Invited Paper

Chemical Chameleons. Organosulfones as Synthetic Building Blocks

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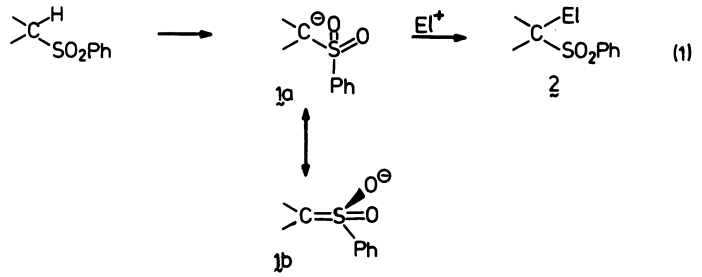
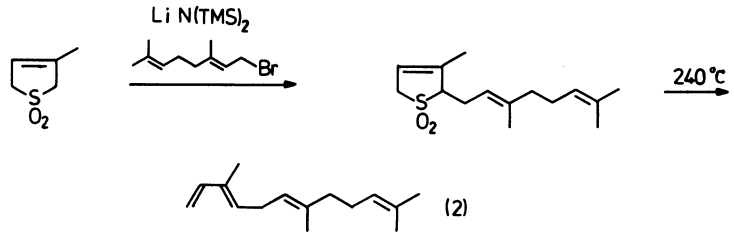
An overview of the duality of function of organosulfones as nucleophiles in basic media and electrophiles in Lewis acidic media, a change of reactivity for which they have been dubbed "chemical chameleons," is presented. In the first phase, transition metal catalysts activate allyl sulfones towards displacements. Use of palladium, molybdenum, and nickel catalysts allow stabilized anions to effect displacement; copper catalysts allow non-stabilized nucleophiles to be used. The use of the anion stabilizing and leaving group abilities of sulfones created a novel three carbon intercalation and a novel cyclocontraction-spiroannulation in which β-hydroxy sulfones participate in a Lewis acid catalyzed pinacol rearrangement. The lability of allyl and tertiary sulfones towards Lewis acids creates a wide array of electrophilic reactions such as Friedel–Crafts type cyclizations, intermolecular alkylations with organoalanes and enol silyl ethers, and ring expansions. The ability to design novel reagents for synthesis based upon this dual reactivity of organosulfones is illustrated by the use of an alkoxy-bis(phenylsulfonyl)methane as a synthon for a carbonyl 1,1-dipole.

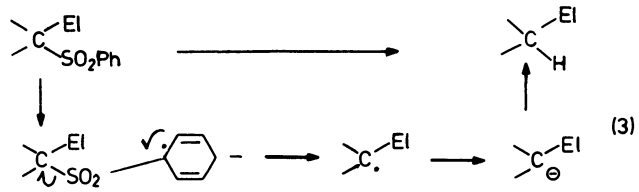
The utility of organosulfones for organic synthesis emerged with the evolution of non-nucleophilic strong bases like lithium dialkylamides and *n*-butyllithium which permit formation of a carbanion[1] (pK_a methyl phenyl sulfone 29[2]). The resulting organometallic appears to be enolate like (**1a**←→**1b**) based on both theoretical[3] and experimental data.[4] A notable discrepancy arises in the case of the organometallic generated from allyl phenyl sulfone where the carbanion center appears to be pyramidilized.[5] In contrast to enolates, sulfone stabilized anions have little propensity to react at oxygen.[6] Thus, treatment with electrophiles normally leads to smooth addition to carbon to give **2**. Since the sulfone functionality is rarely present in the final synthetic target, the major obstacle then becomes removal of the sulfone.

