetate (**152**) as the starting material[109]. Comparison of the latter with the structure of strophanthidin (**151**) indicated four strategic steps: hydroxylation in positions 5β and 14β, oxidation of the angular methyl C(19) into CHO group, and oxidation of C(21) followed by construction of the unsaturated lactone ring. For the functionalization of C(14) we intended to use chemistry[110] in which the 5,6-double bond of **152** would interfere so that a protection of this part of the molecule was required. Fortunately, the methodology known[111] for oxidation of C(19) could also serve as a masking technique for the 5,6-double bond.

Thus, it was obvious that the C(19) functionalization should be done in an early stage of the synthesis. A number of methods are available for the construction of the lactone ring[112] and some of them appeared mild enough to tolerate functional groups in our intermediates. Finally, a method for the stereo- and regiocontrolled 5β-hydroxylation has been developed in our laboratory[10,13] (see Chapter 1) and had the promise of bringing the major short-cut of our synthesis. After some experimentation with timing of the particular steps and compromising the yields, the synthesis was carried out as follows.

Dienone **152** was first converted into diaxial bromohydrin **153** which on radical cyclization with lead tetraacetate[111] afforded the cyclic bromoether **154** in an 83% yield (Scheme 26). Having thus simultaneously functionalized the angular methyl and protected the 5,6-double bond we could now introduce the 14,15-double bond through radical allylic bromination[110] of **154** followed by dehydrobromination (**154** →**155**). The next step, i.e. selective reduction of the dienone system in **155** at the central double bond, turned out to be a difficult problem. After numerous unsuccessful attempts using known methods[107,113] we found that **155** can be transformed to **156** by palladium-catalyzed hydrosilylation which, under specific conditions[114], produced the desired enone **156** in a 68% yield. The following oxygenation of C(21) was carried out by a modified procedure, originally developed for the construction of the corticoid side-chain[115], which employs the reaction of lead tetraacetate with the kinetic enol-ether generated in situ from the methyl ketone by $MeOH/BF_3$. Resulting acetoxy derivative **157** was selectively saponified with $KHCO_3$ at the primary position and the product **158** was esterified by diethylphosphonoacetic acid to give ester **159** which on reaction with *t*-BuOK readily cyclized to the lactone **160** (81%).

The bromoether moiety in **160** was then reduced with zinc in boiling acetic acid to furnish unsaturated alcohol **161** that was converted to formate **162** (86%). The formate group was introduced in order to control the regio- and stereochemistry of the next step, i.e. addition of HOBr to the 5,6-double bond. As expected (see Chapter 1), employment of 2 equivalents of HOBr (generated in situ from NBA) resulted in the simultaneous hydroxylation in positions 5β and 14β as the crucial step. One equivalent of the reagent reacted with the 14,15-double bond in consonance with Markovnikov rule[110]. The required regiochemistry of the addition of the second equivalent of HOBr was successfully ensured by $6(O)^{\pi,n}$-*exo*-*Trig* participation of the formate group so that we have obtained a product with diequatorial arrangement of 5β-OH and 6α-Br rather than the diaxial one (compare with the addition in the absence of a neighboring group **152** → **153**). The double bromohydrin **163** resulting from this one-pot reaction was unstable and was immediately transformed to diol **164** by radical reduction with two equivalents of Bu_3SnH in a 58% overall yield.

Subsequent selective hydrolysis of the formate group with $KHCO_3$ produced strophanthidol 3-acetate **165**, which on Jones oxidation furnished strophanthidin acetate[116] **166** whose saponification to strophanthidin **151** was described earlier[117].



a, NBA, Et_2O, H_2O; **b**, $(AcO)_4Pb$, I_2, C_6H_6, reflux; **c**, NBS, AIBN, CCl_4, reflux; **d**, LiI, Li_2CO_3, DMF, 100 °C; **e**, Ph_2SiH_2, $(dppe)_2Pd$, $ZnCl_2$, $CHCl_3$; **f**, $(AcO)_4Pb$, MeOH, $BF_3.Et_2O$, r.t.; **g**, $KHCO_3$, C_6H_6, MeOH, H_2O; **h**, $(EtO)_2P(O)CH_2CO_2H$, DCC, DMAP, Et_2O, C_6H_5, r.t.; **i**, t-BuOK, THF, r.t.; **j**, Zn, AcOH, 80 °C; **k**, HCO_2H, 70 °C; **l**, 2 eq. NBA, H_2O, dioxane, r.t.; **m**, 2 eq. Bu_3SnH, AIBN, C_6H_6, reflux; **n**, CrO_3, Me_2CO, H_2SO_4, 0 °C; **o**, Et_3N (ref. 117)

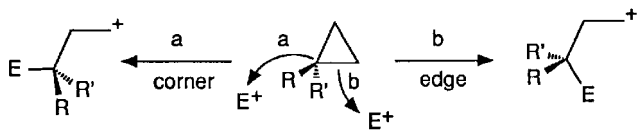
SCHEME 26

In conclusion, this 16-step sequence showed that strophanthidin (**151**) can be synthesized from a common, commercially available steroid **152** in a much shorter way than previously reported by the Japanese authors[107] in their 24-step approach. These results have also demonstrated how the methodology we have developed for controlling additions to cyclohexene systems can be applied to construction of a relatively complex natural product.

3. STEREOCHEMISTRY OF THE CLEAVAGE OF CYCLOPROPANE RING BY METAL REAGENTS AND TRASMETALATION OF THE PRODUCTS

For about a decade we have studied electrophilic additions whose regio- and stereochemistry were controlled by neighboring groups. As a further logical step we have recently become interested in the cleavage of cyclopropane ring, particularly by means of metallic reagents. It appears that the stereo- and regioselective cleavage of cyclopropanes (which in turn can be synthesized with high selectivity)[1,118] by means of metal complexes could serve as an attractive strategy for the construction of up to three contiguous chiral centers and thus supplement the current synthetic arsenal.

The mechanism of cyclopropane opening was little understood until very recently. Two different pathways can be proposed for the electrophilic cleavage of cyclopropanes, namely the "corner" or the "edge" attack by the electrophile[118], which would result in the inversion or retention, respectively, at the center to which the electrophile becomes linked. The mode of cleavage will then be reflected in the stereostructure of the product[118] (Scheme 27). Transition metals (Pd, Pt, and Rh), capable of back donation, favor the "edge" approach[119] and halogens (Br and Cl) follow the same pattern[120]. For the alternative "corner" opening[118,121], there was a lack of direct evidence until very recently. While this project was in progress, the first example of exclusive "corner" opening was reported for a proton[122] and mercury(II) (refs[122,123]).

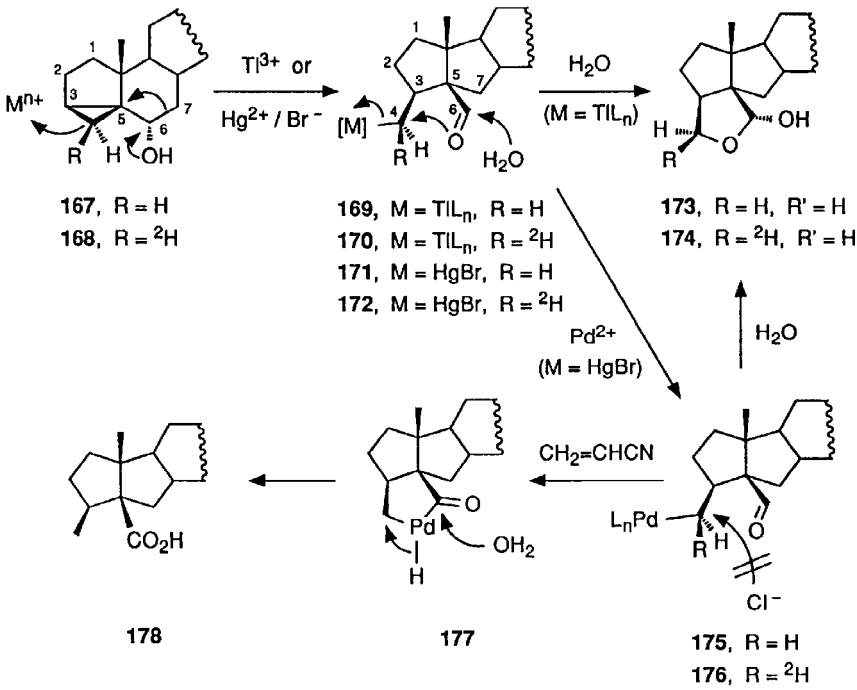


SCHEME 27

Thallium(III), an isoelectronic ion with mercury(II), is another ion capable of the cleavage of cyclopropanes[124], although only a handful of examples are known from the literature[125]. However, the stereochemistry and mechanism of these reactions have not been established and their synthetic potential is largely unexplored. We also felt that more examples for the mercury(II)-mediated opening should be sought.

