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NUCLEOPHILIC AND ORGANOMETALLIC DISPLACEMENT REACTIONS OF ALLYLIC COMPOUNDS: STEREO- AND REGIOCHEMISTRY

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Abstract—Allylic alcohols, esters, halides and related compounds have been of mechanistic and synthetic interest for years. This Report focuses on the stereo- and regiochemical aspects of three reaction types: the S_N2' reaction (bimolecular nucleophilic substitution with allylic rearrangement); displacement reactions effected by organometallic reagents; the conversion of allylic alcohols into halides.

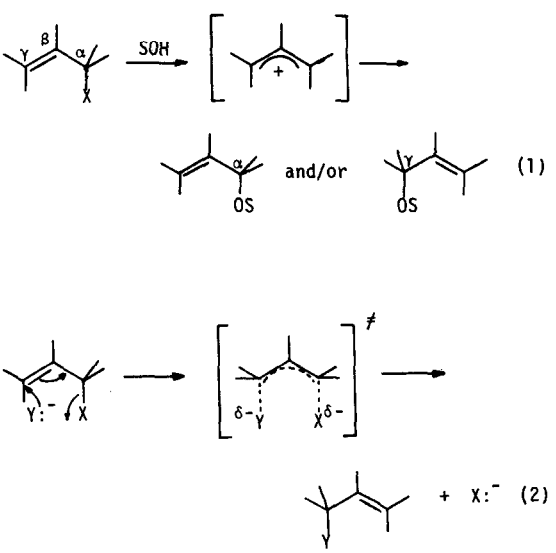
INTRODUCTION

Allylic compounds have been of synthetic, mechanistic, and biochemical importance for more than fifty years. Among the many fascinating aspects of their behavior, the stereo- and regiochemistry of their reactions have received considerable attention. Because there has been no comprehensive review of this topic since the 1960s,[1] it seemed appropriate to summarize recent developments in this Report. As a means of narrowing the rather vast literature in the area, three principal subjects will be reviewed. First, the stereochemistry (and, in part, the regiochemistry) of nucleophilic displacements (S_N2 and S_N2') will be discussed. Then, the many recent applications of organometallic reagents to selective C–C bond formation with allylic substrates will be covered. Finally, methods will be examined for the regioselective conversion of allylic alcohols into the corresponding halides.

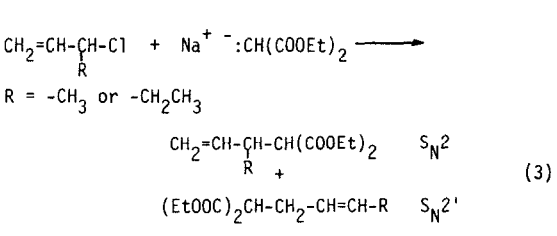
Excluded from this Report are such reactions of allylic compounds as: solvolysis and other S_N1 processes; electrophilic and free radical substitution; rearrangements (ionic and pericyclic). Also omitted are the many parallel explorations of the behavior of propargylic compounds. Every effort has been made to include all of the pertinent literature through June 1979.

NUCLEOPHILIC SUBSTITUTION: S_N2 AND S_N2' REACTIONS

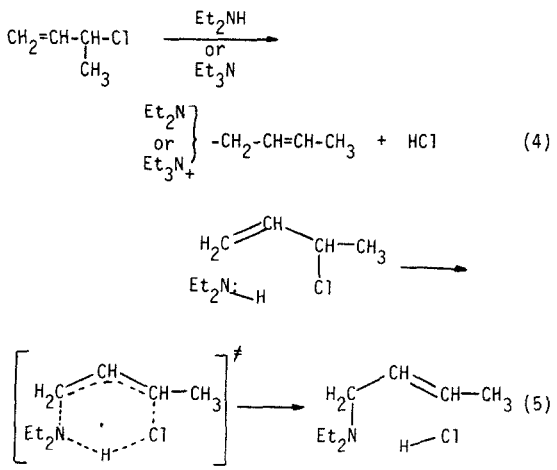
The S_N2' reaction (bimolecular nucleophilic substitution with allylic rearrangement) has had a controversial and "amusing"[2] history. In the 1920s, it was already well-established that allylic halides produce a pair of allylically-isomeric products upon S_N1 solvolysis (eqn 1). In the late 1930s, three chemists[3] independently conceived of the possibility of a *concerted* mechanism for nucleophilic formation of rearranged product, a process which was given the label S_N2' (eqn 2).



Early efforts to detect such a process using conventional anionic nucleophiles failed,[4] but in 1949 Kepner *et al.*[5] reported two examples (eqn 3). These workers were careful to exclude alternative mechanisms for the formation of "abnormal" product. At about the same time that the American chemists were uncovering this and, subsequently, other examples, the English school had concluded on experimental and theoretical grounds that an S_N2' reaction could not compete with the normal S_N2 pathway.[4d]



In the 1950s, several additional examples of S_N2' reactions were reported by groups on both sides of the Atlantic. Of particular interest was the discovery[6] that α-methylallyl chloride with diethyl- or triethylamine produces the abnormal product exclusively (eqn 4). The substantially greater reaction rate in the case of the secondary amine was attributed to a cyclic transition state in which nucleophilic "push" by N is accompanied by electrophilic "pull" by H (eqn 5). For this reason, Ingold[7] argued that such a mechanism should properly be designated S_Ni'.

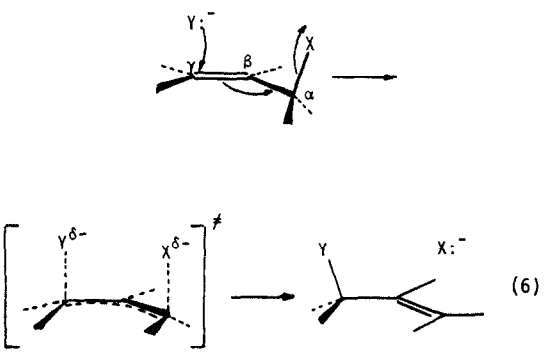


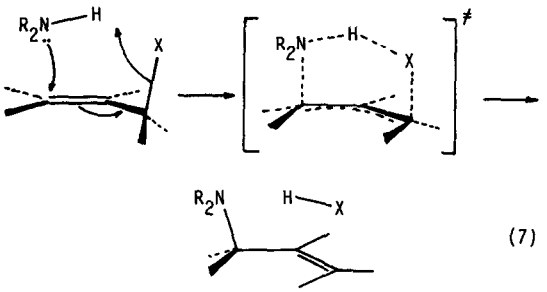
In the succeeding years, Young *et al.*[8] showed that other neutral nucleophiles (dimethyl- and trimethylamine, thiourea and N,N'-diphenylthiourea) similarly give substantial or exclusive abnormal substitution. They concluded that although the H-bonded transition state bears a major responsibility for the high rate and exclusive formation of rearranged products with secondary amines, substantial amounts of S_N2' reaction can occur in its absence. Whether, in fact, such reactions are concerted and whether the cyclic transition state is required were questions addressed in two kinetic isotope effect studies. Fry[9a] measured positive $^{12}C/^{14}C$ isotope effects at the α, β and γ carbons of α-methylallyl chloride with dimethylamine; as positive $^{35}Cl/^{37}Cl$ effect was also reported. He therefore decided that the reaction *is* concerted, nucleophilic attack by N at C_γ occurring simultaneously with π-bond migration and rupture of the C_α–Cl bond. Dittmer and Marcantonio[9b,c] studied the reactions of the same allylic chloride with deuteriated amines (Et_2ND and $Ph(CH_3)ND$) and found no difference in rate between labeled and unlabeled reagents; their conclusion was that hydrogen bonding is *not* a significant feature of the transition state.

In England, too, several examples of the S_N2' reaction were identified. Radioactive bromide or chloride were observed to effect concurrent S_N2 and S_N2' reactions on α- and γ-methylallyl bromides and chlorides, respectively.[10] Similarly, ethoxide and phenylmercaptide were shown to produce abnormal substitution with a variety of allylic halides.[11]

Thus, the UCLA and University College groups gradually came to the common belief that the S_N2' mechanism is a rational explanation for diverse examples of abnormal nucleophilic displacement, although they continued to disagree as to whose examples were the more valid demonstrations of the process. Recently, however, Bordwell[2] has begun to question the entire concept of concerted mechanisms for a wide variety of established reactions (including the S_N2' process). Based upon investigations extending over more than 25 years,[12] he has concluded that S_N2' reactions occur by nucleophilically assisted heterolysis of the allylic compound to an intermediate ion pair (or, more precisely, an ion triplet) followed by bond formation at the γ-carbon; thus the concerted process proposed in 1937–38 is a "myth". Kinetic studies of nucleophilic substitutions on saturated and allylic substrates have similarly prompted Sneen *et al.*[13] to reject the "intellectually unreasonable . . . unprovoked attack by nucleophile at the γ-position of an allylic system, three atoms removed from the leaving group" and to replace it with the stepwise ion pair mechanism. On the other hand, McLennan,[14] among others, has disputed these arguments for a discrete intermediate; instead, he favors a concerted process wherein the substrate becomes polarized as nucleophile attacks (an "ion pair more intimate than intimate") but no energy minimum is involved along the way to product. Experimental support for this idea has recently been presented for the reaction of nucleophilic solvents with allylic chlorides.[15]

Regardless of the precise timing of the bond-breaking and bond-making steps, one can still inquire into the stereochemistry of the reaction. The earliest suggestion of a stereoelectronic preference is due to Winstein[16] who postulated that nucleophilic attack occurs on the face of the allylic system syn to the leaving group (eqn 6). Although never fully elaborated in print, the essence of the argument seems to be that this approach displaces the π electrons in such a direction as to allow them to attack the C_α–X bond from the rear. Clearly, syn attack would be required (regardless of stereoelectronic considerations) in those cases for which a cyclic transition state has been implicated (eqn 7).

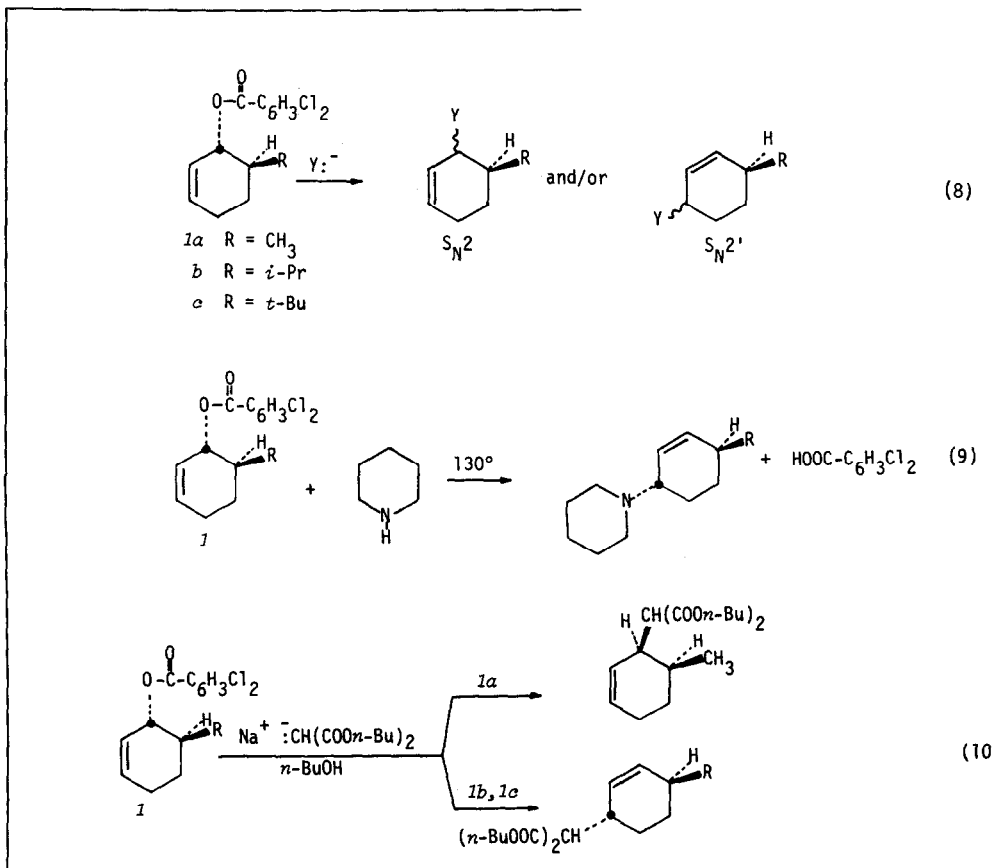




(7)

Subsequent theoretical studies have, for the most part, supported the syn attack notion. Fukui,[17] employing a variety of qualitative molecular orbital methods, reasoned that syn approach of nucleophile would always be favored. The same conclusion was reached by Drenth,[18a] Miller,[18b] Mathieu[18c,d] and Jefford.[18e,f] Anh,[19] treating the S_N2' transition state according to the Woodward-Hoffmann analysis of sigmatropic reactions, made the interesting prediction that a fully synchronous process would occur in the anti (or antarafacial) mode; only in those cases where leaving group departure is advanced relative to nucleophilic attack (but still a concerted process) would the syn (or suprafacial) mode be preferred. Liotta[20] employed an orbital distortion technique to predict that the S_N2' stereochemistry would be preferentially syn; he rationalized the contrary cases of anti attack by organometallic reagents on 1,3-cyclohexadiene monoepoxide in terms of a single-electron-transfer mechanism. Finally, Yates *et al.*[21] described *ab initio* and semiempirical molecular orbital calculations which led them to postulate that neutral nucleophiles would attack in syn fashion but that the approach of anionic nucleophiles would be anti.

Experimental evidence bearing on the stereochemical question is meager and often contradictory. In the first (and, until recently, the definitive) study of the process, Stork and White[22] examined the reactions of nucleophiles with *trans*-6-alkyl-2-cyclohexen-1-yl 2,6-dichlorobenzoates (**1**). The alkyl group served as a positional marker for distinguishing S_N2 and S_N2' reactions, as a stereochemical marker for both reactions, and as a steric impediment to S_N2 reaction (eqn 8). Reaction of **1a**, **1b** and **1c** with piperidine proceeded regio- and stereospecifically to the syn S_N2' product (eqn 9). On the other hand, di-n-butyl malonate gave mixed results: for **1a**, only inverted S_N2 product was observed; with the bulkier alkyl groups of **1b** and **1c**, syn S_N2' reaction was the exclusive outcome (eqn 10). All reactions obeyed second-order kinetics, and various alternative formulations (S_N1; S_N2 followed by rearrangement; etc.) were excluded.



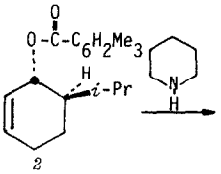
(8)

(9)

(10)

Stork and Kreft[23] have recently re-investigated the reaction of isopropyl derivative **1b** with piperidine and found minor amounts of inverted S_N2 product and what appeared to be anti S_N2' material; the latter was shown to be an artifact, arising from prior allylic

rearrangement of the dichlorobenzoate followed by S_N2 reaction; the same observations were made by Dobbie and Overton.[24] In contrast, the less reactive cyclohexenyl mesitoate displayed no tendency to rearrange and, so, its behavior with various nucleophiles was studied.[23] Reaction of *trans*-mesitoate **2** with piperidine gave exclusively S_N2' product which was almost entirely syn material (eqn 11). Similarly, *cis*-mesitoate **3** yielded syn S_N2' product and, not surprisingly, inverted S_N2 compound (eqn 12). Changing the nucleophile to sodium propanethiolate, however, gave quite different results. Ester **2** afforded mostly inverted S_N2 product (68.5% in refluxing 1-butanol, 60% in hexamethylphosphoramide) along with syn S_N2' material (28% in both solvents) and considerable amounts of anti S_N2' compound (3.5% and 12%, respectively). Ester **3** with the same reagent in 1-butanol yielded mostly inverted S_N2 product (50%), but now the anti S_N2' material (32.5%) was predominant over the syn (17.5%). Finally, under solvolytic conditions (refluxing propanethiol), **2** and **3** each gave substantial quantities of all four substitution products (i.e. inversion and retention at both C_α and C_γ).