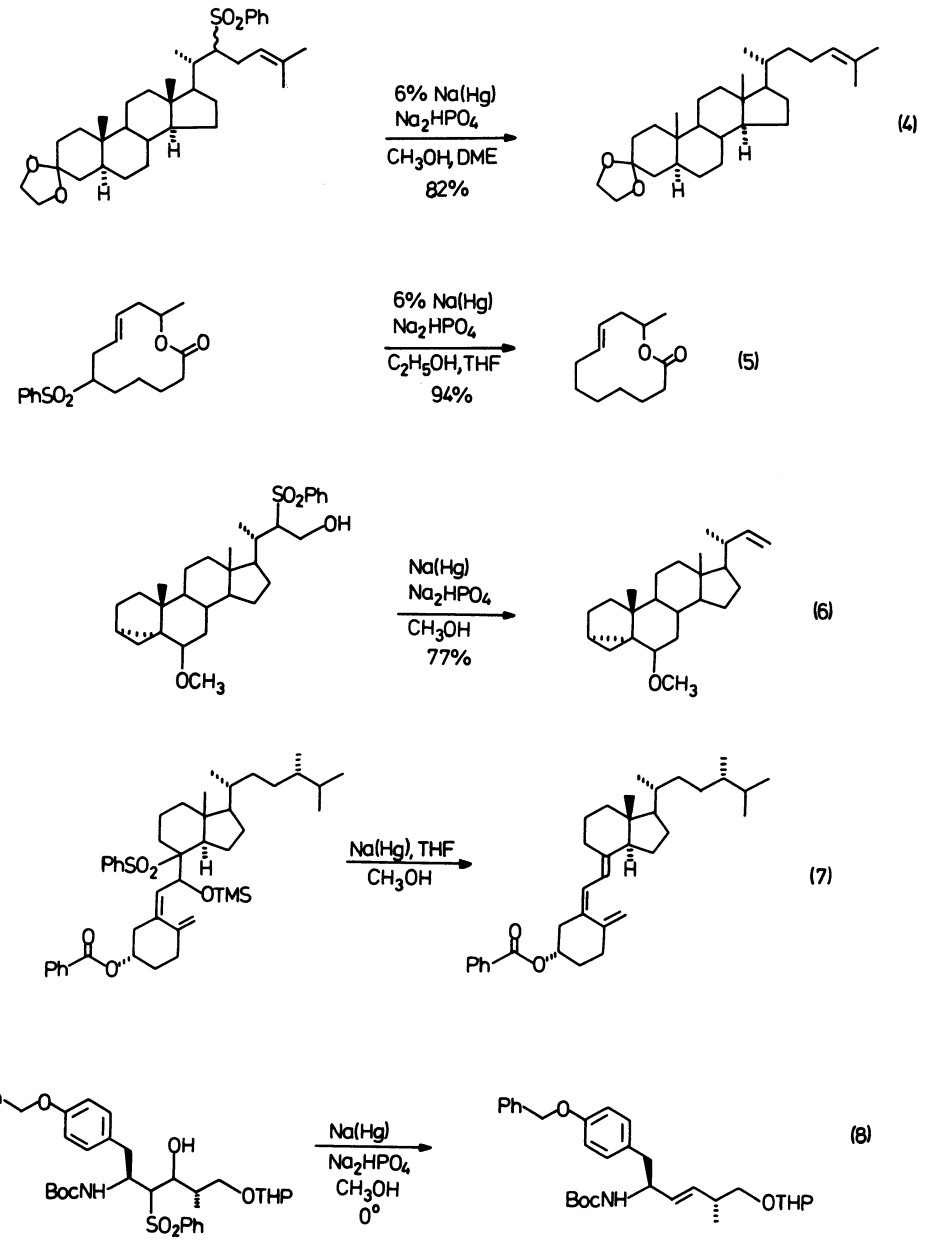
Early Applications. The early applications of organosulfones relied upon extrusions of sulfur dioxide in the base treatment of α-halo sulfones to give olefins (Ramberg–Bäcklund rearrangement)[7] or thermally in the case of sulfolenes as in a recent synthesis of farnesene (Eq. 2).[8]