Treatment of model compound **167** with $Tl(NO_3)_3 . 3 H_2O$ in dioxane at room temperature for 5 h led to essentially a single product (later identified as **173**) in 73%

isolated yield[126] (Scheme 28). The reaction can be summarized as follows. The C(4)–C(5) bond of the cyclopropane ring is cleaved[127] with concomitant migration of the antiperiplanar C(6)–C(7) bond and the reaction is completed by substitution of thallium by oxygen during the closure of the lactol ring.



SCHEME 28

Since the stereochemistry of the cyclopropane fission could not be established directly with **167**, a stereospecifically labelled compound **168** was synthesized[126] and subjected to the reaction with Tl(III) (Scheme 28). Analysis of the ^{1}H NMR spectrum of the product **174** unequivocally established (by NOE) the configuration of deuterium as being 4β and was indicative of a stereochemically homogeneous reaction as no other isomer could be detected. This result is in agreement with double inversion at C(4), i.e. with the initial "corner" cleavage of cyclopropane to give thalliated intermediate **170**, followed by S_N2 substitution by the neighboring carbonyl. The same product could be conjectured to arise from a double retention pathway involving edge activation, and replacement of Tl with OH (from water) to give the corresponding alcohol, which would then spontaneously cyclize to lactol **174**. However, when the reaction of **167** with Tl(III) was run in dioxane containing water enriched in ^{18}O by 25%, incorporation of the label was observed solely into the hydroxy group of the lactol **173**, which further

supports the double inversion pathway shown in Scheme 28. In a complementary experiment, the alcohol **167** labelled by ^{18}O in OH group was treated with Tl(III). The product obtained (^{18}O-labelled **173**) had the label located solely in the ether oxygen, which proves the carbonyl oxygen participation in the ring closure[128], so that the double retention mechanism can be ruled out[129]. These experiments thus provided conclusive evidence for the double inversion pathway involving corner activation of the cyclopropane ring by Tl(III), which we have reported for the first time[126].

Treatment of steroidal cyclopropyl alcohol **167** with $Hg(NO_3)_2 . H_2O$ in CH_3CN at room temperature for 30 min led, after KBr workup, to a single product **171** in 94% isolated yield[131,132] (Scheme 28). In contrast to the Tl(III)-mediated reaction, where the organothalliated species **169** undergoes an instantaneous conversion to lactol **173**, the organomercurial **171** could be isolated as a stable compound.

We assumed that the stereochemistry of cyclopropane fission could be established in a way analogous to that we have employed for thallium[126], i.e. by using stereospecifically deuterated cyclopropyl alcohol **168**. To this end, we needed to assign the NMR signals of the two diastereotopic protons at C(4). However, in the spectrum of **171**, they appeared at 1.93 ppm (dd, J = 8.7 and J = 11.7 Hz) and 2.05 (dd, J = 8.1 and J = 11.7 Hz), respectively, so that the assignment was not possible at this stage[133]. Hence, transformation of **171** to a compound in which C(4) would be conformationally fixed, was required. After much experimentation, $PdCl_2$ was found to convert **171** to lactol **173** (via **175**), for which the 4α-H and 4β-H were easily identified by NOE experiments[126].

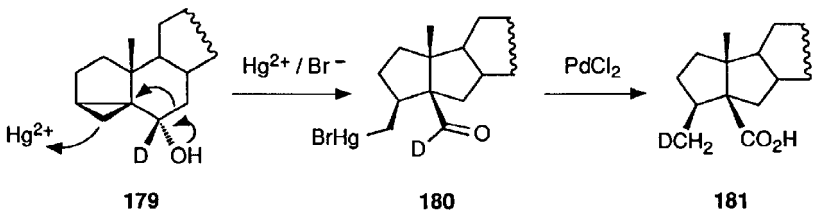
Stereospecifically labelled cyclopropyl derivative **168** was then treated with $Hg(NO_3)_2 . H_2O$ in the same way as was the unlabelled analogue **167** and quenched with aqueous KBr. Catalytic reaction with $PdCl_2/CuCl_2$ in DME/H_2O, which is assumed to proceed with retention of configuration[134] via **176**, furnished lactol **174**, identical with the product of the Tl(III)-mediated fission; the other stereoisomer could not be detected[135]. This experiment thus provided a conclusive evidence for the mechanism of the whole sequence and showed that opening of the cyclopropane ring in **168** by Hg(II) occurred solely in a "corner" fashion.

The thallic and mercuric ion have thus been shown to attack exclusively at the "corner" of the cyclopropane which allows similar orbital arguments[122] to be used. Neither Hg^{2+} nor Tl^{3+} are good back-donors so that the back-donation of their d_π electrons to the LUMO Walsh orbital is negligible; therefore the "edge" activation is apparently disfavored. On the other hand, the observed corner attack by Tl^{3+} and Hg^{2+} reflects the favorable interaction of the degenerate HOMOs of the cyclopropane with vacant *d* orbitals on the metal. Our experiments thus provide further support for the mechanistic picture and orbital considerations recently published by Coxon et al.[122].

The two isoelectronic cations (Tl^{3+} and Hg^{2+}) not only share the same reactivity in the initial step, but also in the following events, namely the unique skeletal rearrangement (**167** → **169** or **171**). The difference between Tl and Hg is only seen in the fate of

the organometallics generated in this way. While the organomercurial **171** is fairly stable, can be isolated in pure state and used for subsequent transformations, its thallated counterpart is more reactive and undergoes the nucleophilic ring closure (**169** → **173**). This divergence of reactivities can serve as a clear example for delicate control of the reactivity by closely related metals.

When transmetalation of the organomercurial **171** with $PdCl_2$ was attempted in the presence of a π-acid (acrylonitrile, benzoquinone, or 2-cyclohexenone), acid **178** was isolated as the main product, contaminated by a few percent of lactol **173**. Apparently, the presence of a π-acid dramatically changed the reactivity of Pd. This rather unexpected result can be rationalized as follows. Rather then undergoing the $5(O)^{\pi,n}$-*exo*-*Tet* ring closure to **173**, in this instance, the transient organopalladium **175** preferred an intramolecular insertion into the C–H bond of the aldehyde group[136]. This step generated palladacycle **177** which eventually transferred hydrogen from Pd to C(4) and collapsed to acid **178** by replacing Pd at the carbonyl carbon by water. In order to verify this mechanism, deuterated aldehyde **180** was prepared from 6β-^{2}H-alcohol **179** (Scheme 29; ref.[136]). Reaction of **180** under the same conditions as applied to its unlabelled counterpart (i.e. $PdCl_2$, LiCl, CH_2=CHCN, DME, room temperature) resulted in the formation of acid **181** labelled in the methyl group[137]. By contrast, no insertion was observed with the Wilkinson rhodium catalyst[136].