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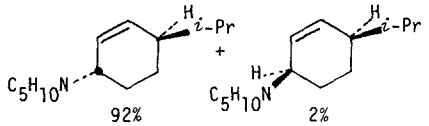
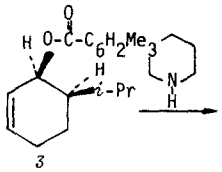


92% 2% (11)



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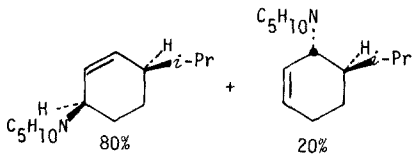
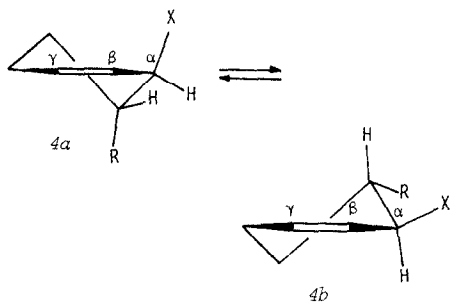


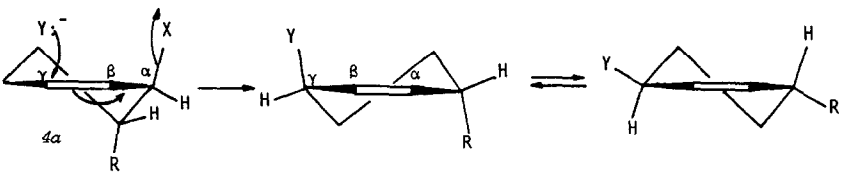
80% 20% (12)

The applicability of these results to a stereochemical generalization for all S_N2' reactions is doubtful because a cyclohexenyl system has an inherent conformational bias which can force syn attack, independent of any stereoelectronic preference that the reaction may have. Esters **1** and **2** exist as a rapidly equilibrating pair of half-chair conformations (eqn 13). Although the position of equilibrium is irrelevant to the argument which is presented below, it is useful to note that diaxial conformation **4a** is not greatly disfavored relative to diequatorial **4b**. It is well-known that an axial C_4 substituent in cyclohexene suffers less repulsion than in a cyclohexane;[25] at the same time, a quasi-axial electronegative C_3 substituent is actually favored relative to the quasi-equatorial position.[26] One can therefore estimate that although the energy of **4a** is raised by 0.8 kcal/mole (the value for the single diaxial methyl-hydrogen interaction in 3-methyl-*exo*-methylenecyclohexane[27]), it is lowered by 0.45 kcal/mole (the known preference for a quasi-axial acetoxy group[26a]), yielding a net increase in energy of but 0.35 kcal/mole. Conformation **4B** experiences a ***gauche*** methyl–acetoxy interaction; although the two bonds do not have a perfect diequatorial relationship, the magnitude of the repulsion should be about 0.35 kcal/mole (one-half of the value for axial acetoxycyclohexane[26a]). Thus, conformations **4a** and **4b** have approximately equal steric difficulties and one can anticipate significant populations of both.



4a *4b* (13)

Regardless of the position of equilibrium, one can make a strong case for the proposition that all S_N2' reaction proceeds from conformation **4a** whose C_α–X bond is nearly parallel to the p-orbitals at C_β and C_γ. Thus, when heterolysis begins (either in advance of or synchronously with nucleophilic attack) the developing p-orbital at C_α is better able to overlap with the π system, allowing smooth formation of the C_β–C_α π-bond in the product (eqn 14). The same sort of argument was first advanced by Goering and Josephson[28a] in 1962 for the cleavage of protonated cyclohexenols (and for the reverse reaction, attack by water on a cyclohexenyl cation) and has received overwhelming experimental support.[28b] Granted that the reactive species is conformation **4a**, the question is simply whether attack from above (syn) or below (anti) is preferred (eqn 15). Because syn transition state **5a** leads to a more stable half-chair conformation while anti transition state **5b** resembles a boat, the former should be the predominant pathway to product; naturally, the initially formed diaxial half-chair will undergo conformational inversion to the more stable diequatorial form (eqn 14). Toromanoff[29] has used a more sophisticated conformational analysis, but has come to the same conclusion: whenever the leaving group is quasi-axial, syn stereochemistry is to be expected; on the other hand, if the leaving group is quasi-equatorial, a change to anti attack is likely. Eisenstein *et al.*[30] have performed quantum mechanical calculations to similarly argue that attack of either nucleophiles or electrophiles at C_γ of a conformation like **4a** will occur from above (*anti*-parallel or axial approach). In summary, the syn behavior of esters **1–3** may have very little to do with the inherent stereoelectronic predilections of S_N2' reactions.



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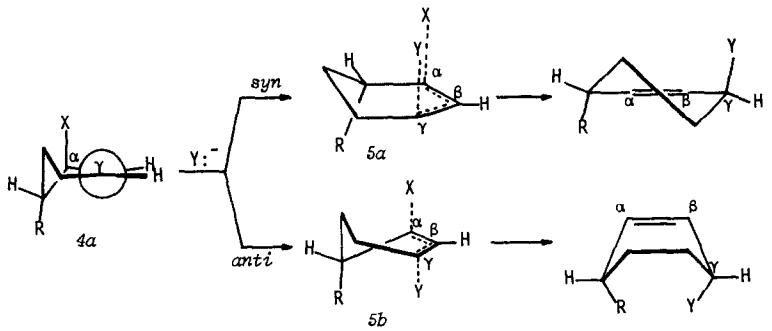
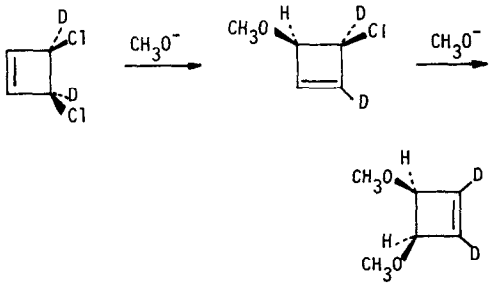


(15)

Stork and White[22b] favored reaction via conformation **4b** and noted that, whereas the normally written 6-membered H-bonded transition state between piperidine and the quasi-equatorial leaving group would be precluded, a cyclic 8-membered arrangement involving the ester CO would be possible. The importance of such H-bonding, they suggest, may well be overrated, given that α- and β-chlorocodide, each having a rigid structure with quasi-equatorial chlorine, undergo facile syn S_N2' reaction with piperidine in a kinetically second-order process[31] (eqns 16 and 17). However, data on such frozen structures are not necessarily applicable to conformationally mobile systems in which the leaving group can become quasi-axial. In fact, models very clearly indicate that the lower face of the double bond in α- and β-chlorocodide, **6** and **7**, is quite hindered; thus, both S_N2 attack with inversion and anti S_N2' reaction are retarded, leaving piperidine no choice but to give syn S_N2' product.

chlorocyclobutene-3,4-d_2 undergoes consecutive syn S_N2' displacements with methoxide ion (eqn 18). What is especially intriguing is that the first attack by nucleophile occurs on the side of the molecule which is sterically and electrostatically hindered by the non-reacting chlorine; similarly, attack by the second methoxide is also syn despite the presence of a *cis*-methoxy group.



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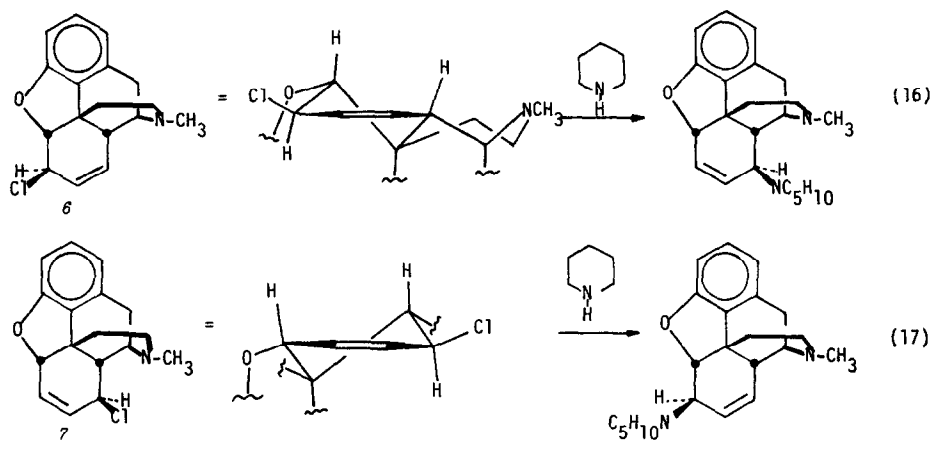


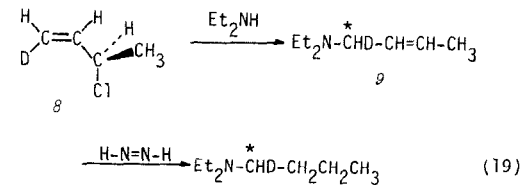
(16)

(17)

There is, however, one stereochemical study of the S_N2' reaction of a cyclic substrate which is not subject to reservations arising from conformational ambiguity. Kirmse *et al.*[32] found that *cis*-3,4-di

It was specifically to avoid conformational qualifications of the sort developed above that Magid and Fruchey[33] chose an acyclic substrate to investigate the S_N2' stereochemistry. Stereospecifically

deuterated optically active (*R*)-chloride **8** reacted with diethylamine to give a 99:1 mixture of S_N2' and S_N2 products; the rearranged product proved to be a 95:5 mixture of *E* and *Z* allylic amines **9** (eqn 19). Diimide reduction of the double bond gave optically active N,N-diethyl-1-aminobutane-1-*d* whose specific rotation was compared with that of an authentic sample synthesized from optically pure 1-butanol-1-*d*. The conclusion was that (*E*)- and (*Z*)-**9** were formed with at least 96% syn stereospecificity (eqn 20). Unlike the cyclohexenyl cases discussed earlier, chloride **8** has two reactive conformations, each with the C_α–Cl bond parallel to the p-orbitals at C_β and C_γ, which are each attacked in syn fashion. Similarly, reaction of the enantiomeric (*S*)-chloride with dimethylamine or piperidine gave S_N2' products with at least 95–99% syn preference.



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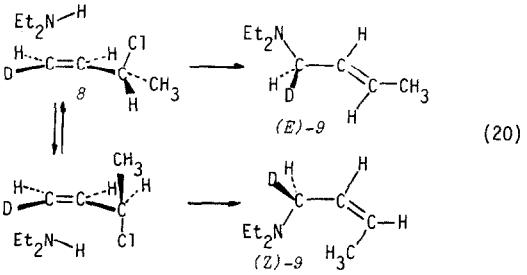
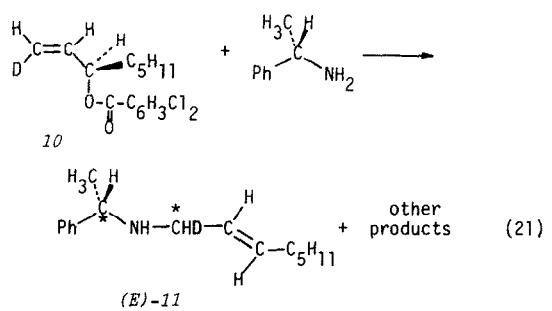


(20)

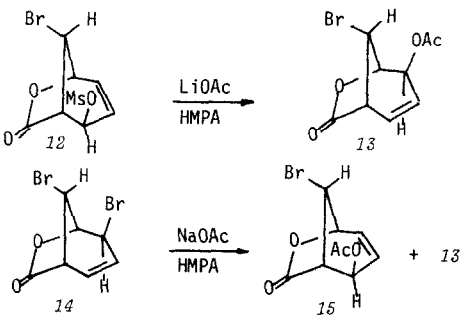
A closely related study was subsequently reported by Oritani and Overton.[34] Stereospecifically deuteriated (*R*)-2,6-dichlorobenzoate **10** reacted with (*S*)-α-methylbenzylamine to produce 80% of γ-attack product (a 19:1 *E*:*Z* isomeric mixture) along with 20% of α-attack (nearly 100% inverted) (eqn 21). NMR analysis of the diastereomeric centers in (*E*)-**11** revealed a preferential (but not overwhelming) syn:anti ratio of 62:38. Similarly, (*S*)-**10** with (*S*)-amine or (*S*)-**10** with (*R*)-amine gave syn:anti ratios of 62:38 and 59:41, respectively. Finally, reaction of the 2,6-dichlorobenzoate related to chloride (*R*)-**8** with (*R*)-amine gave syn:anti = 64:36. In these systems, therefore, the syn process is favored over the anti by only about 0.5 kcal–mole.



(21)

It is difficult, at this time, to rationalize the very different results obtained from chloride **8** and ester **10**. Obviously, the methods for determining the syn–anti ratios are different, but this should not cause the discrepancy. Oritani and Overton[34] suggest that the chloride's high preference for syn displacement might be due to more effective H-bonding than is possible with the ester; however, the lack of isotope effect with R_2NH–R_2ND,[9b,c] the facile syn displacement of quasi-equatorial chlorine in the chlorocodides,[31] and the ready abnormal displacement reactions with tertiary amines[6,8] all tend to discount the importance of H-bonding. An intriguing suggestion by Whiting[35a] is that the secondary amines employed with chloride **8** differ in polarity from the primary amine used with ester **10**; indeed, allylic chlorides do behave differently with such amines, and the α:γ attack ratios can be rationalized based on polarity differences of the amines as solvents.[35b] It is also possible that the timing of bond-making and -breaking is different for chloride **8** and ester **10**, the latter behaving more S_N1-like by virtue of having a better leaving group. Because of uncertainties in the maximum rotations of chloride **8** and of the saturated amines derived from **9**, only lower limits (>95% syn) were able to be assigned to the stereoselectivity of the reaction; should 5% of anti process be occurring, the syn preference here would be only 1.7–2.0 kcal/mole (depending on reaction temperature), not very different from the 0.5 kcal/mole found with ester **10**.

Aside from organometallic reactions (see next section), the only other stereochemical study of an *inter*molecular S_N2' reaction is due to Ikota and Ganem.[36] Mesylate **12** is cleanly and quantitatively converted by acetate into syn S_N2' product **13** in a kinetically second-order process (eqn 22). Two qualifications of this result should be noted. First, mesylate **12** (a cyclohexenyl derivative) might be subject to conformational influences not encountered with acyclic compounds **8** and **10**; in fact, the *exo* side of **12** is undoubtedly more exposed than is the *endo*.[37] Second, the closely related bromide **14** gives equal amounts of acetates **13** and **15** under essentially the same reaction conditions (eqn 23);[36] since S_N2 reaction with retention of configuration is unprecedented, the formation of **13** must be due either to prior allylic rearrangement of starting bromide followed by syn S_N2' reaction on the allylic pair or to intervention of the Bordwell–Sneen ion pair mechanism;[2,12,13] alternatively, neighboring group participation by oxygen in **14** is a possibility. If either of the latter explanations were correct, then the concerted S_N2' mechanism postulated for mesylate **12** is less secure.



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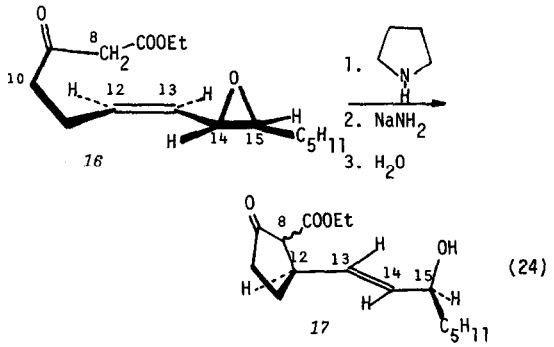
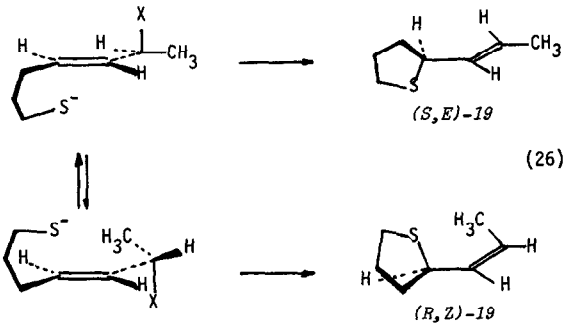
Several *intra*molecular S_N2' reactions have been studied and have yielded mixed results as to a definitive preference for syn or anti attack. Martel *et al.*[38] used the anticipated syn predisposition to design a stereospecific synthesis for chiral centers C_{12} and C_{15} and for double bond C_{13}–C_{14} in the prostaglandin nucleus. Racemic (*Z*)-alkene, (*E*)-epoxide **16** (shown as a single enantiomer) can exist in *transoid* and *cisoid* conformations about C_{13}–C_{14}. Because the former is more stable and because the resulting product **17** has an *E* double bond, it was expected[39] that S_N2'-type cylization, if syn, would produce C_{12} and C_{15} with *R,S* (shown) and *S,R* stereochemistry (eqn 24). Attempts to induce cyclization of keto ester **16** failed to proceed cleanly, owing mostly to formation of O-alkylated material. On the other hand, preparation of the pyrrolidine enamine followed by proton removal by $NaNH_2$ (or other strong base) gave **17** in high yield, accompanied by small amounts of cyclopropane product (bonding from C_{10} to C_{12}).



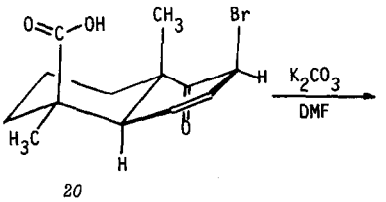
(24)

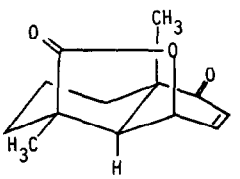
In contrast, anti stereochemistry was observed by Stork and Kreft[40] in a very similar cyclization process. Treatment of (*S*),(*E*)-mesitoate **18** with $LiOCH_3$–THF afforded a 52% yield of a 93:7 mixture of (*E*)-**19**:(*Z*)-**19** (eqn 25); with $LiOCH_3$–HMPA or with $NaOCH_3$–THF, the *E*:*Z* product ratio was 68:32 or 74:26, respectively. Comparison with an authentic sample of (*S*)-**19** having *E*:*Z* = 97:3 allowed the authors to conclude that "cyclization... has taken place very largely, and possibly entirely, by addition of the thiolate ion anti to the departing mesitoate" (eqn 26). Because the *E*:*Z* ratios of cyclized material and authentic **19** were not identical and because the optical purities of reagents were not accurately known, it is impossible to know precisely the stereoselectivity of the reaction. What is striking, however, is the change in stereochemistry from the Martel case (eqn 24), a change which had been presaged by the considerable proportion of anti displacement by propanethiolate ion on mesitoate esters **2** and **3**.[23]



(26)

Another example of stereochemical reversal in S_N2' cyclizations comes from experiments reported by Welch *et al.*[41] and Schultz *et al.*[42] In the former, deprotonation of carboxylic acid **20** gives syn γ-attack (eqn 27) whereas in the latter, the conjugate base of lactone ester **21** cyclizes by anti reaction (eqn 28). Of course, neither **20** nor **21** can partake of the alternative stereochemical mode, but the fact that both reactions occur in high yield and under mild conditions is noteworthy.