A major advance arose by the recognition of







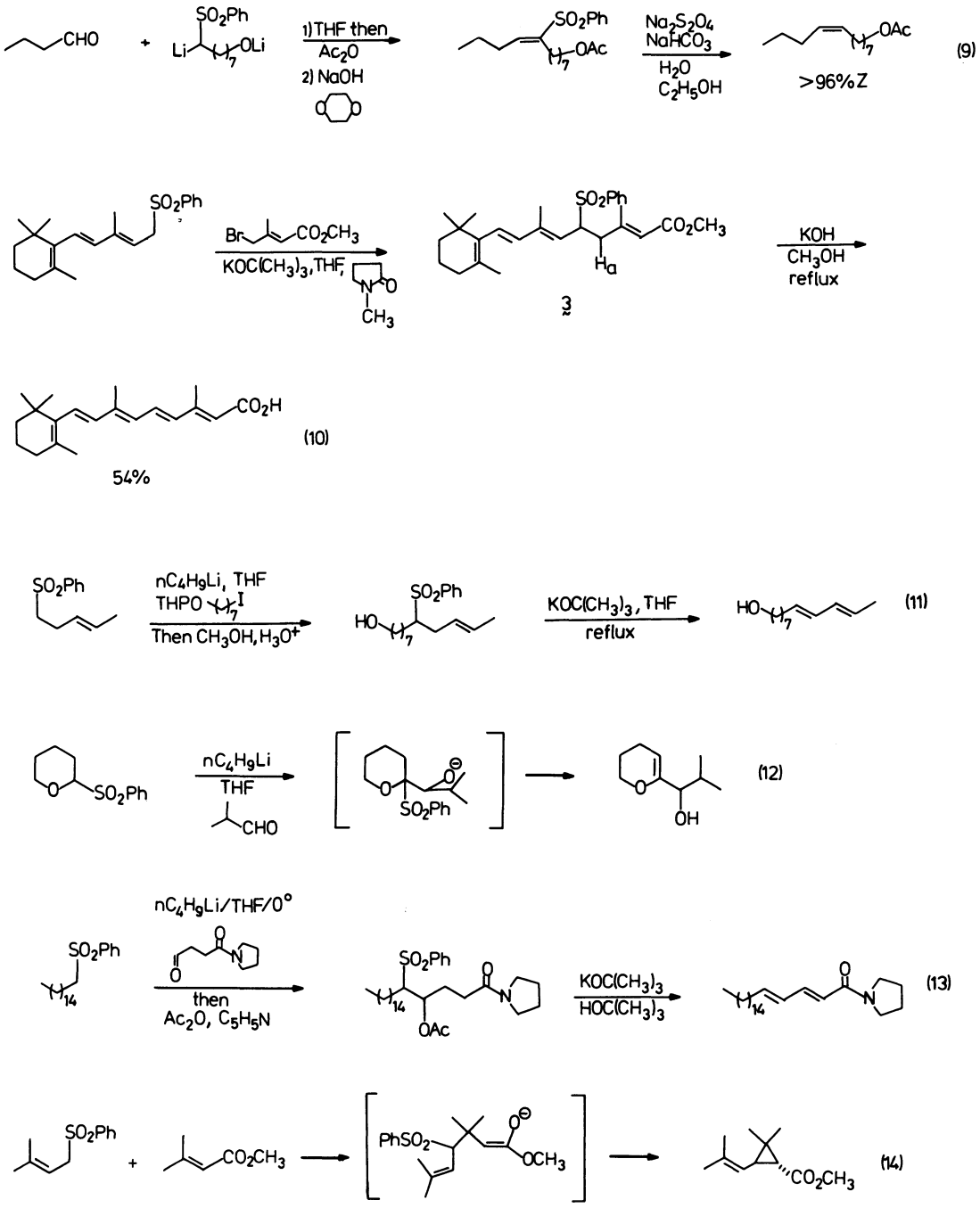


reductive desulfonation of aryl sulfones using dissolving metal reductions which permits the overall transformation shown in Eq. 3. Sodium amalgum in alcoholic solvents buffered with disodium hydrogenphosphate is a particularly mild way to effect such cleavages[9] (Eqs. 4[10] and 5[11]). In this reaction, the cleavage presumably occurs from the radical anion as depicted in Eq. 3. Its efficacy, therefore, depends upon the reduction potential of the sulfone and the stability of the resulting carbon radical. Thus, both "activated" sulfones, as in the case of an allyl system, and "unactivated" sulfones, represented by the saturated alkyl systems as in Eqs. 4 and 5, successfully cleave.