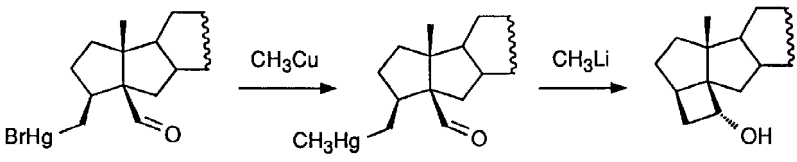


179 **180** **181**

SCHEME 29

The rearrangement of the cyclopropyl alcohol **167** represents an attractive synthetic avenue for the stereoselective construction of the triquinane skeleton or spirocyclic lactones. Although the experiments were confined to the steroidal skeleton, we believe that our finding is of a general nature and might be used as the key step for the construction of complex natural products. The organopalladium intermediate **175** offers further opportunities for tuning of the reactivity: here, it is the ligands attached to the same metal that have the decisive influence. Aside from the Pd-mediated conversion of **171** to **173**, or **178**, we have found that, e.g., Wittig olefination can be performed with **171** without losing the –HgBr functionality. Moreover, Me_2CuLi and related reagents quantitatively convert the organomercury bromide **171** to methylmercury derivative **182**, which itself represents a new and extremely mild method (–78 °C, 1 min) for the

synthesis of dialkyl mercury derivatives (Scheme 30). Treatment of the latter product with MeLi resulted in the formation cyclobutyl alcohol **183**. This unique sequence starting from cyclopropyl derivative **167** represents a completely new strategy for a stereospecific construction of the "5,5,4" skeleton; it could be further modified and might become a novel, general way for a stereospecific ring closure[131].



171 **182** **183**

SCHEME 30

4. PALLADIUM-CATALYZED ALLYLIC SUBSTITUTION: *syn-anti* DICHOTOMY IN THE FORMATION OF (π-ALLYL)PALLADIUM COMPLEXES

4.1. *General Aspects*

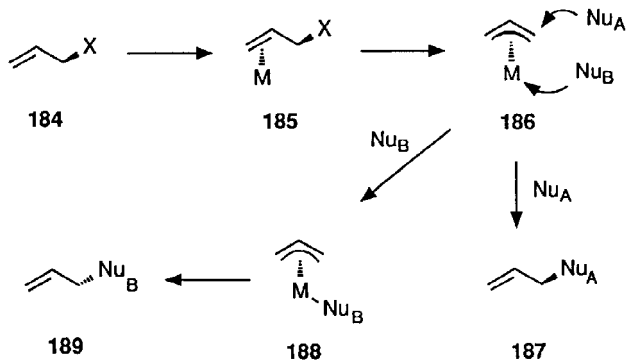
Of prime importance for organic synthesis is carbon–carbon bond formation. Aside from the classical nucleophilic substitution and Michael addition, allylic substitution is another good candidate for an efficient method in view of its experimental simplicity. In its traditional version, however, this is a capricious reaction that can afford a variety of products due to the competing S_N1, S_N2, S_N2', and elimination processes[138]. Moreover, the S_N2' reaction can proceed in an *anti*- or *syn*-fashion[138 – 140], so that mixtures of products are often obtained[141 – 145], unless an inherent bias in the substrate molecule strongly favors one particular pathway[138a,144h – 144j,146]. Generally, allylic substitution in its classical way is difficult to control in the desired direction, and further fundamental investigation more or less ceased in the early 80s.

The advent of transition metals has had a tremendous impact on organic chemistry and new avenues for highly efficient synthesis have been opened up[2]. Allylic substitution has become a particularly fruitful area for demonstrating the power of reactions performed on metal templates (Pd, Cu, and others), mainly because the classical methods failed to meet the challenges of modern organic synthesis.

Tsuji[147] was the first to report (in 1965) on the stoichiometric reaction of (π-allyl)-palladium complexes with nucleophiles, effecting an overall allylic substitution. Later (in 1970), Walker[148] and Hata[149] discovered that the allylic displacement of OR groups with a variety of nucleophiles requires only a catalytic amount of palladium. These

findings opened a vast area of further studies and applications. The refinement of this reaction owes much to the work of Trost[150], Tsuji[151], Bäckvall[152], and others[153], who recognized its potential. Since the mid 70s the palladium-catalyzed allylic substitution has evolved into a very mild, efficient and generally stereospecific method for C–C, C–N, and C–O bond formation in both inter- and intramolecular versions[150 – 154].

Stereochemical studies demonstrated that formation of the intermediate (π-allyl)-palladium complexes from allylic esters[155] or carbonates[156] (oxidative addition) uniformly proceeds via an *anti*-mechanism (**184** → **185** → **186**)[157]. The following reaction with stabilized C-nucleophiles (Nu_A) leads to **187**, again via an *anti*-mechanism (Scheme 31)[155,156]. In contrast, reactions of the complexes with organometallics[158] (Nu_B), such as aryl- and vinylzinc halides[157c,159,160] and aryl- and vinyltin[161] and zirconium[158] reagents give *syn*-products in the second step (**186** → **188** → **189**). Reaction with O-nucleophiles, such as carboxylates, may be controlled from highly *syn*-selective to almost pure *anti*-addition by adding Cl^- (whose role is to prevent coordination of AcO^- to Pd and the subsequent intramolecular delivery of the latter)[155d,162]. Reactions of Cl^- and N- and S-nucleophiles are usually *anti*-selective[163 – 166].



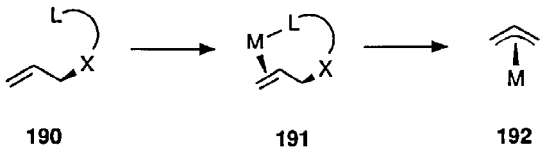
SCHEME 31

In sharp contrast to the variability of the stereochemistry of the second step, the initial oxidative addition has been found to invariably occur in an *anti*-fashion[155 – 157]. However, a *syn*-mechanism for this step should also be stereoelectronically allowed, in spite of being apparently higher in energy. If attainable, this reversal of stereochemistry would largely broaden the synthetic scope of the palladium-catalyzed allylic substitution.

4.2. *Reversion of the Stereochemistry of the Oxidative Addition*

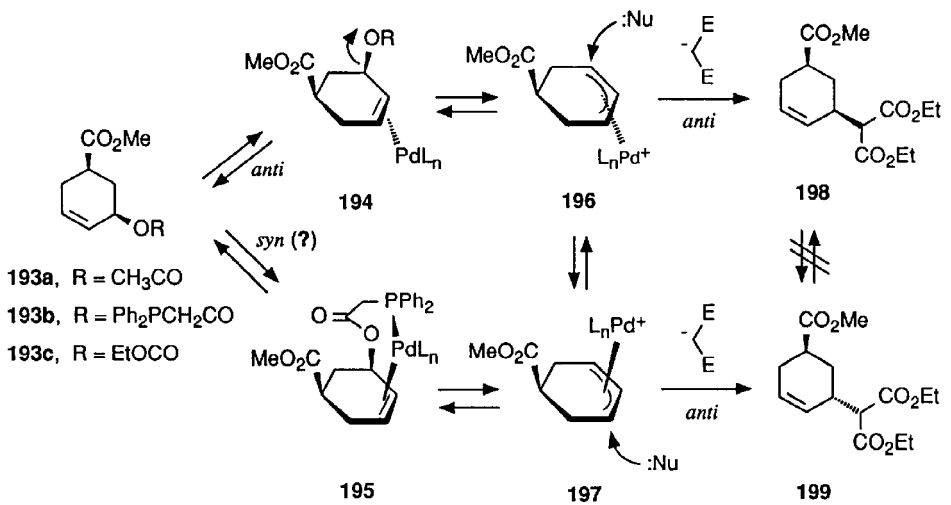
We reasoned that the *syn*-route for the oxidative addition of Pd(0) to the allylic substrate (Scheme 32) might be boosted by pre-coordination of the Pd(0) reagent to the leaving group (**190** → **191** → **192**). This type of coordination has been observed in the

reactions of allylic carbamates with organocuprates[167], and steering a reagent by precoordination to a neighboring group has become an established method of stereocontrol for a number of other reactions such as epoxidation[168], cyclopropanation[169], mercuration[170], carbonylation[171], hydroboration[172], hydrogenation[173], addition of Grignard reagents[174], and others[1,175]; for a review, see ref.[79].