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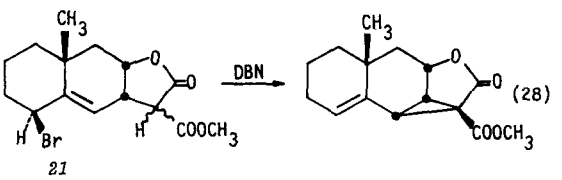
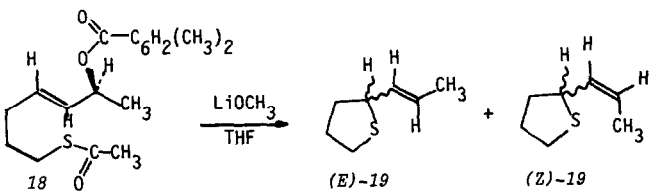


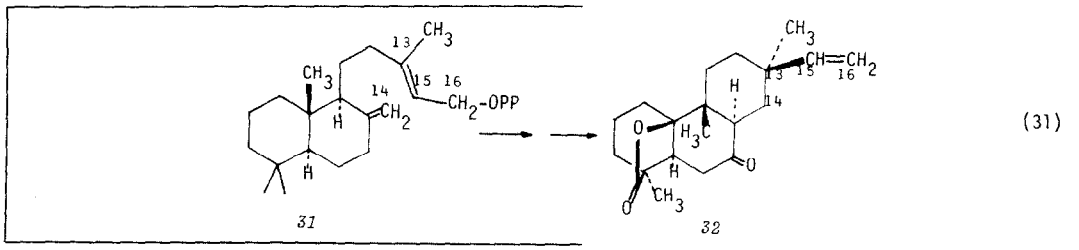
(28)

Keeping in mind the caveat discussed earlier concerning *inter*molecular S_N2' reactions on cyclohexenyl derivatives, a pair of *intra*molecular reactions provides an interesting contrast in stereochemical behavior. Chliche *et al.*[43] examined the cyclization of carboxylic acids **22–25** under basic and neutral conditions (eqn 29). In aqueous acetone containing a slight excess of pyridine, the relative



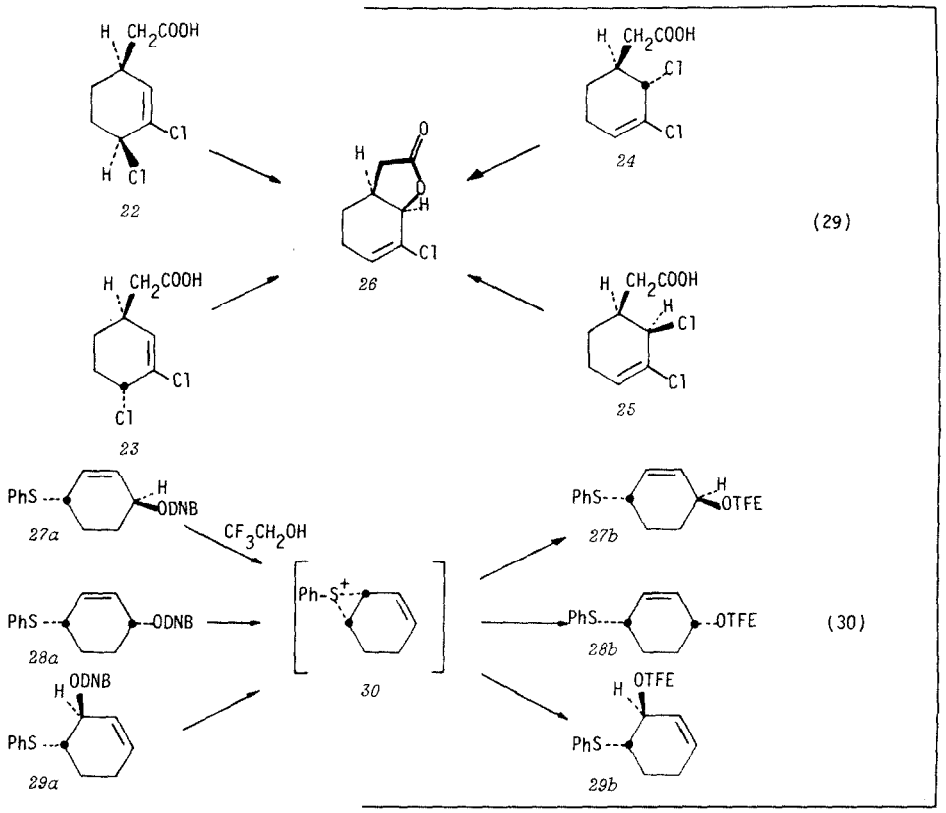
(25)

rates of formation of **26** from **22**:**23**:**24**:**25** were 1:0.004:3:0. In aqueous acetone but in the absence of pyridine, the reaction was about 100 times slower and the relative rates of cyclization were 1:0:3:0. As expected, S_N2 reaction by either carboxylate ion or unionized acid occurred only when inversion of configuration could be achieved (compare **24** and **25**). As for S_N2' reaction, syn cyclization of **22** is enormously preferred relative to anti reaction of **23** under both sets of conditions; this conflicts with the theoretical prediction[21] that neutral nucleophiles would prefer the syn mode but anionic nucleophiles the anti. Uebel *et al.*[44] found that allylic dinitrobenzoates **27a**, **28a** and **29a** in 2,2,2-trifluoroethanol gave a nearly identical 1:1:5 distribution of solvolysis products **27b**:**28b**:**29b** (eqn 30). A common intermediate, episulfonium ion **30**, was thereby indiacated. The relative reaction rates of **27a**:**28a**:**29a** were found to be 5.11:1.00:109. Thus, there is but a slight preference for anti S_N2' formation of **30** from **27a** and essentially no anti:syn preference for nucleophilic S_N2' opening of **30** to **27b** or **28b**.[45]



(31)

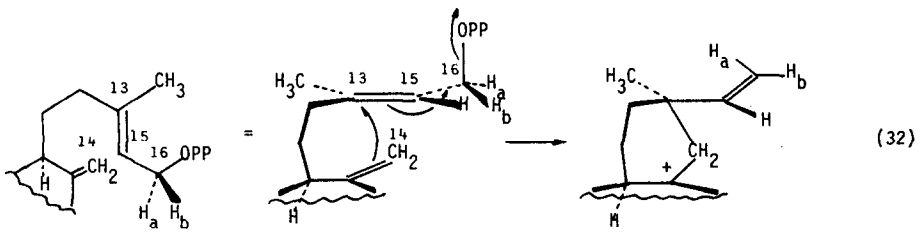
An S_N2' olefin cyclization like that of eqn (31) but occurring non-enzymatically has been studied by Gottfredsen *et al.*[48] (−)-Linalool (and its esters) is transformed under acidic conditions into (+)-α-terpineol (eqn 34). Through the use of ^{2}H-labeled linalool, hydrolysis of its *p*-nitrobenzoate was determined to proceed according to eqn (35) (once



(29)

(30)

The stereochemistry of a biochemical S_N2' reaction has been established in an elegant study by Cane and Murthy.[46] Biosynthesis of rosenonolactone (**32**) is believed to involve precursor **31** (derived from mevalonate through geranylgeranyl pyrophosphate) in which formation of the C_{14}–C_{13} bond is formally an intramolecular S_N2' process; concurrent hydride and methide shifts generate the skeleton of **32** (eqn 31). The use of stereospecifically ^{2}H-labeled mevalonate (both enantiomers) allowed the assignment of anti stereochemistry (at least 80%) to the cyclization step (eqn 32). Not unrelated is a biological S_Ni' reaction, the conversion of *trans,trans*-farnesyl pyrophosphate into nerolidyl pyrophosphate, whose stereochemistry has been elucidated by Cane *et al.*[47] Through the use of labeled (1-^{2}H, ^{3}H)-(*R*)-farnesyl pyrophosphate[47a] and (1-^{18}O)-farnesyl pyrophosphate,[47b] syn transposition via the biochemical equivalent of an intimate ion pair has been established (eqn (33) with the two experiments superimposed).



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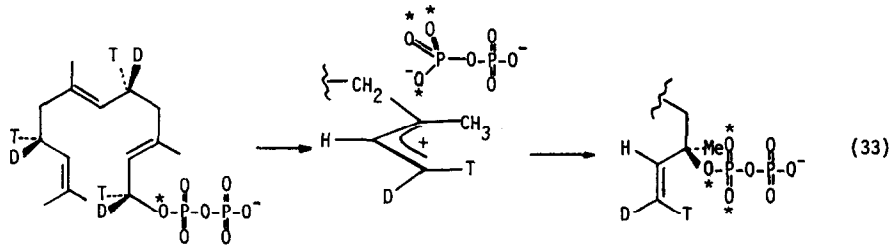
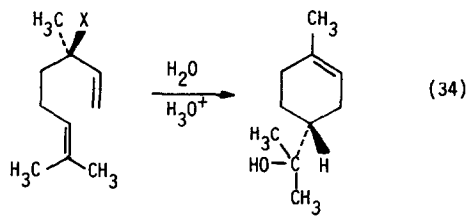


(33)

again, two experiments superimposed). Like the biological version, this reaction also occurs with about 85% anti stereochemistry.



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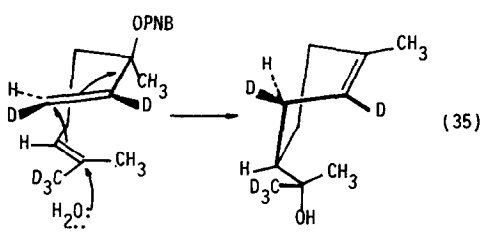
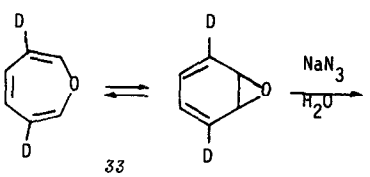


(35)

Many of the theoretical reports on S_N2' stereochemistry[17–20] have also touched on related reactions such as the S_N2'' and the E2′ (or 1,4-elimination). Although the experimental data are sparse, some information is available on the course of both processes. Chemists at NIH and MIT have used oxepin–benzene oxide-3,6-d_2 (**33**) to study the mode of reaction of arene oxides with nucleophiles.[49] Most of the experiments involved organometallic reagents (and will be described in the next section) but several reactions with simple nucleophiles are of interest. Reaction of **33** with alkoxide or phenylmercaptide proceeds exclusively by S_N2 inversion attack at the epoxide carbon. Although ammonia and amide ion proved to be unreactive, aqueous sodium azide led to the *trans*-azido alcohol whose labeling pattern revealed a 60:40 mixture of S_N2 and S_N2'' pathways (eqn 36); as anticipated by theory, the latter process has occurred anti. In the only reported example of a base-catalyzed E2′ reaction, Hill and Bock[50] have demonstrated predominant (85–90%) *syn* stereoselectivity, in agreement with theoretical predictions (eqn 37). There is a well-known biochemical version of the E2′ reaction in the conversion of shikimic acid (**34**) via enolpyruvate **35** into chorismic acid (**36**) (eqn 38). When each epimer of stereospecifically labeled **34**-*d* was subjected to the enzymatic system (eqn 39), 98–100% loss of the anti D or H was observed;[51a] a related study with tritiated material[51b] yielded the same result. Thus, either the enzymatic 1,4-elimination has proceeded anti (in contrast to theory an to the chemically induced process, eqn 37) or an alternative mechanism obtains.[46b] One of these[51b] is of particular interest to this Report since it involves the use of a nucleophilic group on the enzyme to perform a syn S_N2' reaction on **34**-*d* yielding an intermediate from which conventional anti 1,2-elimination affords **36**.



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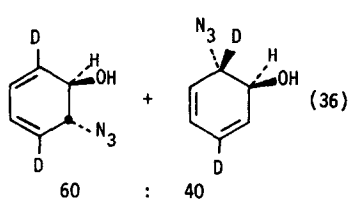

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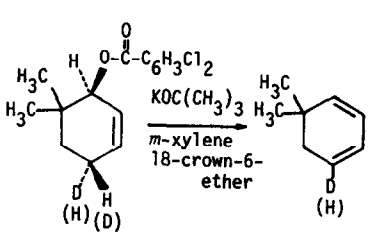

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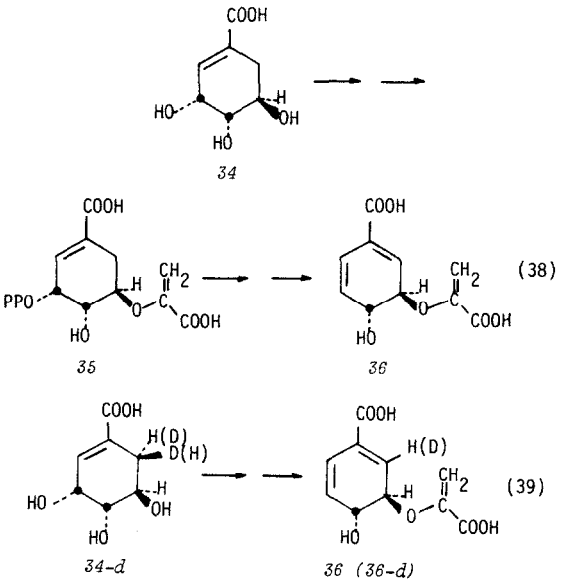
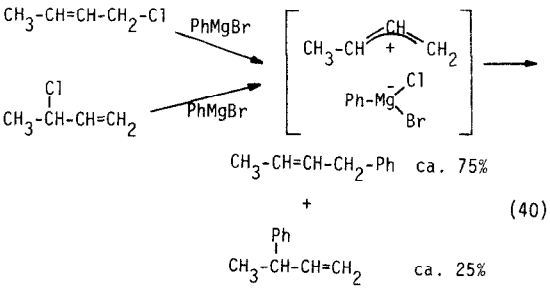


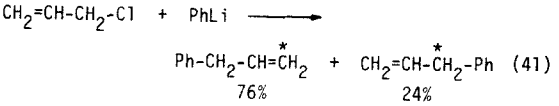
REACTIONS WITH ORGANOMETALLIC REAGENTS

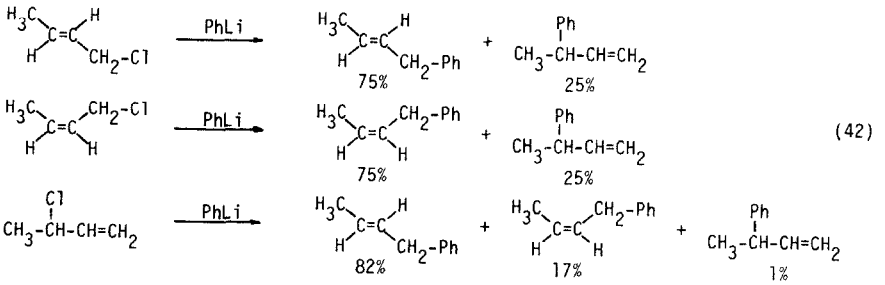
The abecedarian reaction for organic synthesis is the formation of the C–C bond. Displacement reactions using organometallic reagents have been used for this purpose for years. With the realization that the allyl moiety is an integral feature of many natural products and biosynthetic intermediates,[52] it became important to develop methods which would lead to controlled C–C bond formation at either the α- or γ-position of an allylic substrate. The recent accomplishments in this area constitute the material for this section of the Report.

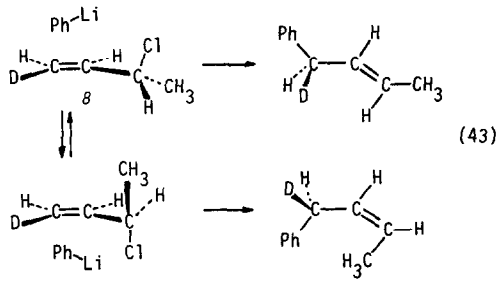
Most of the early mechanistic studies focused on the coupling reactions of allylic halides. To account for the nearly identical product distribution from the reactions of phenylmagnesium bromide with α- and γ-methylallyl chloride, Wilson *et al.*[53a] suggested the formation of a common ion pair intermediate (eqn 40). The same sort of mechanism was favored by Cristol *et al.*[53b] to justify the identical product mixtures from the above allylic chlorides with phenyllithium. Czernecki *et al.*[54] similarly invoked ion pair intermediates in their very thorough study of the reactions of *cis*- and *trans*-crotyl chloride and α-methylallyl chloride with a variety of alkyllithiums, -sodiums and -magnesium halides. Finally, the ion pair route was used by Wawzonek *et al.*[55] to explain the apparent loss of double bond geometry from *cis*- and *trans*-crotyl chloride with phenyllithium or -sodium. On the other hand, allylic *radicals* have been advanced as the reactive intermediate in the reactions of allylic halides with either Grignard reagents[56a] or nitro- and ester-stabilized carbanions;[56b] free radicals have also often been suggested as discrete intermediates in the coupling of organometallic reagents with alkyl halides, although some very recent data[56c] seem to suggest that at least some of these reactions have all of the characteristics of a conventional concerted S_N2 process.