SCHEME 32

Since phosphines are known to be particularly good ligands for palladium we turned our attention to (diphenylphosphino)acetic acid[176] (DPPAcOH) and prepared the corresponding ester[177] **193b** (Scheme 33). The latter was treated with alkali salt (Li or Na) of diethyl malonate and a catalytic (5 mole %)-to-stoichiometric amount of Pd(0) in various solvents, using a range of temperature, and various ligands (Table I). While acetate **193a** is known to predominantly afford the product of overall retention of configuration (entry 1) with high selectivity (93 : 7 to 98 : 2), we found that with our DPPAcO derivative **193b** we could achieve up to 3 : 2 ratio of the products **198** and **199** (entries 2 – 4). Since no epimerization of **193b** was detected at ca 50% conversion,



SCHEME 33

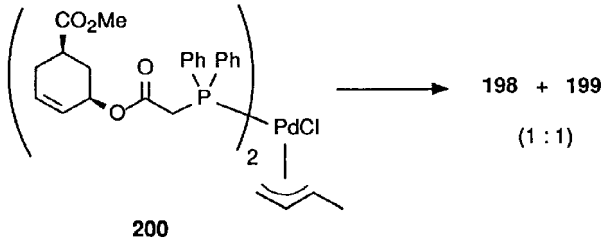
it was conceivable that the minor product **199** might really arise by the mechanism we looked for, involving pre-complexation of the palladium reagent to the Ph_2P– group and formation of the complex **195**. But still, the competing mechanism of the oxidative addition remained the dominant reaction pathway, giving eventually **198** as the major product[178].

At this stage it became obvious that evidence for the coordination of the Pd(0) reagent to the DPPAcO group was clearly needed. This would have been difficult in the catalytic mode and we have therefore synthesized a relatively stable complex **200** in 52% yield by reaction of **193b** with $[(\pi\text{-crotyl})PdCl]_2$ in the presence of maleic anhydride. When **200** was submitted to the reaction with sodiodiethyl malonate in THF at room temperature for 30 min (Scheme 34), a 49 : 51 mixture of **198** and **199** (71% isolated yield) was obtained rather than the expected pure **199**. A possible explanation could be as follows. About half of the molecules may react in an intramolecular fashion employing a *syn*-mechanism for the formation of the η^3-intermediate, which is eventually converted to **199**. The other half of the molecules react in an intermolecular way utilizing the second molecule of **200**, or the released Pd(0) species, as a reagent for the *anti*-mechanism, eventually producing **198** (refs[179,180]).

TABLE I
Reaction of **193** with $LiCH(CO_2Et)_2$/Pd(0) in THF at concentration 0.03 mol l^{-1}

Entry	Compound	Catalyst mole %	*T* °C	*t* h	Ratio **198 : 199**	Yield[a] %
1	**193a**	$(Ph_3P)_4Pd$ 5	50	16	93 : 7	91[b]
2	**193b**	$(Ph_3P)_4Pd$ 10	50	1	67 : 33	42
3	**193b**	$(Ph_3P)_4Pd$ 25	50	1	58 : 42	95[c]
4	**193b**	$(Ph_3P)_4Pd$ 100	50	1	57 : 43	78
5	**193b**	$(Ph_3P)_4Pd$ 25[d]	50	1	73 : 27	51
6	**193b**	$(dppe)_2Pd$ 5	50	1	>95 : 5	62
7	**193b**	$(Ph_3P)_4Pd$ 25	0	1	92 : 8	53
8	**193b**	$(Ph_3P)_4Pd$ 20	20	1	72 : 28	87

[a] Isolated yield. [b] With $(dppe)_2Pd$ the ratio was 98 : 2 (ref.[161d]). [c] When the reaction was carried out at concentration 0.003 mol l^{-1}, the ratio was 89 : 11. [d] With 100 mole % of Ph_3P as an added ligand.



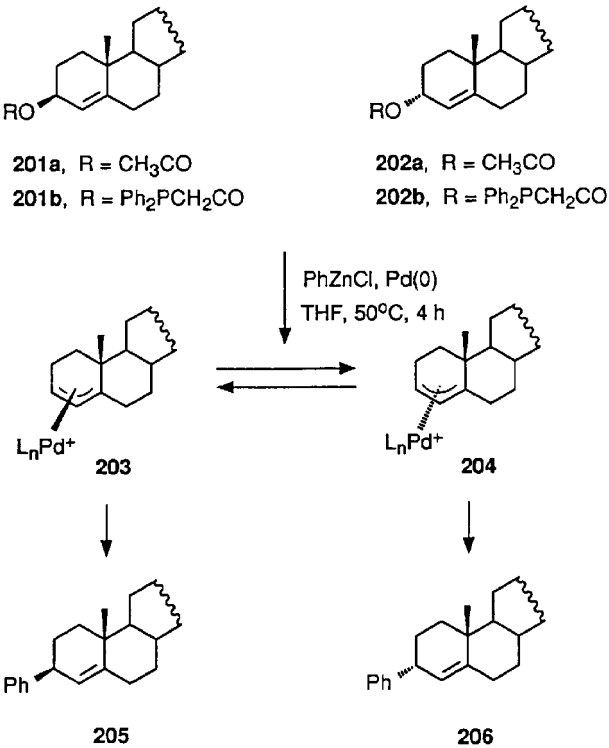
200

SCHEME 34

Since not even the complex **200** was particularly prone to the *syn*-mechanism, an alternative rationalization was sought for the reactivity of our DPPAc derivatives. Bosnich has demonstrated that optically active (π-allyl)palladium complexes may be partly or fully racemized by an excess of the Pd(0)-reagent[184]. Assuming that isomerization can occur at the stage of η^3-complexes, it is conceivable that **200** is first converted to the (π-allyl) complex (one way or another) and the latter is isomerized prior to its reaction with sodiodiethyl malonate. Similarly, in the catalytic reaction, **193b** would initially produce a η^3-complex which would then isomerize to a mixture of **196** and **197**; this sequence would be reflected in the product ratio. In order to find which of the two diastereoisomeric η^3-complexes is formed first from **193b** (prior to the isomerization), we have elucidated the temperature effect on the catalytic reaction (entries 3, 7, and 8). At 0 °C (entry 7) the reaction of **193b** gave approximately the same ratio of the products as that obtained from acetate **193a**. Raising the temperature to 20 °C (entry 8) and further to 50 °C (entry 3) resulted in a continuing increase of the proportion of **199**. Further increase (to 80 °C in DME) had no effect indicating that an equilibrium had been reached. This behavior suggests that the η^3-complex is predominantly formed via the *anti*-mechanism even for **193b** with subsequent thermodynamic equilibration **196** $\rightleftarrows$ **197** at elevated temperature.

To gain further support for this rationalization, it was of interest to explore the reaction with other substrates. To this end we prepared steroidal esters **201** – **202** (Scheme 35). To our surprise, we found all of them either to be inert toward the Pd-catalyzed substitution with sodiodiethyl malonate or to give complex mixtures of products under harsh conditions[185]. On the other hand, these esters reacted with PhZnCl in the presence of a catalytic amount of $(Ph_3P)_4Pd$. While 3β-derivatives **201a** and **201b** gave similar compositions of the products **205** and **206**, slightly favoring the former (~ 3 : 2), **202a** reacted differently from **202b**. While acetate **202a** gave approximately the opposite ratio of **205** to **206** (~ 2 : 3) to that obtained from its epimer **201a**, the DPPAcO derivative **202b** clearly favored inversion to give almost pure **205** (≥95 : 5). Since organometallics are known to react stereospecifically with the (π-allyl)palladium complexes using a *syn*-mechanism, the results obtained with **201a**, **201b**, and **202a** are consistent with the existence of both diastereoisomeric Pd-complexes **203** and **204** as intermedi-

ates; the product ratio indicates that equilibration of these complexes has occurred, although apparently not to completion. In contrast, the formation of a single phenyl derivative **205** from **202b** is probably due to substantial elimination occurring in this case, which may well have been the major reaction pathway for the β-diastereoisomeric complex **203**.



201a, R = CH_3CO
201b, R = Ph_2PCH_2CO

202a, R = CH_3CO
202b, R = Ph_2PCH_2CO

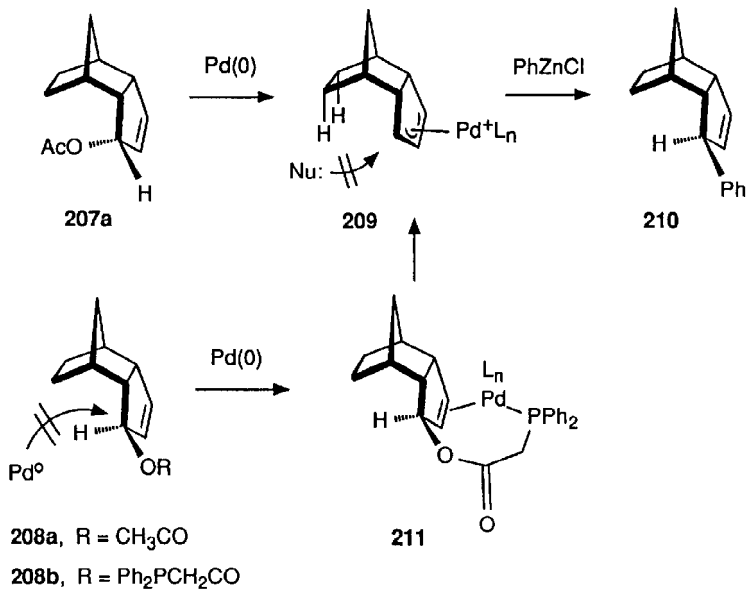
203 **204**

205 **206**

SCHEME 35

Although the initial results achieved with **193b** were encouraging (and we hoped to be on the right track) those obtained later were not. Nevertheless, we wished to explore systems, where the ordinary *anti*-pathway for oxidative addition would be strongly disfavored by, e.g., steric congestion, to find out if this would finally promote the *syn*-mechanism. A suitable pair or model compounds **207a** and **208a** to address this issue was found in the literature[160] (Scheme 36). The acetate **207a** is known to form the intermediate Pd complex **209** via an ordinary *anti*-mechanism and produce phenyl derivative **210** on subsequent *syn*-reaction with PhZnCl; no reaction is observed with sodiodiethyl malonate, due to the severe steric hindrance the nucleophile would experience from the *anti* (i.e. *endo*) face of the double bond in **209**. In contrast to **207a**, the epimeric acetate **208a** has been reported to be inert towards Pd-catalyzed reactions,

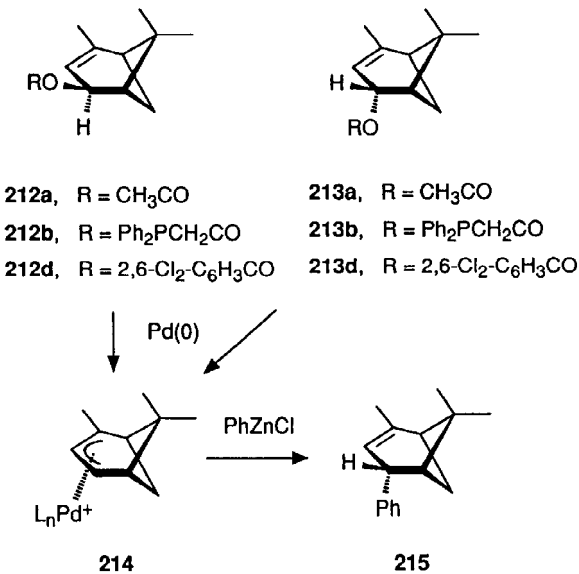
because the *endo* face of the allylic system required for the *anti*-mechanism is, again, severely hindered[160]. The DPPAc derivative **208b**, of the same configuration as the inert acetate **208a**, turned out to readily react with PhZnCl/Pd(0), giving **210** as the sole product (in 80% isolated yield), identical with the compound obtained from the acetate **207a** (Scheme 36). Since the second step is known[160] to proceed stereospecifically in a *syn*-fashion, the intermediate η^3-complex formed from **208b** should be the same as that arising from **207a**, suggesting a *syn*-mechanism of its formation. Moreover, while the reaction of **207a** requires 2 h at 20 °C to reach completion, **208b** reacted within 30 min at the same temperature[187].



SCHEME 36

Similar steric bias to that in **207** and **208**, could be expected in *trans*- and *cis*-verbenol derivatives **212** and **213** (Scheme 37). Acetate **212a** and DPPAc **212b** turned out to react sluggishly with PhZnCl/$(Ph_3P)_4$Pd affording, after 36 h at 20 °C, the phenylated product **215** in 20% and 29% isolated yield[188], respectively. In contrast, epimeric acetate **213a** and DPPAc **213b** differed dramatically from one another. Whereas acetate **213a** reacted sluggishly again (20 °C, 40 h, to furnish only 18% yield of **215**), the reaction of **213b** was complete within 1 h at 20 °C and produced **215** in 53% yield[188]. This dramatic acceleration is in agreement with a mechanism encompassing pre-coordination of Pd to the Ph_2P– group and a *syn*-type oxidative addition to generate inter-

mediate complex **214**. It appears that in the *cis*-isomers **212a** and **212b** the alignment of the C–O bond and the π-orbitals (required for the reaction to occur)[155f,186] is difficult to achieve due to the steric congestion imposed by the geminal dimethyl group. This seems to be the rationale for the slowing down the reaction. Even the 2,6-dichlorobenzoyloxy group, generally known to react much faster than other allylic esters[141a,144h,189], did not accelerate the reaction: both **212d** and **213d** needed approximately the same time for >90% conversion as did the acetates **212a** and **213a** (ref.[190]).

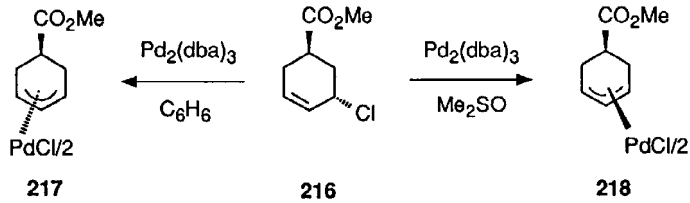


SCHEME 37

4.3. *Discussion*

Searching for evidence in favor of a *syn*-mechanism for the formation of (π-allyl)palladium complexes from allylic substrates, we have carried out initial experiments with **193b** (Table I, namely entry 3) and with stereochemically biased substrates (Schemes 36 and 37). While the results obtained with **193b** were tentatively interpreted as possible evidence for the *syn*-pathway (competing with the traditional *anti*-mechanism), the behavior of **208b** and **213b** was strongly supportive of the *syn*-route. At this stage we have published our conclusions in a preliminary communication[187a] as the first example of formation of a palladium η^3-complex in a *syn*-fashion. Later, a second example was found with

allylic chlorides, by Kurosawa[191,192] (Scheme 38). Allylic chloride **216**, when treated with $Pd_2(dba)_3$ in a non-coordinating solvent (benzene), furnished pure **217** (100 : 0) as a result of domination of a *syn*-mechanism. In contrast, strongly coordinating solvents (Me_2SO or MeCN) shifted the reaction to the *anti*-mechanism[193], producing **218** (97 : 3).



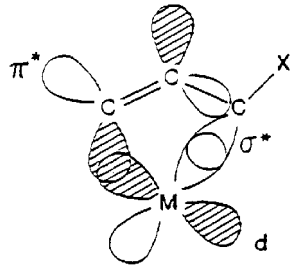
217 **216** **218**

SCHEME 38

Reactivity of the DPPAc esters **208b** and **213b** demonstrated that the *syn*-mechanism of the palladium η^3-complex formation can be achieved if the ordinary *anti*-reaction is precluded by strong steric congestion. Moreover, acetate **208a**, previously reported to be inert[160], was also found to react (in a *syn*-fashion)[194], but the reaction is dramatically slower than that with the DPPAc ester **208b**, and the yield of the product is low. Similar behavior was observed for acetate **213a**. This indicates that pre-coordination of the Pd(0)-reagent is not a categorical prerequisite for the *syn*-mechanism to operate, but has a beneficial accelerating effect on the reaction, which is also reflected in a high yield of the product. Thus, for the substrates where the Pd-catalyzed substitution would be extremely slow, the DPPAcO group can be used to facilitate the reaction via a *syn*-mechanism for the oxidative addition.