The proposed involvement of a resonance-stabilized allylic cation or radical was disputed by Magid and Welch[57] who found that allyl chloride, labeled at the α-position with either ^2H or ^{14}C, did not yield the required 50–50 mixture of α- and γ-coupled products with phenyllithium (eqn 41). Further evidence against a symmetrical intermediate in the reaction of allyl-1-^{14}C chloride with allylsodium[58a] or diphenylmethylpotassium[58b] has been published, although, interestingly, both of these reactions give exclusive α-attack (*cf*, the 3:1 $\gamma:\alpha$ attack ratio with phenyllithium in eqn 41). Furthermore, Magid *et al.*,[59] showed that not only are identical mixtures *not* obtained in the reaction of phenyllithium with α- and γ-methylallyl chloride[53b] but also there is *no* loss of double bond stereochemistry from the *cis*- and *trans*-γ-methyl compounds as had been claimed[55] (eqn 42). Similarly, there was no evidence for involvement of an allylic cation or radical in the reactions of phenyllithium with β-methylallyl-1,1-d_2 chloride ($\alpha:\gamma$ attack = 57:43), with *cis*- and *trans*-β,γ-dimethylallyl chloride (double bond geometry is preserved in the α-coupling products), and with α,β-dimethylallyl chloride (product mixture different from that of the β,γ-dimethyl isomers). All of these data[59] are most economically explained by a concerted mechanism for the phenyllithium–allylic chloride reaction, an idea which receives additional support[60] from the nearly exclusively syn stereochemistry in the γ-coupling products from phenyllithium with (*R*)-allylic chloride **8** (eqn 43).



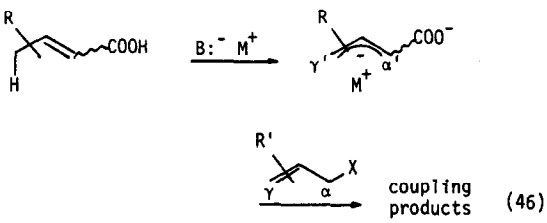




(43)

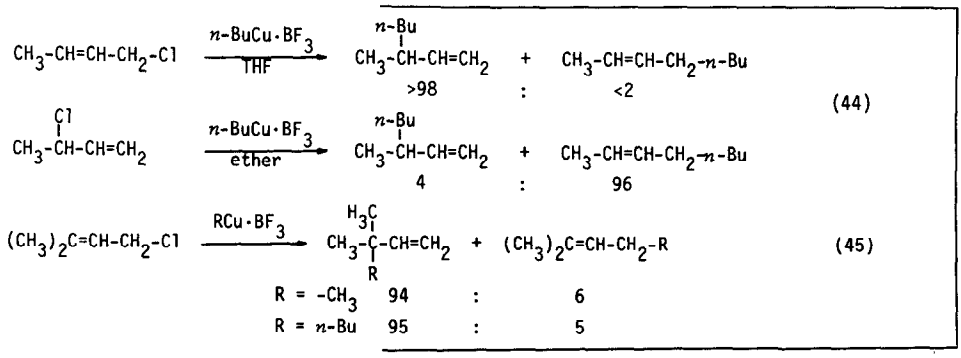
Many workers have employed the coupling reaction of allylic halides with a variety of organometallic reagents for synthetic purposes,[61] but with the exception of primary halides which give mostly α-attack[61b-g] or hindered substrates which proceed γ,[61a] the lack of regioselectivity has precluded wider acceptance of the method. There are, however, a few recently reported procedures which appear promising enough to merit detailed comment. In a somewhat sketchy first report,[62] Miyaura *et al.* have described the behavior of copper(I) tetraalkyl borates with allylic halides. In the one example for which regiochemistry could be determined, cinnamyl chloride gave a 96% yield of exclusively γ-product when treated with $[(C_3H_7)_3BCH_3]Cu$ in THF; interestingly, only the n-propyl group was delivered to the organic substrate. The high yield ($>90\%$) reaction of various alkyl copper reagents with allylic halides was investigated by Maruyama and Yamamoto[63] who found that the 74–26 γ–α attack ratio on cinnamyl chloride with CH_3Cu could be increased to about 90–10 when CH_3Cu was complexed with a trialkylborane and, most significantly, to $>99.5-<0.5$ when complexed with BF_3. In fact, $RCu{\cdot}BF_3$ reagents, in general, were found to transfer R to the γ-position with very high regioselectivity, as illustrated for the pair of allylic chlorides in eqn (44). Even with a γ,γ-disubstituted allylic halide, high γ–α ratios were observed (eqn 45).

attempts to control regiochemistry on the allylic halide. Whereas the copper salt derived from α,β-unsaturated acids gave nearly exclusive γ'–γ coupling with allyl-3-*d* bromide, the hindered γ,γ-dimethylallyl bromide gave only γ'–α product; furthermore, β,γ-dimethylallyl bromide gave a 34–66 mixture of γ'–α and γ'–γ products while its allylic isomer, α,β-dimethylallyl mesylate, afforded a 26–74 ratio of γ'–α and γ'–γ materials. High regioselectivity, however, was observed with the more hindered α-butyl-β-methylallyl mesylate which gave better than 95% γ'–γ product. A further complication is the question of *E*–*Z* stereochemistry of both double bonds in the product. Thus, even in those reactions that gave regiochemically clean results, stereoisomeric mixtures were often encountered.



(46)

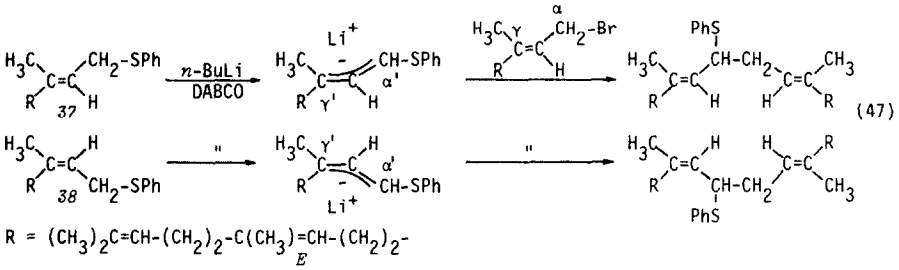
An attractive alternative for solving the above-described regio- and stereochemical problems was reported by Biellmann and Ducep.[66] α-Mercapto allylic anions were found to alkylar and allylate selectively at $C_{\alpha'}$; in addition, these anions proved to be configurationally stable. Thus, deprotonation of (*E*,*E*)-farnesyl phenyl sulfide (**37**) followed by reaction with (*E*,*E*)-farnesyl bromide gave exclusively the α'–α product which could be desulfurized by $Li{-}CH_3CH_2NH_2$ to (*E*,*E*,*E*,)-squalene; similarly, *E*,*Z* sulfide **38** afforded *E*,*Z*,*E*,*E* product (eqn 47). A related approach by Caates *et al.*[67] allowed the stereospecific synthesis of various nor-methyl



(44)

(45)

An additional regiochemical complication arises in the reactions of allylic halides with allylic organometallic reagents because now one has the possibility of α or γ bond formation on each reagent.[64] A partial solution to this problem was realized by Katzenellenbogen and Crumrine:[65] with regard to α'–γ' selectivity on the organometallic moiety (eqn 46), it was found the lithium salt gave 98–100% α' bonding whereas the copper salt formed bonds selectively (62–100%, depending on the other partner) at the γ' position. Less successful were derivatives of geranylgeraniol. Through a modification reminiscent of that employed by Katzenellenbogen,[65] Oshima *et al.*[68] found that the regioselectivity at *both* partners is changed to γ'–γ when lithium is replaced by copper in these thioallylic species, as illustrated in eqn (48). A third mode of coupling, γ'–α, occurs with the lithium salts of allylic borates with allylic halides (eqn 49)[69] and this can be reversed to α'–γ (α' with respect to sulfur) through the use of lithium salts of alkylthio-substituted allylic borates, as illustrated in eqn (50).[70]



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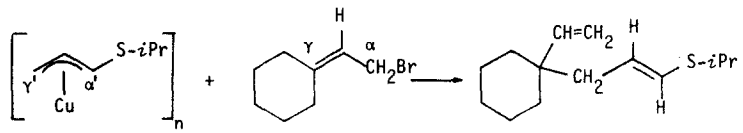

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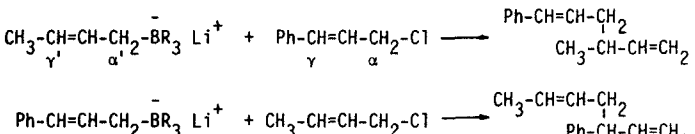

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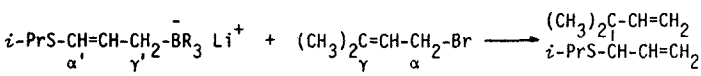
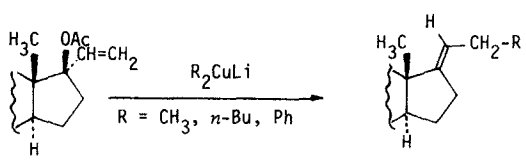


(50)

One of the most effective and best studied procedures for regiospecific reactions of allylic substrates is the coupling of lithium diorganocuprates with acetates (and related leaving groups). The reaction was discovered by Rona *et al.*[71] who found that steroidal allylic acetates underwent exclusive γ-attack, but in only fair yield, providing the (*E*)-alkene (eqn 51). In a follow-up study of the stereochemistry, Rona *et al.*[72] reported that allylic acetate **39** similarly gave the more stable (*E*)-alkene by exclusive γ-attack, but epimeric acetate **40** gave a 50–50 mixture of geometrical isomers (eqn 52); a rationalization based on population of conformations having acetate axial for stereoelectronic purposes was advanced (*cf* the arguments for conformations **4a** and **4b** in eqns 13–15).



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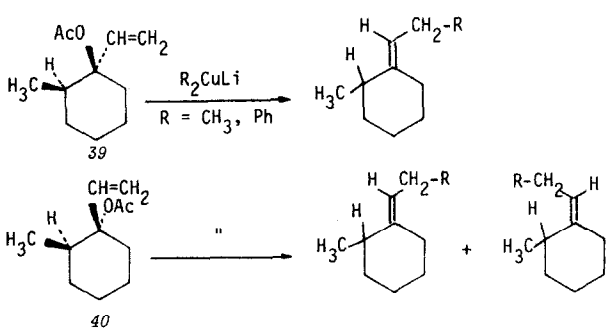
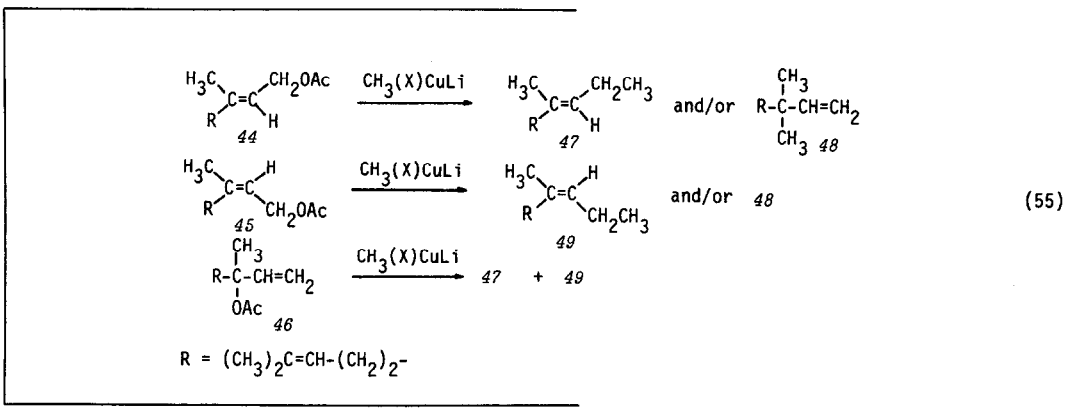


(52)

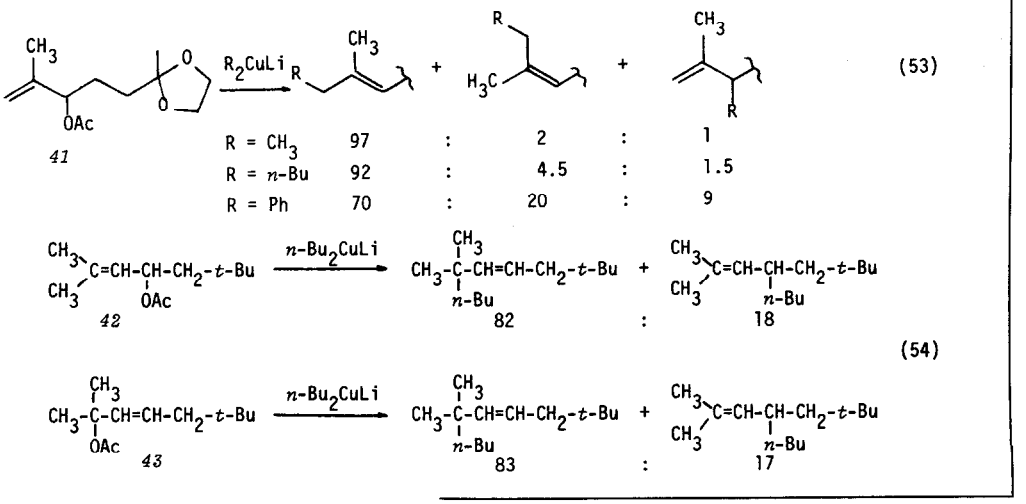
An extensive study of the regio–stereochemical aspects of the process was described by Anderson *et al.*[73a] α,β-Disubstituted allylic acetates (e.g. **41**) gave primarily γ-attack with *E* stereochemistry when the reaction was performed in ether (eqn 53); with THF as solvent, a substantial enhancement of α-attack resulted. Importantly, the allylic pair **42** and **43** gave essentially the same product composition, suggesting the formation of a common intermediate (perhaps an allylic radical) (eqn 54); thus, bond formation does not necessarily occur at the less substituted carbon of the allylic system. In a subsequent investigation, it was found that the already high *E*–*Z* and γ–α ratios of acetates having substitution patterns like that of **41** could be enhanced with poorer leaving groups (e.g. trimethylacetate) or decreased with leaving groups of lower basicity (e.g. dinitrobenzoate).[73b]

primary acetates **44** and **45** suffered exclusive γ-attack yielding **48** as the only product; tertiary acetate **46** again gave a mixture of **47** and **49**, 54:46, through γ-attack. Finally, mixed behavior was observed in the reaction of **44** with $CH_3(SPh)CuLi$ which produced a 25:75 mixture of **47** and **48**. For the case of $(CH_3)_2CuLi$, a π-allyl copper complex which retains stereochemistry and which is sterically disposed to deliver CH_3 to the less hindered carbon seems reasonable. For $CH_3(CN)CuLi$, two geometric isomers about Cu are possible in the π-allyl intermediate; the authors use this to satisfactorily explain why **48** alone is formed from **44** or **45**, but offer no rationalization for why **46** persists in giving γ-substitution products **47** and **49**.



(55)

The question of a preferred stereochemistry between leaving group configuration and C–C bond



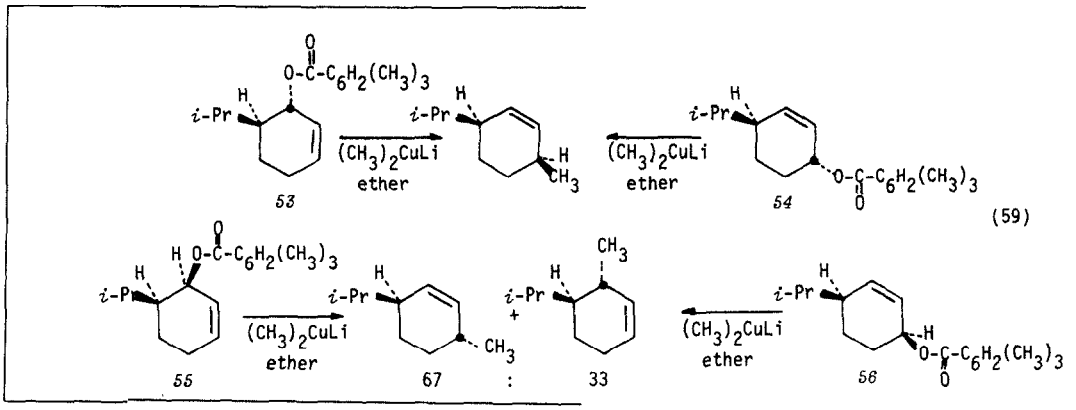
(53)

(54)

A test for the proposed intermediacy of an allylic radical was performed by Levisalles *et al.*[74] on geranyl, neryl, and linalyl acetates, **44**, **45** and **46**, respectively (eqn 55). With $(CH_3)_2CuLi$, primary acetates **44** or **45** went cleanly to α-substitution product **47** or **49** with total preservation of double bond geometry; tertiary acetate **46**, through exclusive γ-attack, produced a 60:40 mixture of **47** and **49**. A complete reversal in regiochemistry was found when the organometallic reagent was $CH_3(CN)CuLi$: now, formation was first addressed by Goering and Singleton.[75] Cyclohexenyl acetates **50** and **51** were found to react with $(CH_3)_2CuLi$ with >98% stereoselectivity to the product of anti attack (eqn 56). Furthermore, C–C bond formation occurred essentially equally at the α- and γ-carbons of the allylic system (eqn 57), the failure to find a 50–50 product ratio being attributed to a systematic error in the analytical method; unreacted acetate showed no configurational or positional change. A symmetrical

intermediate (like the allylic radical or π-allyl copper complex discussed already) would account for the regiochemistry. To explain the stereochemistry, the authors suggest that reaction occurs via a conformation whose leaving group is quasi-axial (recall the stereochemical argument[28a] invoked with regard to eqns 13–15); interestingly, however, rather than using the same stereoelectronic reasoning to argue for syn attack by methyl (as had been done earlier[28a] in the attack by water on a cyclohexenyl cation), the authors are forced to conclude that the allylic radical is sterically disposed to be attacked only from the underside (eqn 58). Perhaps a better rationalization of the results would be in terms of the π-allyl copper species. Johnson and Dutra[76] had earlier shown that lithium diorganocuprates give inversion of configuration on alkyl tosylates and proposed that