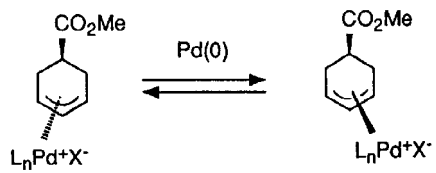
It appears that although the oxidative addition of palladium can really occur in a *syn*-fashion, the *anti*-mechanism normally dominates unless precluded by structural effects. Clearly, the *anti*-mechanism must be lower in energy. This parallels the *anti*-stereospecificity of the substitution of allylic esters by organocuprates. The latter has been rationalized by Corey as resulting from an effective overlap between *d* orbitals of copper with the antibonding orbitals of C=C (π^*) and C–X (σ^*) in the transition state[196] (**219**; M = Cu). We feel that similar arguments may be used to account for the preferred *anti*-stereospecificity in case of palladium (**219**; M = Pd). A higher activation energy for the *syn*-mechanism may be attributed to the lack of the orbital stabilization and to steric congestion.

The reactivity of **139b**, **201**, and **202** suggest that isomerization took place at the stage of palladium allylic complexes. Isomerization of η^3-complexes by added Pd(0) was first observed by Tsuji[197] and Bosnich[184,198] and recently studied by Bäckvall[199] in



219

detail. Backvall has investigated equilibration (Scheme 39) of *cis*- and *trans*-complexes **220** and **221** (originally existing as pure compounds) and arrived at the following conclusions: (i) Free Pd(0) is responsible for the isomerization of η^3-complexes as confirmed by studies of both stoichiometric and catalytic reactions. The equilibrium of **220a** : **221a** was found to be 55 : 45, and can be achieved by addition of $(Ph_3P)_4Pd$ to each of the latter complexes at −14 °C in less than 5 min! (ii) Addition of Ph_3P shifts the equilibrium $(Ph_3P)_4Pd \rightleftarrows (Ph_3P)_3Pd \rightleftarrows (Ph_3P)_2Pd$ to the left and slows down the rate of equilibration, due to decreasing the nucleophilicity of Pd(0). (iii) Complexes with bidentate ligands, such as dppe (ref.[200]) (**220b** and **221b**), do not isomerize and no isomerization was observed even after addition of excess of $(dppe)_2Pd$. This is in accord with the expected absence of "semi-naked" Pd(0) species that are required for the nucleophilic isomerization.



220 **221**

a, $L_n = (Ph_3P)_2$, $X = CF_3SO_3$; **b**, L_n = dppe, $X = CF_3SO_3$

SCHEME 39

In view of Bäckvall's findings, our observations can be interpreted as follows. Elevated temperature and increased amount of catalyst (up to 25 mole %) expedite the *trans*/*cis* equilibration of η^3-complexes **196** and **197**. The product ratio (**198** : **199**) finally achieved with our system (58 : 42 or 57 : 43; Table I, entries 3 and 4) is almost identical with that observed for the palladium complexes **220** : **221** (55 : 45). Furthermore, decreasing the concentration of all components 10 times (Table I, footnote *b*) resulted in considerable suppression of the isomerization (due to lowering the concen-

tration of active Pd-reagent) as reflected in product ratio (88 : 11). These results strongly support the mechanistic picture that encompasses the *anti*-mechanism producing intermediate η^3-complex **196** which is then isomerized prior to the reaction with sodiodiethyl malonate. Participation of the *syn*-pathway (if any) seems negligible in this instance.

The reactivity of the steroidal substrates **201** and **202** conforms to this mechanistic picture. The reluctance of acetate **201a** to react even under really harsh conditions apparently reflects unfavorable alignment of the C–O bond with the π-system.

4.4. *Conclusions*

Using stereochemically biased substrates **208** and **213**, we have obtained evidence that the *syn*-mechanism of formation of palladium η^3-complexes from allylic esters may be achieved if stereochemical congestion precludes the ordinary *anti*-mechanism. Pre-coordination of the Pd(0) reagent to the leaving group (as in **208b** and **213b**) dramatically accelerates the reaction and improves the overall yield. In principle, however, this pre-coordination is not essential for the *syn*-mechanism to operate, as demonstrated by allylic acetates **208a** and **213a**.

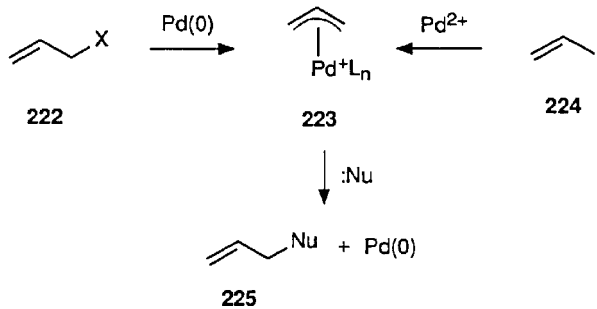
Substrates lacking stringent stereochemical hindrance (**193**, **201**, and **202**) react via an ordinary *anti*-mechanism to produce the corresponding palladium η^3-complexes as intermediates. Apparently, the possible pre-coordination of the Pd(0) reagent to the DPPAcO group does not counterbalance the higher activation energy for the *syn*-mechanism, so that the *anti*-process still dominates. At elevated temperatures the intermediate η^3-complexes isomerize prior to the reaction with a nucleophile. The isomerization can be facilitated even with allylic acetates and carbonates by addition of DPPAcOH as an external ligand.

We believe that our results, in conjunction with those obtained by other investigators, provide better insight into the mechanism of Pd(0)-catalyzed allylic substitution and broaden its applicability. Our findings show that in substrates where the classical *anti*-route of complex formation is impaired by severe steric congestion, our new leaving group enables the catalytic reaction to occur readily due to the operation of *syn*-mechanism as a stereoelectronically allowed alternative. Finally, we are confident that present knowledge of the mechanistic picture can open the way to rational design of novel chiral catalysts to effect asymmetric induction with a broader range of substrates.

5. PALLADIUM-CATALYZED ALLYLIC OXIDATION AND ITS SYNTHETIC APPLICATION

As shown above, (π-allyl)palladium complexes (**223**) can be generated from allylic substrates (**222**) and can react with C-, O-, N-, or S-nucleophiles effecting an overall allylic substitution (**225**). Since palladium enters and leaves (after the reaction with a

nucleophile) the sequence in the same form, i.e. as Pd(0), only a catalytic amount is required[2,153] (Scheme 40).



SCHEME 40

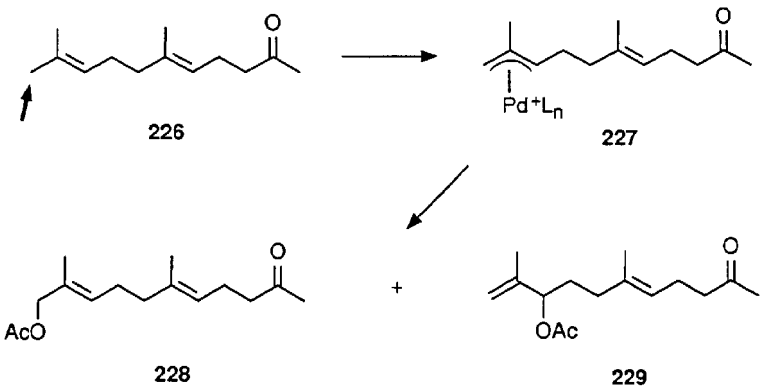
A different situation is encountered with olefins (**224**). These can react with Pd(II) to produce (π-allyl)palladium complexes (**223**) identical to those that arise from, e.g., allylic acetates, but reaction of the latter complexes with nucleophilic reagents releases Pd(0), so that a *stoichiometric* amount of palladium is needed[2,153]. We reasoned that developing a method that would reoxidize Pd(0) to Pd(II) would considerably improve the utility of this reaction. Moreover, if successful, we planned to employ this method for a synthesis of several natural products.

5.1. *Developing a Highly Selective Catalytic Method for Allylic Oxidation*

As a first step for synthesis of germacrane sesquiterpenes we were faced with a need to selectively oxidize commercially available geranylacetone (**226**) at the terminal methyl. However, this had not been previously achieved. The problem is one of selectivity: six of the eight saturated carbon centers in **226** are allylic and the remaining two are α to the carbonyl. After numerous unsuccessful attempts using known methods[201] of allylic oxidation based on SeO_2, we concluded that development of a new method was required.

Geranylacetone (**226**) was known[202] to react with a stoichiometric amount of $(CF_3CO_2)_2Pd$ in a highly selective manner through C–H insertion on a terminal allylic position to give a single η^3-complex **227** (Scheme 41). In analogy with other η^3-Pd complexes we assumed that **227** may also react with O-nucleophiles to effect allylic oxidation. However, the synthetic value of the sequence would be strongly attenuated by its stoichiometry. Therefore a method of reoxidizing Pd(0) back to its 2+ oxidation state was sought to complete the catalytic cycle[203].

After much experimentation[204] with many different oxidants[205], we found that the selective allylic oxidation could best be accomplished using a reagent mixture containing 5 mole % of $(CF_3CO_2)_2Pd$, 2 equivalents of benzoquinone (BQ)[206], and 0.2 equivalents of *o*-methoxyacetophenone as added ligand in acetic acid at 20 °C for 48 h. Under these conditions, an 85% isolated yield of allylic acetates **228** and **229** was obtained (2 : 1 ratio). Product yields and selectivity are influenced both by the oxidant and by the added ligand. With benzoquinone as oxidant and *o*-$MeOC_6H_4COMe$, product yield was high and 2 : 1 preference was observed for formation of terminal acetate **228**. With duroquinone as oxidant and diethyl malonate as ligand, the reaction required 90 °C for 48 h and the yield was much lower (32%) and preference for the undesired isomer **229** (24 : 1) was noted. In no case were products derived from oxidation of other than a terminal methyl group observed.



226 **227** **228** **229**

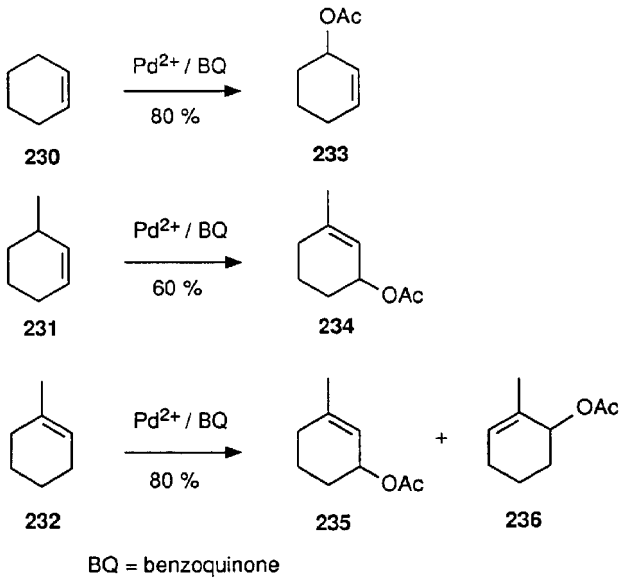
SCHEME 41

A brief oxidation study of several other olefins (**230** – **232**) was also carried out (Scheme 42). Good yields were obtained in all cases, although, as expected[150 – 153], a mixture of allylically isomeric products was obtained in the oxidation of 1-methylcyclohexene (**232**). 3-Methylcyclohexene (**231**), however, gave only a single product.

Our method was further refined by Åkermark and Heumann[207] and serves now as a useful tool for allylic oxidation. It is noteworthy that the selectivity of this reaction derives from factors different from those normally involved in SeO_2 or radical-type allylic oxidations. Thus, the method's value is particularly apparent in the oxidation of diene such as **226**.

The utility of this Pd-catalyzed oxidation is moderated by the lack of higher regiochemical control observed for acetate ion attack on the (π-allyl)palladium intermediate,

which leads to the formation of a mixture of two allylic acetates. For many applications, however, such as further Pd-catalyzed alkylation[150 – 153] this does not necessarily represent a drawback.



SCHEME 42

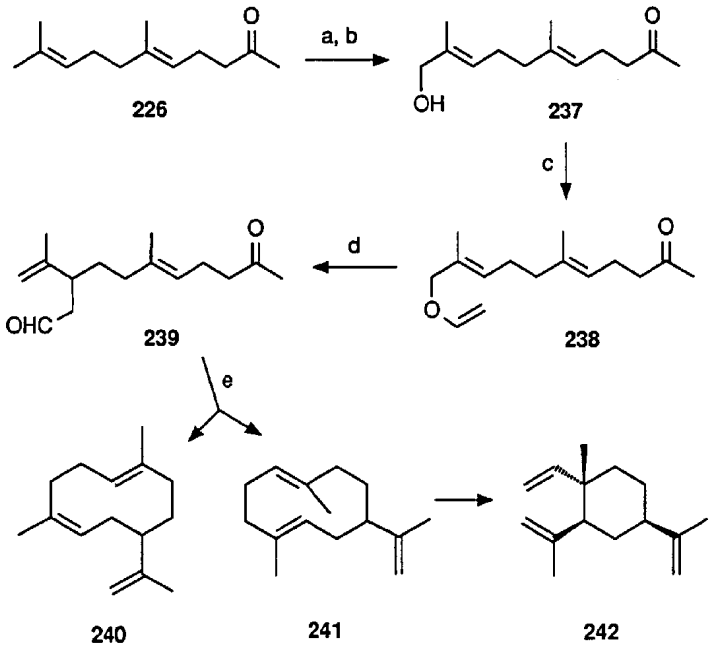
5.2. *Synthesis of Helminthogermacrene and* β*-Elemene*

Helminthogermacrene (**240**) is a naturally occurring macrocarbocyclic sesquiterpene[208]. Retrosynthetic analysis showed that its 10-membered ring might be closed up by McMurry coupling[209] of the corresponding ketoaldehyde **239** that, in turn, may be available in a few steps from geranylacetone (**226**).

The synthesis[210] was carried out as outlined in Scheme 43. Palladium-catalyzed oxidation of geranylacetone (**226**) described above, followed by saponification and separation of isomers provided keto alcohol **237** in 55% yield. The latter product was converted to vinyl ether **238**, thermolysis of which furnished the necessary dicarbonyl cyclization substrate **239**.

Treatment of the keto aldehyde **239** with $TiCl_3$/Zn–Cu in DME, using high dilution technique and slow addition of the substrate[209,211], initially gave a mixture of germacrenes **240** and **241**, since *E*/*Z* stereoselectivity at the new double bond is rarely ob-

served in these cyclizations[209]. It is known[212], however, that whereas helminthogermacrene **240** is thermally stable, germacrene A (**241**) undergoes Cope rearrangement at room temperature to yield β-elemene (**242**). We therefore expected and obtained a mixture of **240** and **242** (45 : 55, 60% yield) on cyclization of keto aldehyde **239**.



a, Benzoquinone, $(CF_3CO_2)_2Pd$, o-MeO-C_6H_4-COMe, AcOH, 20 °C, 48 h; **b**, K_2CO_3, MeOH; **c**, CH_2=CHOEt, $(CF_3CO_2)_2Hg$, r.t.; **d**, 200 °C, 6 h; **e**, $TiCl_3$, Zn-Cu, DME, reflux, 34 h addition

SCHEME 43

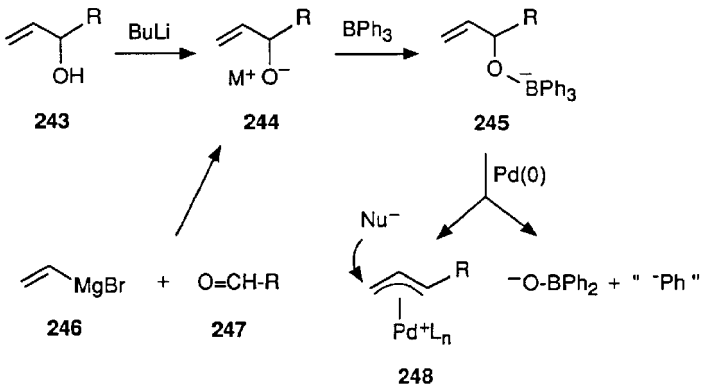
The same substrates were prepared earlier by traditional methodologies and the synthetic routes were much longer[208,213]. This concise synthesis clearly demonstrated the impact of transition metals as reagents (Pd and Ti in this case) on organic synthesis.