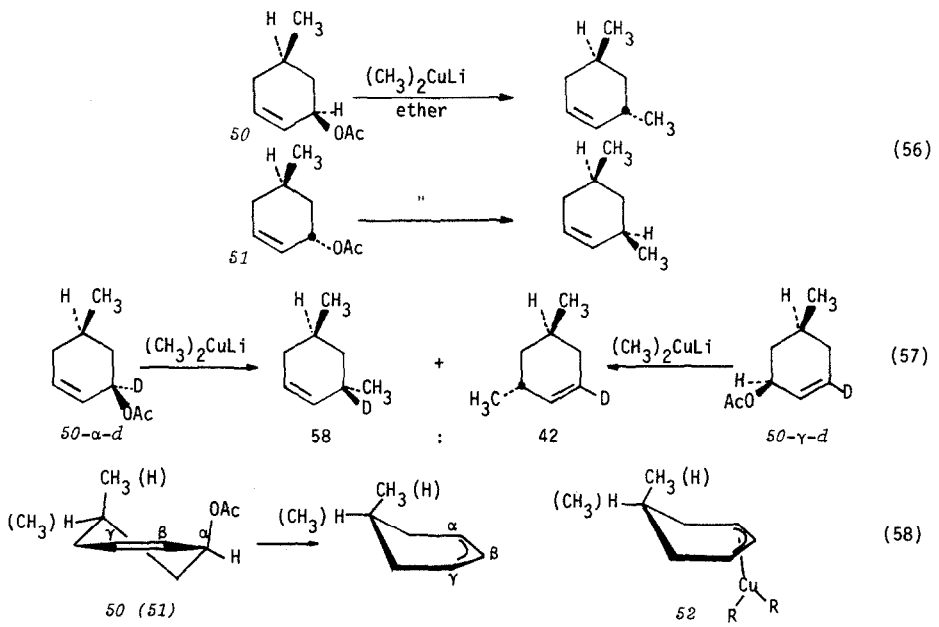
Kreft[77] examined the reaction of lithium dimethylcuprate with a set of cyclohexenyl esters which, unlike the case above, would not produce a symmetrical intermediate. As in the Goering and Singleton examples, the stereochemistry for mesitoates **53–56** was cleanly anti (eqn 59); also, as in the situation with **50**-α-*d* and **50**-γ-*d*, the regioselectivity suggests a common intermediate from *trans*-esters **53** and **54** and a different common intermediate from *cis*-esters **55** and **56**. It is apparent that a π-allyl species (like **52**) formed from **53** or **54** in which isopropyl is *cis* to copper and its ligands would have a strong predilection for delivering CH_3 to the more remote carbon; in contrast, such an intermediate from **55** or **56**, having isopropyl and copper *trans*, would be able to give comparable amounts of α and γ attack.



(59)

nucleophilic attack by R_2Cu^- followed by transfer of R from Cu to C with retention of configuration is the preferred pathway. In the present case, a π-allyl species like **52** would be consistent with the Johnson–Dutra hypothesis and with the stereochemistry observed with **50** and **51**. It is also conceivable that intermediate **52** is preceded by a σ-complex formed by inversion attack of $(CH_3)_2Cu^-$ at C_α.[74]

A remarkable influence of leaving group character on both the regio- and stereochemistry of $(CH_3)_2CuLi$ attack on a cyclohexenyl system has recently been reported by Gallina and Ciattani.[78] Compounds **57** and **58** having formate, acetate, benzoate, carbonate, or tertiary carbamate as leaving groups yielded essentially 50–50 γ–α mixtures of exclusively anti products (eqn 60), totally in keeping

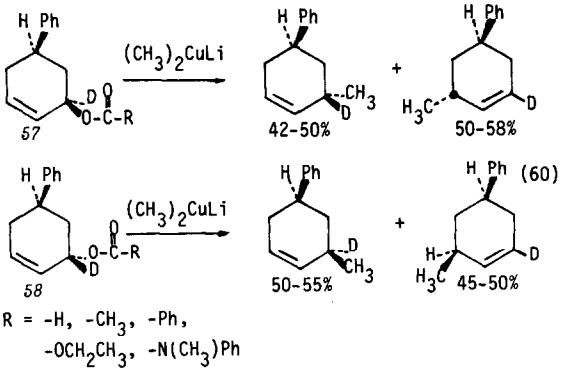


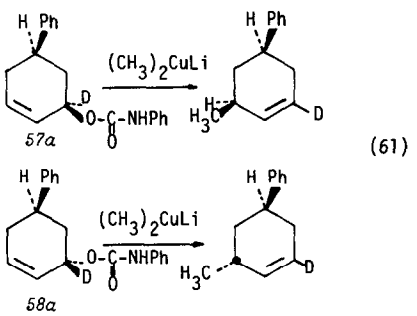
(56)

(57)

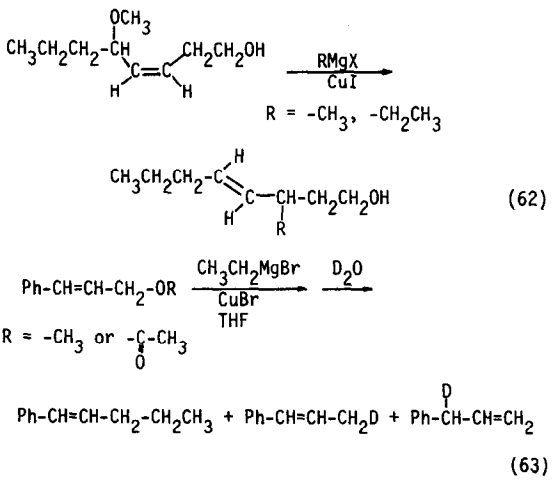
(58)

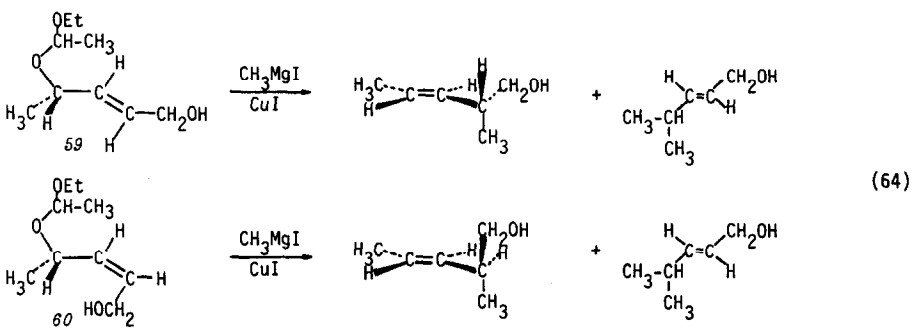
with the results of eqns (56) and (57). Completely unprecedented is the behavior of secondary carbamates **57a** and **58a**, each of which gives exclusively γ-product formed entirely by syn approach (eqn 61). The observed γ-attack is not simply a function of the ring system since the N-phenylcarbamates of nerol and linalol (see eqn 55) also give this regiospecific result. Because **57a** and **58a** possess an acidic proton lacking in the other substrates, it would appear that the leaving group is the conjugate base. In fact, for **57a** and **58a** one equivalent of $(CH_3)_2CuLi$ gives only the lithium salt; a second equivalent is required in order to observe the syn-γ displacement of eqn (61). Why this lithium salt behaves so differently from the esters and tertiary carbamate is not clear, although the authors propose (without clear rationalization) an electron-transfer mechanism for eqn (61) and an ion pair mechanism for eqn (60). In any event, it is fascinating that proton removal from an atom so remote from the allylic C–O bond can alter the course of the reaction. Certainly, other leaving groups with acidic protons will need to be studied before sound mechanistic conclusions can be reached.



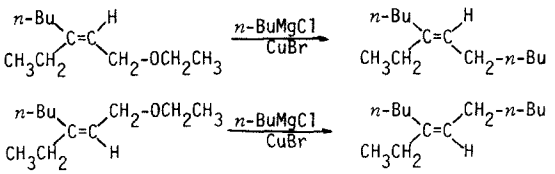


Allylic ethers are unreactive to R_2CuLi[73a] but do react with Grignard reagents in the presence of 10–20% of Cu(I) halides (eqn 62, for example).[79,80] A striking difference in the behavior of allylic ethers and esters with such reagents was described by Claesson and Sahlberg.[81a,b] Reaction of cinnamyl acetate or methyl ether with CH_3CH_2MgBr containing 10 mol% of CuBr followed by workup with D_2O gave substitution product (better than 90% α) and reduction products in an 87:13 ratio from the acetate, 10:90 from the ether (eqn 63); the allylically isomeric acetate and ether gave the same products in roughly the same amounts, thereby suggesting a common intermediate. A σ-bonded copper(III) species with acetoxy or methoxy as one of the ligands was invoked in an explanation of the different substitution:reduction ratios with the two leaving groups. To examine the stereochemistry of this process, Claesson and Olsson[81c] prepared optically active acetals **59** and **60** and subjected them to reaction with CH_3MgI–CuI (10 mol%) (eqn 64). The former gave a 1:2 mixture of γ:α attack in which the γ-product was formed with better than 95% anti stereoselectivity; the latter gave a 4:1 ratio of γ:α attack in which the major product, once again, was formed with greater than 95% anti preference. Thus, the stereoselectivity in this acyclic system is analogous to that observed in the R_2CuLi–cyclic allylic ester reactions of eqns (56)–(60). Interestingly, however, whatever the nature of the copper complex formed, some bond rotation must be able to occur since the α-attack product has exclusively *E* geometry, irrespective of the stereochemistry of the reagent's double bond.



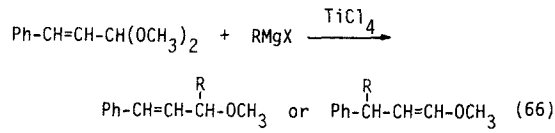


In contrast, total retention of double bond geometry in the α-attack product from allylic ethers with Grignard reagents in the presence of copper(I) salts has recently been reported by Normant *et al.*[82] An extensive study of a wide variety of allylic ethers revealed that the $\gamma:\alpha$ ratio was a sensitive function of steric effects in the ether and was essentially independent of the particular CuX used. With γ,γ-disubstituted allylic ethers, only α-attack occurred with, as illustrated in eqn (65), preservation of the original stereochemistry.



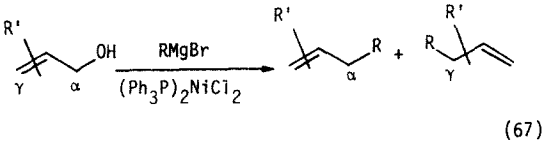
(65)

Finally, a different transition metal salt-mediated Grignard reaction was found to give regiospecificity which depended on the structure of the organometallic reagent. The dimethylacetal of cinnamaldehyde or crotonaldehyde gave exclusive α-attack with most RMgX reagents in the presence of $TiCl_4$ (R = allyl, $-CH_2CH_3$, $-CH_2CH_2Ph$), but with PhMgBr, γ-attack was the exclusive result (eqn 66).[83a] A related reversal of regiochemistry will be commented on shortly (eqn 78). The RMgX–CuX system also permits substitution on acetals and ketals of α,β-unsaturated carbonyl compounds; in every instance examined,[83b] only γ-attack was detected. Since all of the Grignard reagents were alkyl, it is not known if regiochemical reversal would have occurred with ArMgX.



(66)

All of the transformations thus far discussed have involved derivatives of allylic alcohols (esters, halides, acetals, carbamates, etc.). Clearly, a saving in time and yield could be achieved were similar reactions possible with the parent alcohols. Several successful efforts along these lines have been recently documented. Chuit *et al.*[84] have described the reactions of various allylic alcohols with CH_3MgBr or PhMgBr in the presence of bis(triphenylphosphine)nickel dichloride; mixtures of comparable amounts of α- and γ-substituted products are obtained and there is some loss of double bond geometry (eqn 67). In these reactions, the active species is apparently $(Ph_3P)_2Ni(R)MgBr$ which reacts with the magnesium alcoholate, as shown in eqn (68). Although pairs of allylic isomers (like α- and γ-methylallyl alcohol) gave similar (but *not* identical) product mixtures, the identical product mixture *was* obtained from the allylic alcohols shown in eqn (69). This example suggested that a regioselective transformation of ketones, via the vinyl carbinol, into a vinyl substituted quaternary center might be possible. To this end, Buckwalter *et al.*[85] investigated the stereochemical characteristics of the conversion. Alcohol **61** gave the same mixture of alkenes regardless of starting stereochemistry; the α–γ attack ratio is a gratifying 81–19 and the quaternary product is formed stereoselectively (eqn 70). Clearly, stereochemical equilibration of the initially formed π-allyl nickel complex (eqn 68) occurs. Extension of this method toward the synthesis of useful terpene intermediates has had limited success: in several instances, the regioselectivity favored γ-attack. One successful application is shown in eqn (71); the major component in the product mixture was then transformed in several steps into the diterpene hibaene.



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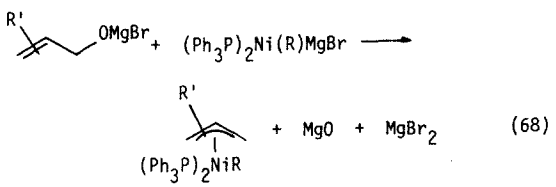

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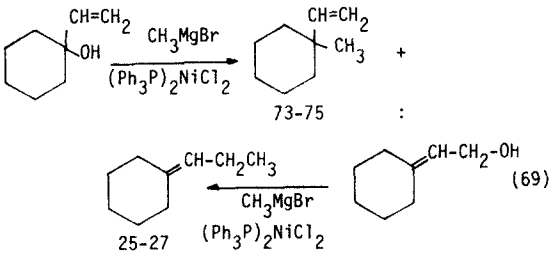

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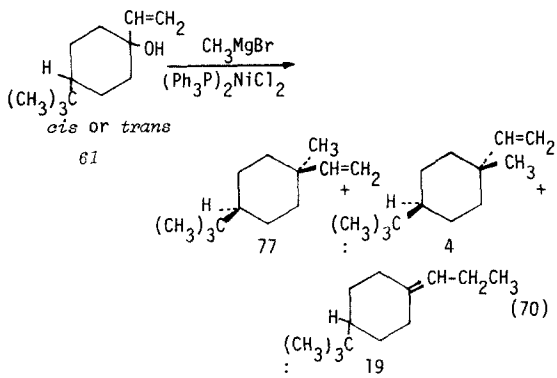

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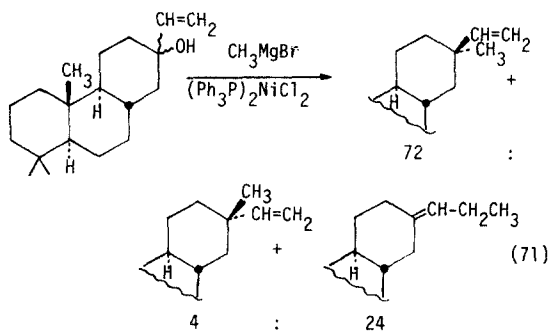
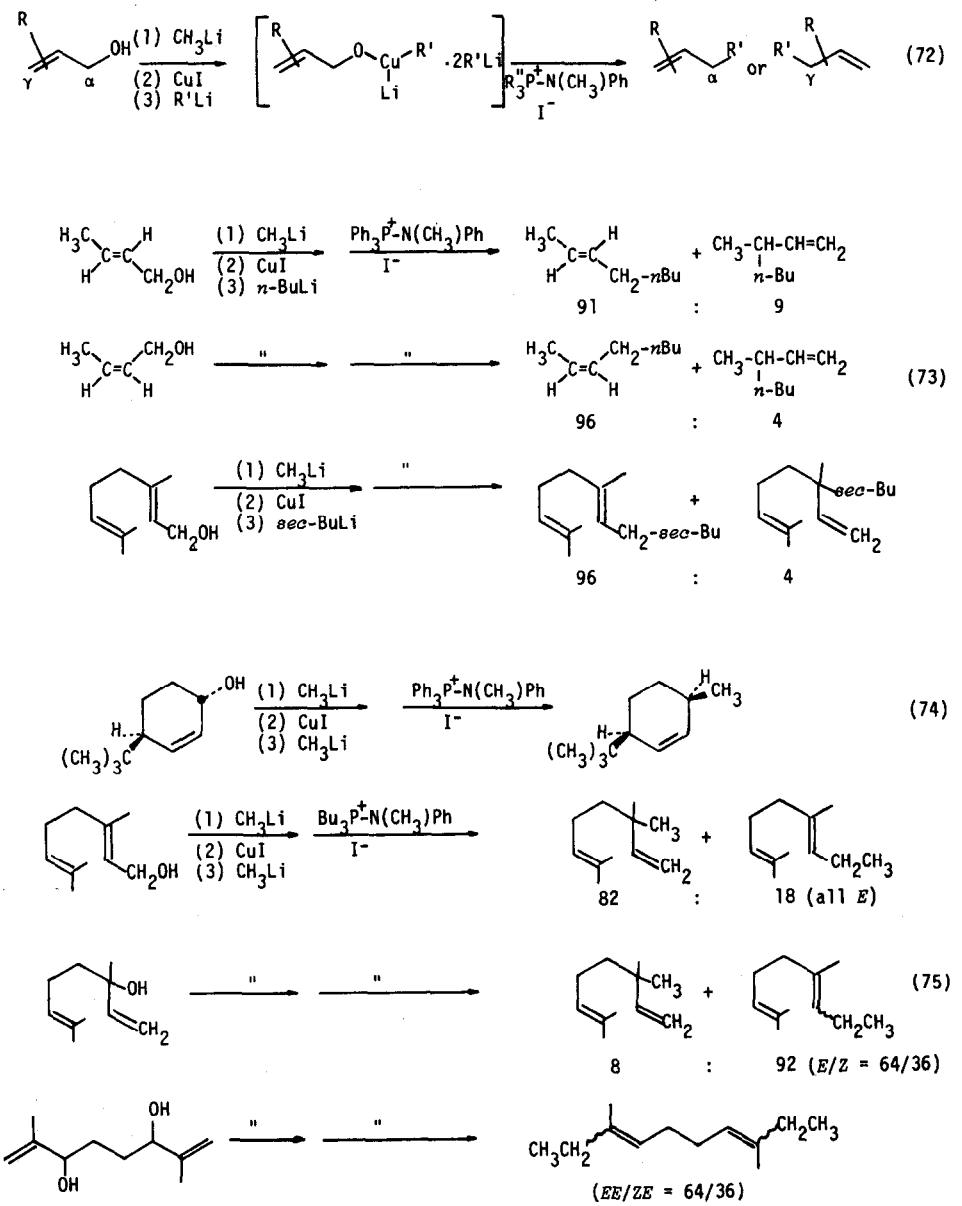
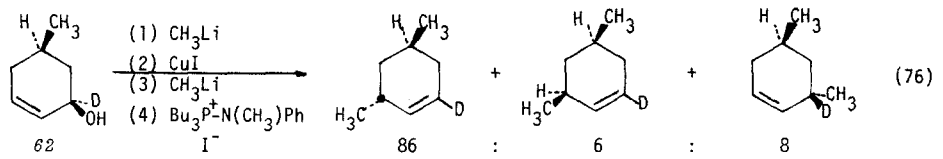