6. PROSPECT

As shown above, palladium(0)-catalyzed allylic substitution[1] is an established, efficient, highly stereoselective, and reliable method for the C–C, C–N, and C–O bond formation, with hundreds of synthetic applications reported to date[1,150 – 153]. Although

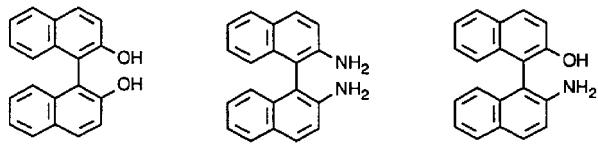
esters, carbonates, carbamates, phosphates, and related derivatives of allylic alcohols have frequently been used as substrates[150 – 153,187] the parent alcohols are generally much less reactive[148,149,214]. This apparently stems from the poor capability of a non-activated hydroxyl to serve as a leaving group. Moreover, a C-nucleophile such as sodiodiethyl malonate would first convert the allylic alcohol to the corresponding alkoxide, nucleophilic substitution of which can hardly be anticipated. Very few attempts have been made to generate palladium η^3-complexes directly from allylic alcohols[148,149,214].

We have now developed a new method[215] which allows palladium(0)-catalyzed allylic substitution to occur between allylic alcohols and anionic C-nucleophiles (Scheme 44): on reaction with Ph_3B (ref.[216]), the allylic alkoxide **244** is first converted in situ into the more reactive species **245** which then undergoes a Pd(0)-catalyzed reaction with lithiodiethyl malonate as a typical C-nucleophile via the η^3-complex **248**. Allylic alkoxides can be generated in situ either by deprotonation of the corresponding alcohol (**243** → **244**, e.g. with BuLi) or via a vinylmagnesium halide addition to the corresponding aldehyde (**246** + **247** → **244**), or via a reduction of α,β-unsaturated ketones. This whole sequence can be carried out as a one-pot procedure and is exceptionally suitable for sensitive allylic alcohols that may not be easily convertible to the more reactive esters or if the attempted allylic substitution would result mainly in elimination.



SCHEME 44

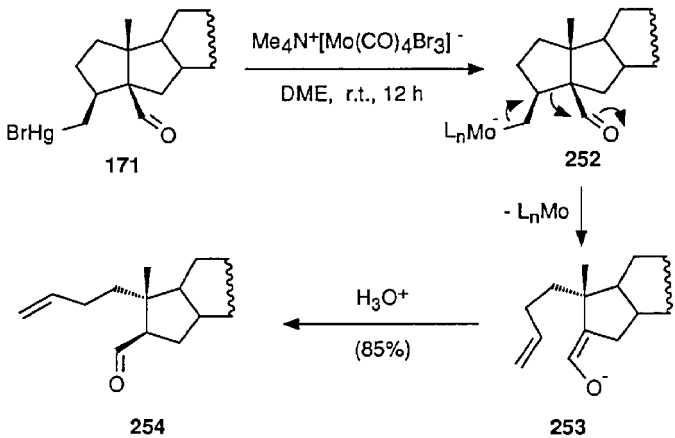
We are now entering a new area of catalytic asymmetric reactions, namely transition metal-catalyzed allylic substitution, reduction, and pericyclic reactions. To this end we are currently working on development of novel chiral catalysts based on binaphthyl ligands[220] (Chart X).



249 250 251

CHART X

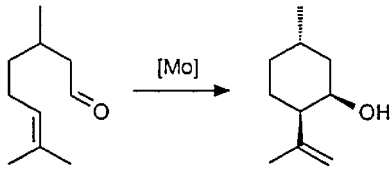
The cyclopropane ring-opening appears to be another fruitful area[221]. A novel, Grob-type fragmentation of the organomercurial **171** (arising from **167** by cyclopropane ring-fission) has recently been discovered with a molybdenum complex[222] (Scheme 45).



171 252 253 254

SCHEME 45

The same molybdenum complex has now been found to catalyze a highly stereoselective, intramolecular ene-reaction of citronellal (Scheme 46). The product has been found to have the opposite relative configuration at the two newly formed chiral centers compared to the product obtained by Lewis acid catalysis, which suggest that the reaction occurs on the metal template[223]. Further investigation into this novel transformation is under way in our Laboratory.



255 **256**

[Mo] = $Me_4N^+[Mo(CO)_4Br_3]^-$

SCHEME 46

Finally, the unique one-carbon degradation of 19-hydroxy steroids (Scheme 7) is now being used as a novel, stereoelectronically controlled route to a 19-norsteroids and A-aromatic steroids, such as estrone[224].

I would like to gratefully acknowledge my students and co-workers who participated in various stages of this research, namely Dr I. Stary, Dr I. G. Stieborova-Stara, Dr M. Pour, Dr M. Smrcina, Dr D. Dvorak, Mr J. Srogl, Mr R. S. Baines, Mr J. M. Grech, Mr G. Ahmed, Dr L. Kohout, Prof. F. Turecek., Dr M. Hanus, Dr M. Polasek, Dr A. Gogoll, Dr V. Langer, Dr J. Zajicek, Dr S. Vasickova, Mrs M. Synackova, Prof. J. Podlaha, and Dr J. Podlahova. Only their enthusiasm, patience, skills, and expertise made this work possible. My sincere thanks are particularly due to my teachers, Prof. O. Cervinka, Dr V. Cerny, and Prof. J. E. McMurry, for inspiration and encouragement and to my one-time colleagues, Prof. J.-E. Backvall, Dr D. Tanner, Dr A. Kasal, and Dr J. Zavada for stimulating discussions. I would also like to thank the Academy of Sciences of the Czech Republic, National Science Foundation (USA), Swedish Natural Science Research Council (NFR), University of Leicester, SERC, Glaxo, Pfizer, Roche, and Merck, Sharp and Dhome for their financial support.

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out this possibility, the reaction was run under the chloride free conditions, with a stoichiometric amount of palladium triflate generated in situ from $(AcO)_2Pd$ and CF_3SO_3H. The product (**174**) was identical with that formed by the $PdCl_2/CuCl_2$ method. Apparently, the intramolecular S_N2 substitution is highly favored in **176** by the steric arrangement and suppresses the intervention of Cl^-.

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179. Allylic substitution has also been reported with complexes of W (ref.[181]), Fe (ref.[182]), Mo (ref.[183]) and Ni, Ru, Rh, and Pt (ref.[3]). Stoichiometric reaction of **193b** with $(MeCN)_2W(CO)_4$, however, afforded the corresponding product of ligand exchange, $[RO_2CCH_2(Ph)_2P]_2W(CO)_4$, (58%), inert to $NaCH(CO_2Et)_2$. Similarly, the reaction of **193b** with $Fe_2(CO)_9$ led to the corresponding complex $RO_2CCH_2(Ph)_2P\text{-}Fe(CO)_4$ (69%), also inert toward $NaCH(CO_2Et)_2$. However, when the latter complex was irradiated by a mercury lamp in the presence of $NaCH(CO_2Et)_2$ (THF, reflux 3 h), a 65 : 35 mixture of **198** and **199** was isolated in 34% yield together with free **193b** (48%), which indicates that dissociation precedes the formation of η^3-complexes.
180. Low yields of substitution products were obtained on reaction of **193b** with MeCu(CN)Li (27%) and Me_3Cu_2Li (36%). While the ratio of retention/inversion products was 11 : 89 for the former reagent, the latter afforded a 31 : 69 mixture. Other cuprates, including Me_2CuLi, MeCu, and MeCu . BF_3, either did not react or produced complex mixtures.
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