(71)

A highly promising single-step conversion of allylic alcohols has been developed by Tabigawa *et al.*[86] Not only are isolated yields of 65–97% obtained but, significantly, the regioselectivity can be altered by an apparently insignificant change in the phosphonium salt (eqn 72). Thus, when R″ is phenyl,[86a] the $\alpha:\gamma$ ratio is very high and the geometry of the double bond is preserved; some representative examples are given in eqn (73); R′ can be alkyl, aryl, 1,3-dithianyl, allyl, or ethynyl. All substrates except one, unfortunately, were primary alcohols and thus the generality of predominantly α-attack is not certain. The one secondary allylic alcohol examined was useful in demonstrating that substitution of OH by R′ occurs with inversion of configuration (eqn 74); unlike the identical product mixtures obtained from stereoisomeric allylic alcohols in eqns (70) and (71) the corresponding *cis* alcohol produced, with inversion again, *trans*-product. Remarkably, when R″ in the phosphonium salt (eqn (72) is n-butyl, the regioselectivity changes in favor of γ-product;[86b] again, R′ can be alkyl, aryl, or 1,3-dithianyl; the allylic alcohol can be primary, secondary, or tertiary.Some representative examples are illustrated in eqn (75). The stereochemistry was elucidated using cyclic allylic alcohol **62** (contaminated by 8% of its *trans*-isomer). From the measured *cis*:*trans* and $\gamma:\alpha$ ratios of products, the numbers given in eqn (76) could be calculated. Thus, 94% of the reaction occurs by anti attack, but, significantly, the $\gamma:\alpha$ ratio is not the nearly 50:50 found for the related acetate **50** with $(CH_3)_2CuLi$ (eqn 57). As eqns (74) and (76) show, the selective α-attack and γ-attack procedures both occur with alkyl substitution anti to the leaving group. As might be recalled from the discussions related to eqns (11)–(15), firm stereochemical conclusions using cyclohexenyl substrates are of doubtful generality since overriding conformational factors could well be dominating any stereoelectronic preference.

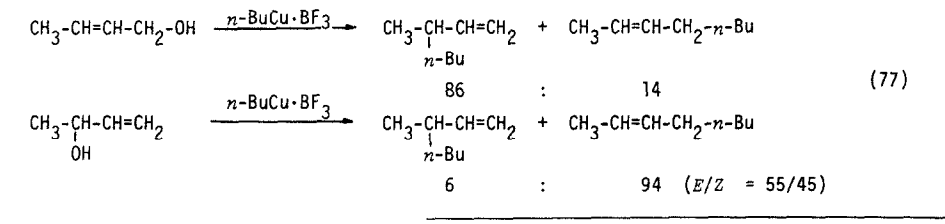




(76)

Although not explored as extensively as the procedure of eqn (72), a very simple one-step transformation of allylic alcohols has been described by Yamamoto and Maruyama.[87] The reagent RCu·BF_3, first developed[63] for the regioselective γ-alkylation of allylic halides (eqns 44 and 45), also reacts (readily) with the corresponding acetates, (sluggishly) with ethers, and, if used in 3-fold excess, with the alcohols themselves. The reaction is nearly quantitative (in the few cases cited) and has very high $\gamma:\alpha$ regioselectivity (see eqn (77) for representative examples). Although the $\gamma:\alpha$ ratio is somewhat lower than with the halides, the convenience of running the reaction on the easily obtained and allylically stable alcohols should not be overlooked.

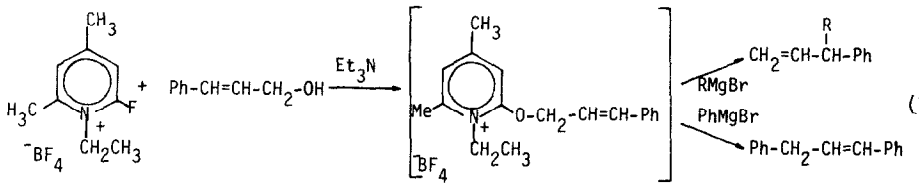
ethylallyl alcohol. It should be recalled (eqn 66) that the reaction of RMgBr–$TiCl_4$ with acetals of α,β-unsaturated aldehydes exhibits a similar reversal of regioselectivity, except that in the earlier situation, alkyl reagents gave α-attack while PhMgBr proceeded γ.[83a] Another one-step reaction is through 2-allyloxypyridine with RMgBr (1.2 equiv) in the presence of $MgBr_2$ (2 equiv).[88b] For ethers of primary allylic alcohols, best yields and regioselectivity are obtained with THF as solvent; for secondary alcohols, benzene is the solvent of choice. As illustrated in eqn (79), primary ethers selectively undergo α-attack while secondary and tertiary substrates react entirely at the γ-position. Interestingly, unlike the situation observed in eqns (66) and (78),



(77)

While not a direct displacement on the alcohol, a single-step regioselective procedure has been developed by Mukaiyama *et al.*[88] 2-Allyloxy-1-ethyl-4,6-dimethylpyridinium salts, prepared *in situ*, are treated with RMgBr.[88a] When R = n-butyl, $-CH_2CH_2Ph$, or cyclohexyl, γ-attack occurs; when R = phenyl, the position of attack is exclusively α. Eqn (78) illustrates this for cinnamyl alcohol, but the same behavior is observed with α-methyl- and γ-

no reversal of regioselectivity occurs when the Grignard reagent is aromatic. Although not discussed by the authors, the necessity for the presence of $MgBr_2$ and the similar product ratios for pairs of allylically related ethers (eqn 79) suggest the possibility of a stepwise mechanism, perhaps via a carbocation intermediate (eqn 80) (recall the similar,[53,55] but discredited,[59,60] suggestion for allylic halides with organolithium reagents and Grignards).



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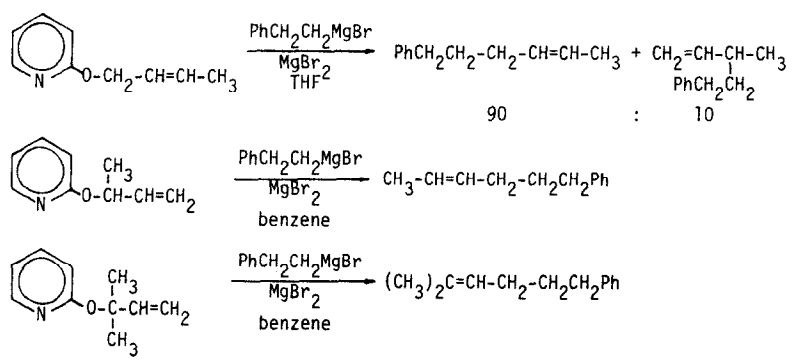

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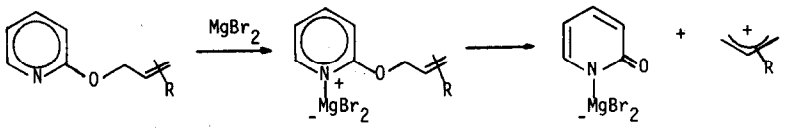
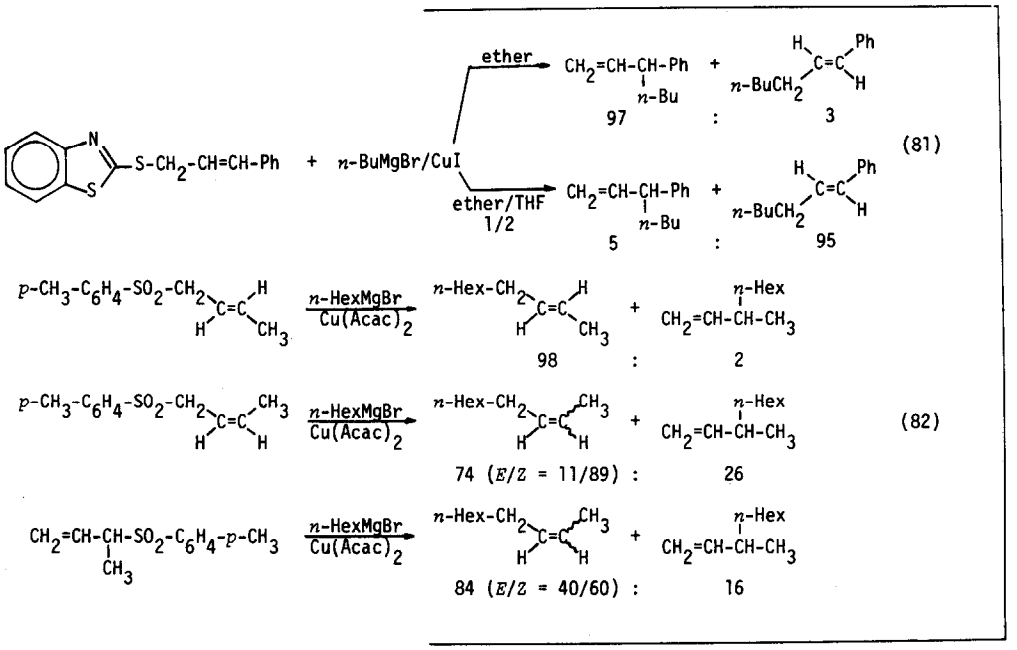


(80)

A very interesting solvent-induced regiochemical reversal occurs in the reaction of allylic derivatives of benzothiazole-2-thiol with Grignard reagents in the presence of CuI.[89] Although examined only with primary allylic groups (eqn (81), for example), ether as solvent promotes γ-attack whereas THF–ether leads to α-product. Sulfones are also displaceable groups with Grignard reagents and Julia *et al.*[90] have found a high regioselectivity although the yields are only fair (see eqn (82) for representative examples); the fact that primary allylic substrates give mostly α-attack while secondary lead to γ products suggests, again, the possible involvement of an allylic intermediate (radical or cationic). Finally, nitrogen, if suitably activated, can be a leaving group in such reactions. Müller and Phuong[91] have found that amines of general structure RCH_2NH_2 can, via their N,N-bistrifluoromethanesulfonyl derivatives, react with R_2CuLi. When allyl amine is thus treated with Ph_2CuLi, $Ph\text{-}CH_2CH{=}CH_2$ is produced in 73% yield. In the only study of regiochemistry, $Ph\text{-}CH{=}CH\text{-}CH_2\text{-}NTf_2$ gave but a 12% yield of α-product with $(CH_3)_2CuLi$.

polystyrene-supported Pd(0) catalyst tends to increase the regio preference.[94] Trost and Verhoeven[93] also looked at the stereochemistry and showed that it was exclusively syn; i.e. cyclic acetates **66** and **67** give product with complete retention of configuration, presumably via the double inversion process illustrated in eqn (84); the $\alpha:\gamma$ attack ratio was not determined, but should be 50:50 if the mechanism is correct. Use of the bulkier $(PhSO_2)_2CH^-$ as nucleophile, however, converted **66** into a 55:45 mixture of retained:inverted product.[95] This was convincingly attributed to a competing process in which liberated acetate attacks the π-allyl palladium complex, as shown in eqn (85), and is then delivered from Pd to C yielding epimeric acetate **67** which, by double inversion, yields the 45% product. A similar stereochemical complication was encountered in the reactions of **66** and **67** with amines.[94] Reaction of either acetate with diethylamine in the presence of $(Ph_3P)_4Pd$ gave allylic amines in roughly a 2:1 retention: inversion ratio. This was again attributed to a competition between the normal double inversion mechanism and attack of amine N on Pd

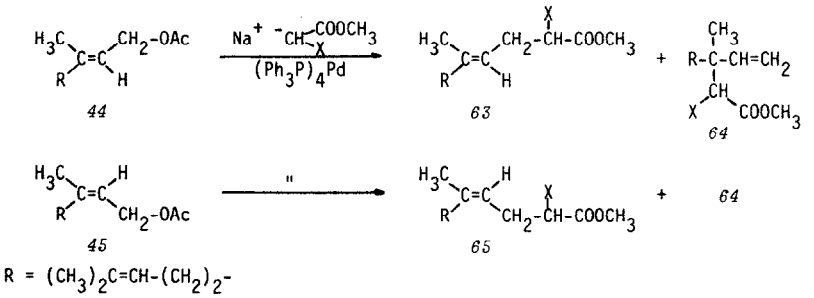


(81)

(82)

A thoroughly explored reaction is that of allylic acetates with stabilized carbanions (or other nucleophiles) in the presence of Pd(0) catalysts. Because Trost has recently reviewed this subject,[92] only a few highlights will be mentioned here. Reaction of geranyl or neryl acetate, **44** or **45**, with carbanions proceeds stereospecifically to **63** and **65**, respectively, although with variable regioselectivity (eqn 83); thus when $X = -COOCH_3$, the $\alpha:\gamma$ ratios for **44** and **45** are 90:10 and 37:63, respectively; when $X = -SO_2Ph$, the ratios are $>97:<3$ and 90:10.[93] Although not examined with **44** and **45**, the use of a

followed by transfer of the amine to the metal-complexed face of the allylic system. The use of the polystyrene-supported Pd(0) catalyst, however, discouraged this side reaction and led stereospecifically to the product of retained configuration. This is reminiscent of the argument presented earlier (see eqns 56–58) with regard to the Goering–Singleton[75] reaction of cyclohexenyl acetates with $(CH_3)_2CuLi$, in which it was suggested that the reagent attacks the acetate from the anti face and the π-allyl copper species serves as a template to deliver CH_3 from that side.



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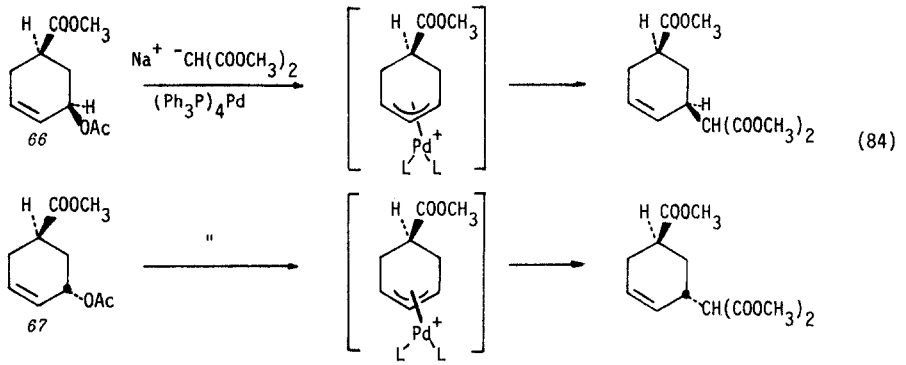
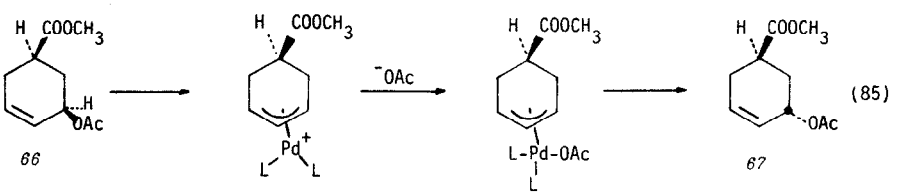
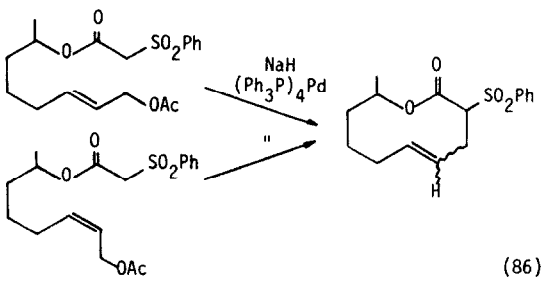


(84)



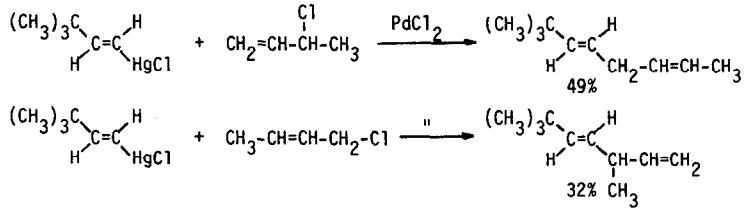
(85)

Several intramolecular variations of the above reactions have been reported in which amine nitrogen[96a] or carbanion[96b] is the nucleophile. From among the latter, eqn (86) is an example showing a preference for 10-membered ring formation relative to 8; from the *E* starting material the *E*–*Z* product ratio was 85–15; from *Z* reagent, it was 65–35. In related cases, 9-membered ring formation was favored over 7, and 8 over 6.



(86)

Other palladium-promoted reactions of allylic compounds, not directly related to alkylations, include: elimination of allylic acetates to dienes;[95] C–O cleavage of allylic acetates by hydride (from formate ion) regioselectively at the more substituted carbon of the π-allyl intermediate;[97a] and intramolecular rearrangements of allylic acetates.[97b] There are, in addition, two Pd(II) mediated reactions which lead to 1,4-dienes in a predictable manner. Allylic chlorides undergo exclusive γ-attack by vinylmercuric chloride as illustrated in eqn (87);[98a] the low yield of diene is a consequence of substantial dimerization of the organometallic reagent. Similarly, mono- and disubstituted alkynes react with allylic bromides and chlorides in the presence of catalytic quantites of $(PhCN)_2PdBr_2$ or $(PhCN)_2PdCl_2$, respectively; γ-attack again occurs, the yields range from fair to excellent, and the vinylic halogen of the product is *cis* to the allylic residue (see eqn (88) for representative examples).[98b]



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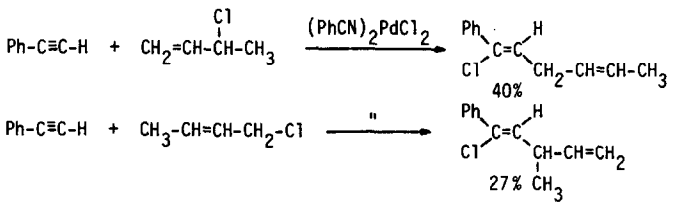
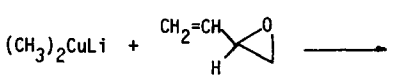
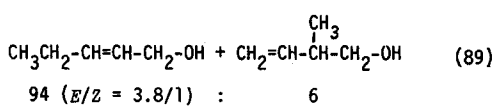


(88)

Discovered just shortly after the dialkylcuprate–allylic acetate reaction (eqns 51–61) and of considerable synthetic importance is the reaction of the same organometallic reagent with vinyl epoxides. Thus, 3,4-epoxy-1-butene, in very high yield, undergoes nearly exclusive γ-attack by $(CH_3)_2CuLi$ (eqn 89) in contrast to its reaction with organolithiums or Grignards which give substantial quantities of direct attack on the epoxide carbons and–or rearrangement;[99a] $(n\text{-}Bu)_2CuLi$ and Ph_2CuLi show similarly high regioselectivity.[99b] The stereochemistry of γ-attack relative to the breaking C–O bond was examined in the case of the monoepoxide of 1,3-cyclohexadiene: with $(CH_3)_2CuLi$ or Ph_2CuLi, comparable amounts of γ- and α-attack products were detected; interestingly, the former was exclusively produced by anti approach of the reagent (eqn 90).[100] In contrast, methyllithium gives only α-attack (with inversion) while phenyllithium and t-butyllithium give mixtures of α- and γ-attack in which the latter is exclusively anti but the former has considerable quantities of *cis*-product. This loss of stereochemical purity was attributed[100a] to incursion of a single-electron-transfer mechanism for ring opening. Not only is the anti stereoselectivity of this pseudo S_N2' process contrary to expectations,[17,18] but the related S_N2'' reaction of benzene oxide with methyllithium is exclusively syn (eqn 91);[49,101] similarly, dimethylmagnesium gives syn S_N2'' product and, as anticipated, direct ring opening with inversion (eqn 92). The stereochemical behavior of both the singly and doubly unsaturated epoxides has been rationalized through orbital distortion analysis by Liotta[20] and conformational arguments by Toromanoff.[29,45]





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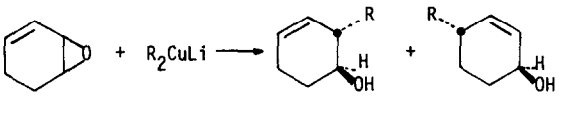
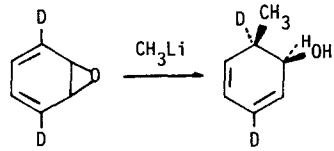


(90)



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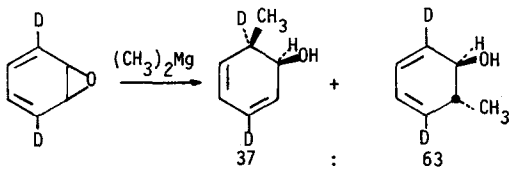
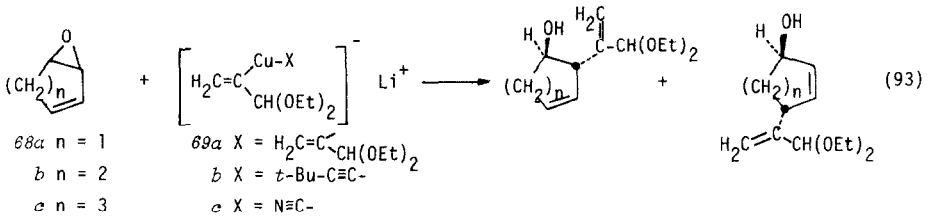


(92)

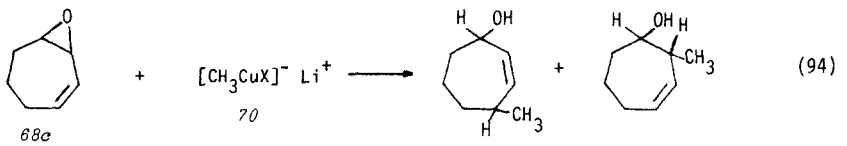
A related study of 1,3-cycloalkadiene monoepoxides **68a–c** with organocuprates (homo **69a** or hetero **69b,c**) showed that once again the products of direct epoxide attack (with inversion) and γ-attack (anti) were obtained (eqn 93).[102] The $\alpha:\gamma$ attack ratios, never very far from unity, could be increased by changing the solvent from THF to ether; highest γ-attack proportions occurred with cyanocuprate **69c**. Greater regioselectivity in favor of γ-attack could be achieved with methylcuprates **70** (eqn 94).[103] The $\gamma:\alpha$ ratios ranged from 70:30 (X = $-CH_3$) to 85:15 (X = $-C{\equiv}C\text{-}nBu$) to 90:10 (X = $-CN$) to 97:3 (X = $-C(COOCH_3){=}CH_2$); yields were uniformly >90%. Stereochemical purity, unfortunately not indicated for most of the products, was *trans*:*cis* 70:30 in the γ-product from **70**, X = $-CH_3$; presumably, the other γ products are also mixtures of stereoisomers and the α product is *trans*. The use of cyanocuprates R(CN)CuLi, R = n-Bu or sec-Bu, gave only γ product (stereochemistry unspecified). Cuprate **70**, X = –CH, with 6-membered ring epoxide **68b** gave exclusively *trans*-1,4-substitution.



68a n = 1
b n = 2
c n = 3

69a X = $H_2C{=}C(CH(OEt)_2)$-
b X = t-Bu-C≡C-
c X = N≡C-

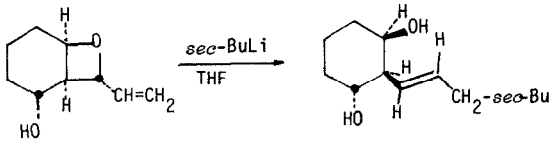
(93)



68c 70

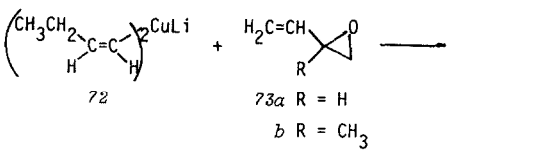
(94)

Two variations on this procedure are noteworthy. In the first, Still[104] demonstrated that vinyloxetanes are also prone to γ-attack by organometallic reagents: oxetane **71** reacts in high yield to give the product shown in eqn (95). In the other, Cahiez *et al.*[105] have developed a regiospecific and stereoselective synthesis of 1,4-dienes as illustrated in eqn (96): vinylcuprate **72** with **73a** gave, in 70% yield, a 96:4 $E:Z$ ratio of products; with **73b**, the yield was 87% and the $E:Z$ ratio was 86:14. The $\gamma:\alpha$ ratio decreases markedly, as does the $E:Z$ selectivity, when vinyllithiums or vinylmagnesium halides are used. On the other hand, the use of allylic Grignards in the presence of CuBr allows the conversion of **73a,b** into 1,5-dienes with complete regio- and stereospecificity.

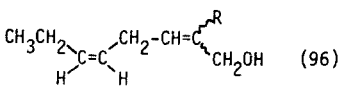


71

(95)

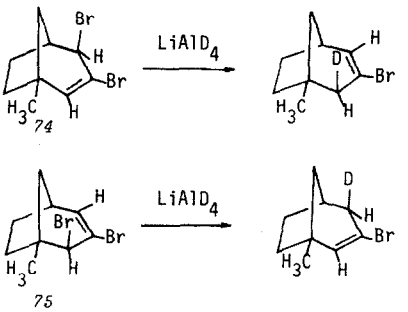


72 73a R = H
b R = CH_3



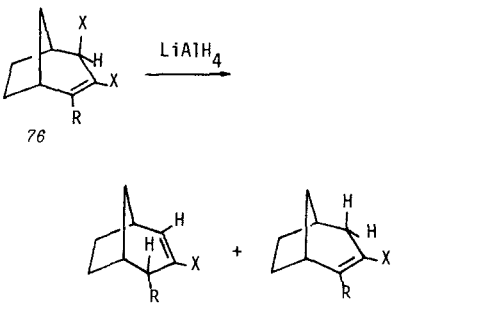
(96)

Related to the delivery of carbon residues to allylic systems are those reactions in which inorganic or organometallic reagents transfer hydride with and–or without allylic rearrangement. The earliest stereochemical studies were those of Jefford *et al.*[18e,106] who looked at the reactions of various bicyclo[3.2.1]octenyl halides with $LiAlH_4$. Allylically isomeric bromides **74** and **75** with $LiAlD_4$ underwent exclusive syn-γ attack (eqn 97); substrate **76**, X = Br or Cl, R = Ph or CH_3, gave a mixture of syn-γ (major) and α attack (eqn 98). In order to explain the formation of α product in the latter examples, the authors suggest the intermediacy of a Bordwell–Sneen[2,12,13] tight ion pair; it is unfortunate that the stereochemistry of the α product was not investigated using $LiAlD_4$. The origin of syn-γ specificity can be a consequence of any or all of the following factors: an inherent preference for syn attack by nucleophiles in general; an intramolecular mechanism in which the metal serves as a template for removal of halogen and delivery of hydrogen; the well-known[28b,37] preference for *exo* attack on a bicyclo[3.2.1]octenyl cation. Similar intramolecular complexation of leaving group and transfer of hydride has been demonstrated in unsaturated sugar derivatives by Tam *et al.*[107]



74 75

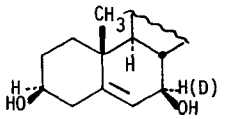
(97)



76

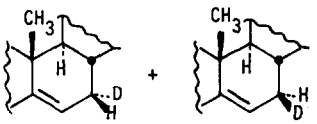
(98)

Allylic alcohols also suffer hydrogenolysis with hydridic reducing agents.[108] Conclusive evidence for an allylic cation intermediate in the $LiAlH_4$–$AlCl_3$ reduction of steroidal alcohols has been presented by Cunningham and Overton.[109] Both 7β- and 7α-hydroxycholesterol, **77a** and **79a**, are attacked by $LiAlD_4$–$AlCl_3$ exclusively at C_7 to give essentially the same product mixture with **78a** ≫ **78b**; the analogous reaction of deuteriated alcohols **77b** and **79b** with $LiAlH_4$–$AlCl_3$ gave **78b** ≫ **78a** (eqns 99 and 100). Clearly, the configuration of the alcohol is irrelevant in deciding the stereochemical outcome; models indicated that the ring B allylic cation should be attacked by hydride preferentially from the α-face, as is observed. In contrast, reaction of 3α- and 3β-hydroxycholest-4-ene, **80** and **82**, gave different proportions of attack from the two faces (eqns 101 and 102). The ring A allylic cation has some conformational flexibility and if one assumes, as did Goering and Josephson,[28a] that C–O cleavage occurs most easily when the bond is quasi-axial and that the cations are attacked by deuteride faster than conformational equilibration can occur, then one can explain the preferential α-attack on **80** and the equal α : β ratio with **82**.



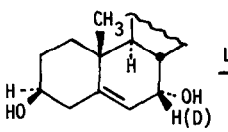
$LiAlD_4(LiAlH_4)$ / $AlCl_3$

77a H	$LiAlD_4$
b D	$LiAlH_4$



(99)

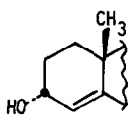
78a	:	*78b*
97	:	3
18	:	82



$LiAlD_4(LiAlH_4)$ / $AlCl_3$

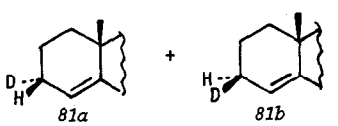
		78a	+	*78b*
79a H	$LiAlD_4$	91	:	9
b D	$LiAlH_4$	12	:	88

(100)



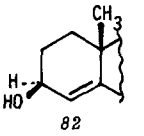
80

$LiAlD_4$ / $AlCl_3$



(101)

81a	:	*81b*
84	:	12



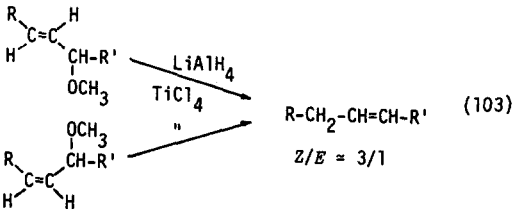
82

$LiAlD_4$ / $AlCl_3$

81a	+	*81b*
48	:	49

(102)

It will be recalled (eqn 66) that acetals of α,β-unsaturated aldehydes react with Grignard reagents in the presence of $TiCl_4$ to give either exclusive α- or γ-attack, depending on the Grignard's structure.[83a] Similarly, $TiCl_4$ promotes the cleavage of allylic ethers by $LiAlH_4$. Thus, both *E* and *Z* ethers suffer, in good yield, exclusive γ-attack producing, roughly, a 3 : 1 mixture of *Z* : *E* alkenes (eqn 103).[110] On the other hand, allylic mesylates and halides have recently been shown to undergo exclusive α-attack by hydride agents: see eqns 104[111a] and 105;[111b] in one case, net inversion of configuration, accompanied by a small amount of γ product, was observed (eqn 106).[111c] Similarly, the di-n-butyl ate complex of 9-BBN gave preferential α-attack on the one allylic substrate examined (eqn 107);[111d] hydride is delivered from the bridgehead position, and this reagent is claimed to be selective for allylic, benzylic and tertiary halides (but is unreactive toward primary and secondary alkyl halides).



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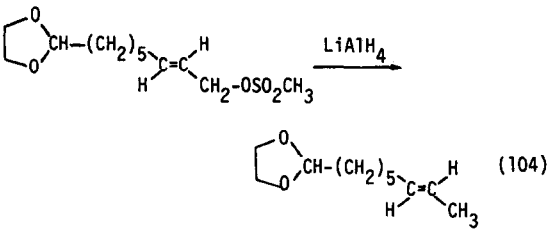

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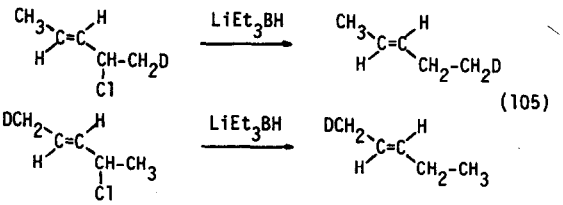
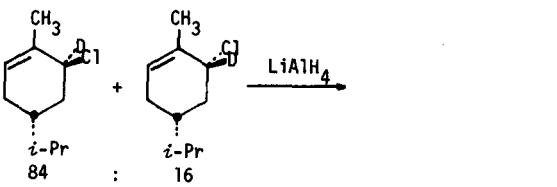
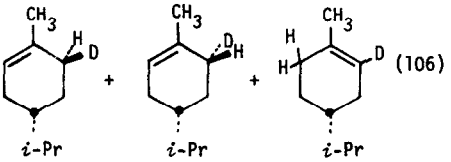
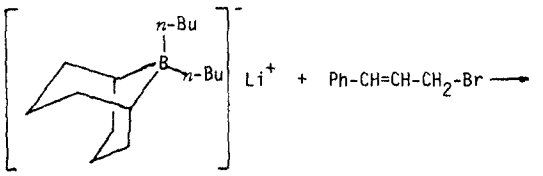


(105)



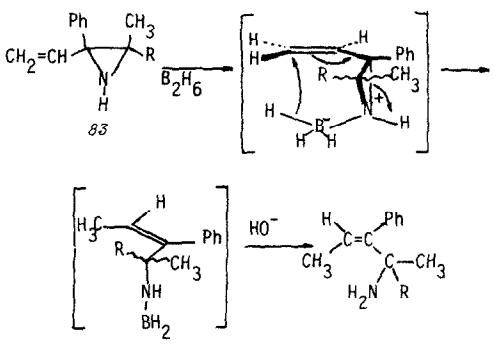


(106)

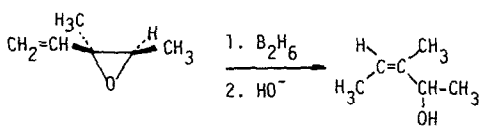


$$\text{Ph-CH=CH-CH}_3 \;:\; \text{Ph-CH}_2\text{-CH=CH}_2 \quad 90 : 10 \qquad (107)$$

Finally, two reactions which are related to the reactions of organometallic reagents with vinyl epoxides (inter- eqn 24) or intramolecular (eqns 89–94)) have been described. Vinyl aziridine **83** (of unspecified stereochemistry), R = H or CH_3, is transformed in 75–79% yield into *Z* allylic amine product by B_2H_6 followed by basic hydrolysis (eqn 108).[112] To explain the stereospecific production of the *Z* amine, intramolecular delivery of hydride from an *s-cis* conformation[39] is proposed. The same sort of conformation is required when vinyl epoxides are converted by B_2H_6; HO^-–H_2O stereospecifically into *Z*-allylic alcohols in moderate yield (see eqn (109) for a typical example).[113]



(108)



(109)

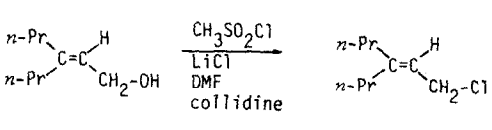
FORMATION OF ALLYLIC HALIDES FROM THE ALCOHOLS

Because so many reactions (including, but not limited to, the examples discussed in the first two sections of this Report) depend on allylic halides, much effort has gone into developing syntheses of these materials. Owing to the nature of the allylic system, preparation from the corresponding alcohol (eqn 110) presents regio- and stereochemical problems not encountered with saturated systems. Desirable features which a synthetic procedure should have are the following: (1) the reaction should be regiospecific, leading exclusively to either the α-substituted or γ-substituted product in a predictable manner; (2) the stereochemistry at the β,γ double bond should be preserved; (3) high optical yields should be obtained when C_α is chiral; (4) the conditions of reaction, work-up and isolation must be mild enough that neither allylic rearrangement of the product nor solvolysis–elimination occurs. There is, at present, *no* general method which satisfies all four criteria for every type of allylic alcohol. Nevertheless, reagent systems have been developed in which regio- and stereochemical selectivity are high in at least some cases. The more successful of these methods will be surveyed in this section.

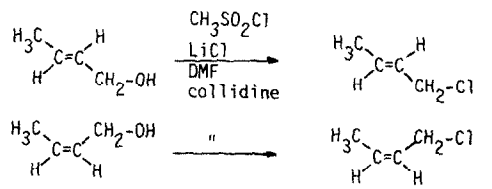
(110)

Conventional halide-producing reagents like $SOCl_2$ or PX_3 have proven to be relatively versatile.[1] Young *et al.*[114] found that $SOCl_2$ in ether gave exclusively rearranged product from both α- and γ-methylallyl alcohol; in the presence of a tertiary amine, however, regioselectivity changed in favor of the unrearranged α-attack product. Unfortunately, optically active α-methylallyl alcohol gave extensive racemization under all conditions. With cyclohexenyl alcohols, $SOCl_2$–ether again gave exclusive γ-attack with syn stereochemistry.[115] The method is not especially good for tertiary allylic alcohols which were found to give mixtures of regioisomers, regardless of whether or not tertiary amine was present.[116] The procedure has found application in the preparation of ^{14}C- and ^2H-labeled allyl chloride[57,58a] and in the synthesis of isoprenoid units for olefin cyclization.[117] Phosphorous halides also work quite well with primary allylic alcohols for which clean formation of unrearranged product has been reported with many substrates under varying sets of conditions.[61b,65,67,118]

A useful procedure developed by Meyers and Collington[119] as a selective reaction for allylic alcohols involves *in situ* formation of the methanesulfonate which is displaced by chloride ion (eqn 111). Primary allylic alcohols react without rearrangement; stereochemistry of the double bond is preserved starting with (*E*)- or (*Z*)-γ-methylallyl alcohol (eqn 112).[120] The procedure is of limited use with secondary alcohols: in an extensive study, Georgoulis and Ville[121] examined a series of such compounds in which R ranged from methyl to t-butyl (eqn 113); it was found that the α : γ ratio was 73 : 27 for R = CH_3, but as the α-alkyl group became bulkier, the extent of rearrangement also increased, so that the α : γ ratio was 5 : 95 when R = t-Bu.



(111)



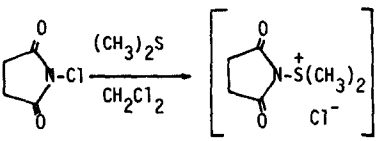
(112)

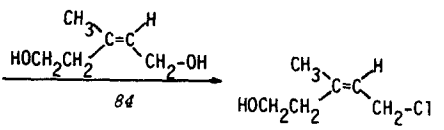
$$CH_2{=}CH{-}\underset{\displaystyle R}{\underset{|}{CH}}{-}OH \xrightarrow[\text{DMF}]{\substack{CH_3SO_2Cl\\ LiCl}} \text{collidine}$$

$$CH_2{=}CH{-}\underset{\displaystyle R}{\underset{|}{CH}}{-}Cl \;+\; Cl{-}CH_2{-}CH{=}CH{-}R \qquad (113)$$

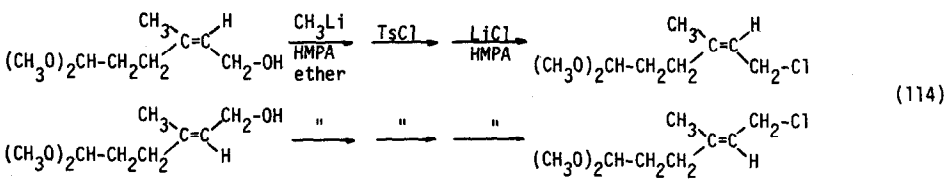
A related method, developed by Stork *et al.*[122] employs chloride ion substitution of a tosylate prepared (without isolation) as in eqn (114). In contrast to the regio- and stereospecificity of this and other examples,[122] a related γ,γ-disubstituted primary alcohol was reported to give an unspecified amount of rearranged chloride.[123] Although the conditions are more strenuous, various β,γ-disubstituted primary alcohols are converted into the unrearranged chlorides by the action of *p*-toluenesulfonyl chloride in pyridine at 80°.[124] The Stork synthesis has been used by others[125] and, in a cyclohexenyl case, has been shown to proceed with nearly complete inversion of configuration (eqn 115).[111c] Except for this last example, the method has not been applied to secondary or tertiary systems. Another very good leaving group, 2,4-dinitrophenoxide, has been exploited for the stereospecific synthesis of primary allylic chlorides (eqn 116).[126]

Another specific reagent for allylic (and benzylic) alcohols was devised by Corey *et al.*[127] N-chloro- or N-bromosuccinimide reacts with dimethyl sulfide to produce a salt which converts allylic alcohols, such as **84**, regio- and stereospecifically into the corresponding halide (eqn 117). The method has been successfully applied to the preparation of other primary allylic chlorides,[61b,f,123] although complications caused by neighboring groups have been claimed.[128] The utility in secondary and tertiary allylic systems has not been tested. Not unrelated is another sulfonium salt intermediate which has found application in the preparation of primary allylic iodides (see eqn (118) for one example).[129]

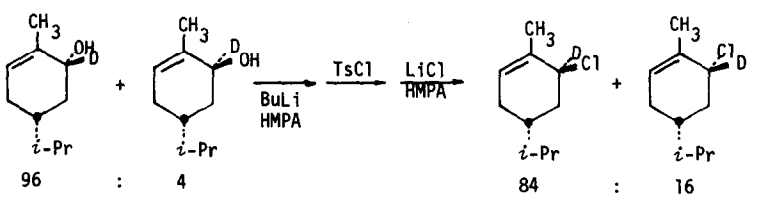




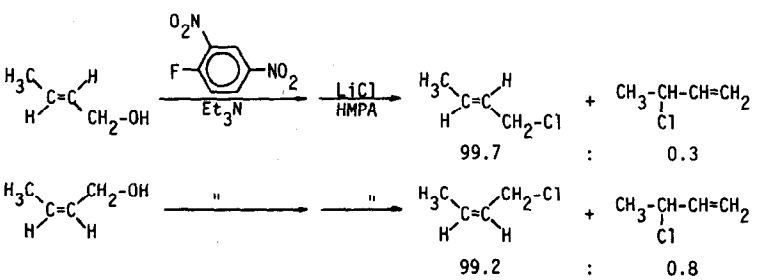
(117)



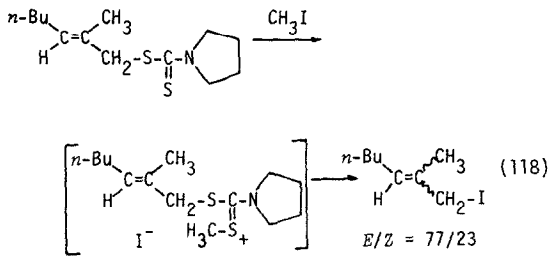
(114)



(115)

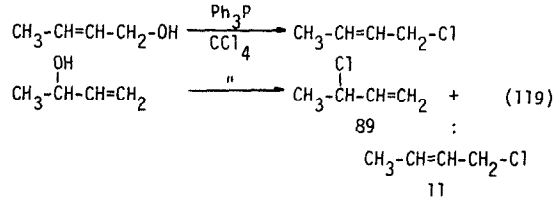


(116)

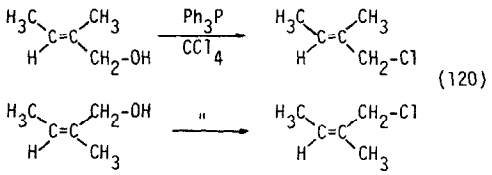


(118)

The reagent system triphenylphosphine–carbon tetrachloride and its several variants have proved very versatile for a number of synthetic purposes, among which is the conversion of alcohols into halides.[130,131] The observations that chloride is formed with complete inversion of configuration and that there is no rearrangement of neopentyl or other systems[132] led Snyder to examine the reagent with allylic substrates.[133] In fact, γ-methylallyl alcohol (as a mixture of stereoisomers) gave only unrearranged chloride while α-methylallyl alcohol gave but 11% of rearranged product (eqn 119). The procedure has been widely used for the preparation of primary allylic chlorides and (through the use of CBr_4) bromides.[134] Retention of double bond geometry accompanies the regiospecificity in primary systems (eqn 120).[61g,135] For secondary alcohols, however, the regioselectivity is far poorer in both cyclic[136] and acyclic[121] cases. Georgoulis and Ville[121] have compared the regiochemistry with secondary allylic alcohols of the Meyers[119] procedure (see eqn 111), the Ph_3P–CCl_4 method, and a modification of the latter using $[(CH_3)_2N]_3P$. The highest proportion of unrearranged chloride from α-alkylallyl alcohols was uniformly obtained with the last-mentioned modification: for α-methyl-, α-n-butyl-, α-isopropyl and α-t-butylallyl alcohols, the ratios of unrearranged : rearranged chloride were 98 : 2, 91 : 9, 64 : 36 and 39 : 61, respectively; in fact, the bulky t-butyl group is the only one to give more than 50% of rearranged product.

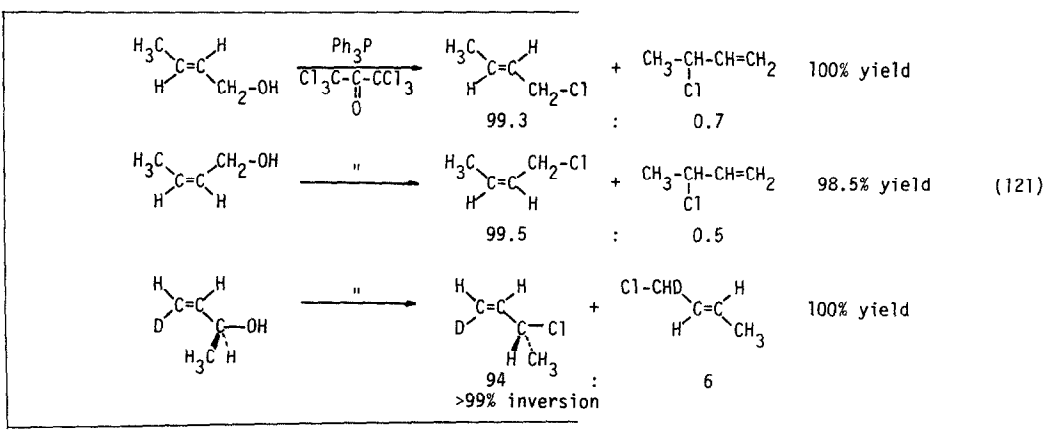


(119)



(120)

The principal drawback to the Ph_3P–CCl_4 method is that lower molecular weight allylic chlorides have boiling points very close to those of reagent CCl_4 and product $CHCl_3$, thereby causing difficulties in isolation (as noted on several occasions[65,121,132d]). To avoid these problems, Magit *et al.*[137] replaced CCl_4 by hexachloroacetone, a higher boiling source of positive halogen. Not only does this modified procedure lead to very high regioselectivity with primary and secondary allylic alcohols, but also double bond geometry is quantitatively preserved and inversion of configuration occurs at C_α (see eqn (121) for representative examples); only tertiary alcohols give extensively rearranged product and–or elimination to dienes. Perhaps the most advantageous aspects of this synthetic method are its mildness, speed and ease of operation: the reaction is accomplished by mixing the alcohol with triphenylphosphine–hexachloroacetone at 10–15° for < 20 min followed by immediate flash distillation. In most cases, the only volatile product collected, in nearly quantitative yield, is the desired chloride without need for further purification.



(121)

ADDENDUM

In the time since the initial submission of this Report, several pertinent articles have been published. With the following very brief discussion of them, this literature survey is now complete through November 1979.

In a study designed to resolve the discrepancy between the syn (eqn 24) and anti (eqns 25 and 26) *intra*molecular S_N2' reaction, Stork and Schoofs[138] have observed anti behavior in the intramolecular attack of a malonate ion on an allylic ester related to **18**. Chapleo *et al.*[139] have shown that various cyclopentenyl bromides suffer anti attack, preferentially at the γ-position, with organocuprates, but when the anti access is too hindered, syn approach is found; morpholine gives exclusively syn γ attack (in agreement with eqn 20) while thiophenylate produces mostly syn attack accompanied by some anti; a related cyclopentadiene monoepoxide gives mostly anti γ attack with organocuprates (as anticipated by eqn 93). Itoh *et al.*[140b] have examined the behavior of cyclohexenyl substrates with $(CH_3)_2Al$–X: with phosphate as leaving group and X = OPh, SPh, NHPh, α attack predominates, mostly from the anti direction; with acetate

as leaving group and X = CH_3, there is no regioselectivity and attack occurs from the less hindered side of the postulated common cyclohexenyl cation from epimeric acetates. A significant advance in controlling the regiochemistry in the reaction of allylic anions with allylic halides (eqns 47–50) has been reported by Ziegler and Tam:[141] the Cu(I) salts of ketene dithioacetals couple with allylic halides and phosphates predominantly in the γ'–γ mode (see eqn 48). Gendreau and Normant[142] have studied the reaction of allylic ethers with RMgX–CuX (eqn 65) through the behavior of cyclohexenyl ethers similar to the acetates of eqn (59); α and γ products are produced entirely by anti attack, and the reaction is most facile when the leaving group is quasi-axial (see eqns 13 and 14). Yamaguchi *et al.*[143a] have shown that allyloxybenzimidazoles behave like allyloxypyridines (eqn 79) and give mixtures of α and γ products when treated with Cu(I) salts of enamines; Mukaiyama[143b] has reviewed the coupling reactions of allyloxypyridinium salts (eqn 78). Calò *et al.*[144] have found that allyloxybenzothiazoles (see eqn 81) with Cu(I) acetylides give γ-attack for secondary substrates, α-attack for primary. Allylic sulfides couple with Grignard reagents in the presence of Ni(II)-phosphine complexes, but without strong regio preference.[145] In contrast, Roustan *et al.*[146] have reported regioselective α-coupling of primary and secondary allylic halides and esters with malonate ion in the presence of various iron complexes. Trost *et al.* have described several valuable extensions of the allylic ester–nucleophile–$(Ph_3P)_4Pd$ reaction (eqn 83–86): whereas the reagent system of eqn (83) fails with allylic acetates bearing alkoxy groups at C_β, a simple modification allows γ-coupling in high yield;[147a] primary allylic amines can be synthesized by regioselective attack at the less hindered carbon of allylic acetates through the action of di-*p*-anisylbenzhydryl amine–$(Ph_3P)_4Pd$ followed by formolysis;[147b] the double inversion mechanism of eqn (84) accounts for a similar stereocontrolled synthesis using acyclic vinyl lactones.[147c] Marino and Hatanaka[148] have applied the regio- and stereospecific anti γ reaction of cyanocuprate **70** with cyclohexadiene monoepoxide (**68b**) (eqns 93 and 94) to the stereospecific synthesis of cyclohexenes having three chiral centers. Finally, Bellarmine *et al.*[149] have used the Corey allylic halide synthesis (eqn 117) followed by regioselective reduction with $LiAlH_4$ or $LiAlD_4$ to prepare specifically labeled alkenes of defined geometry (see eqn 105).

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