If the carbon β to the sulfones bears a potential leaving group, the reaction can be diverted to elimination to an olefin[12,16] (Eqs. 6[13] and 7[14]). Frequently, this method, originally introduced by Julia,[12] provides an olefin geometry complementary to that produced by Wittig type processes (cf. Eq. 8).[15]

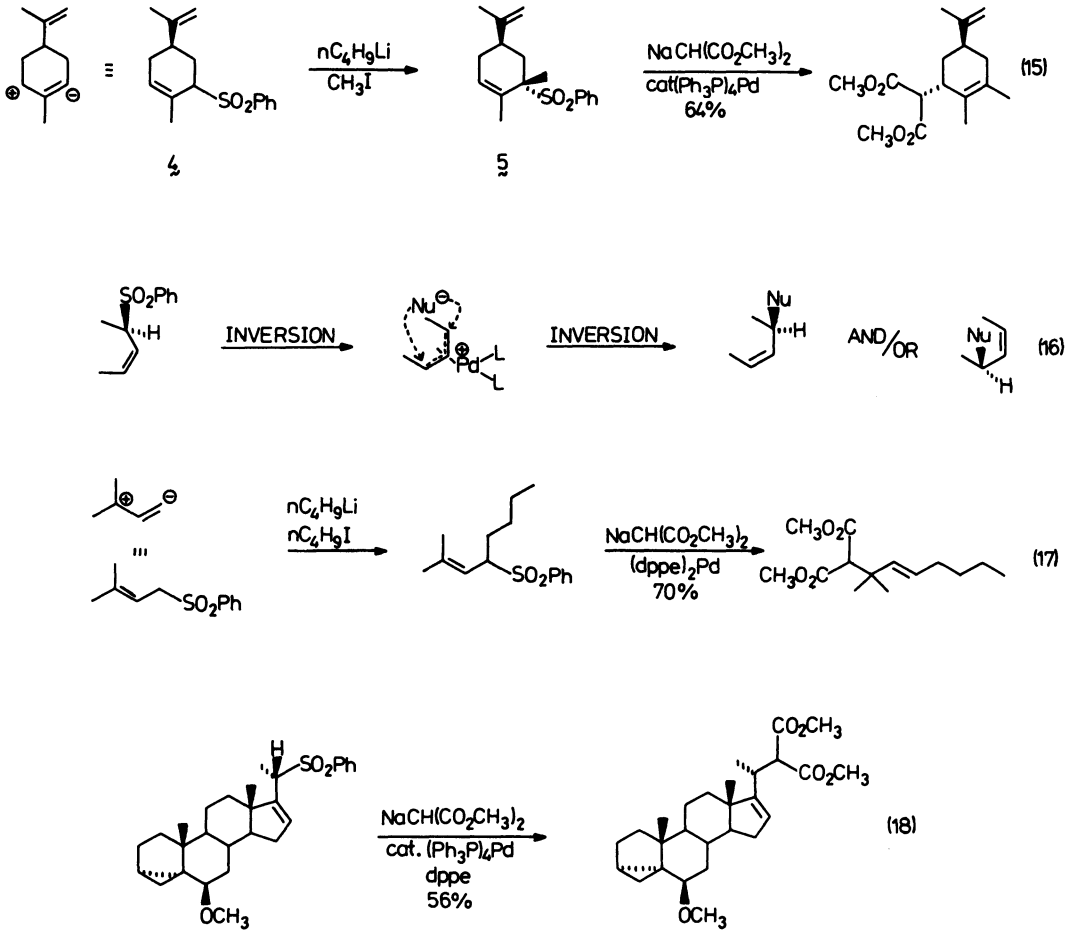
An alternative stereocontrolled introduction of an olefin via organosulfones, also introduced by Julia, relies on the steric bulk of the sulfone to direct placement of the larger alkyl group on the β-carbon of an α,β-unsaturated sulfone to be trans as in Eq. 9.[16] Stereocontrolled replacement of the C–S bond by a C–H using basic dithionite completes a stereoselective approach to (Z)-olefins.

The base-catalyzed elimination of aryl sulfones has also served as a useful approach to olefins. A synthesis



of vitamin A acid illustrates the alkylation–elimination sequence (Eq. 10).[17] The acidification of the proton to be removed (i.e. H_a in **3**) by virtue of its being vinylogously alpha to the ester facilitates the elimination but is not required. An allylic proton proved sufficient in a synthesis of a pheromone constituent of the false coddling moth (Eq. 11) but this elimination requires much harsher base conditions.[18] Activation of the sulfone as a leaving group by placing an electron donating group α to the sulfone has also proven effective (Eq. 12).[19] An interesting variant is a double elimination of β-acetoxy sulfones (Eq. 13)[20] which relies upon 1) facilitation of elimination of the elements of acetic acid by the sulfone, 2) the ease of converting a vinyl sulfone to an allyl sulfone and 3) the vinylogous elimination of the elements of benzenesulfinic acid.

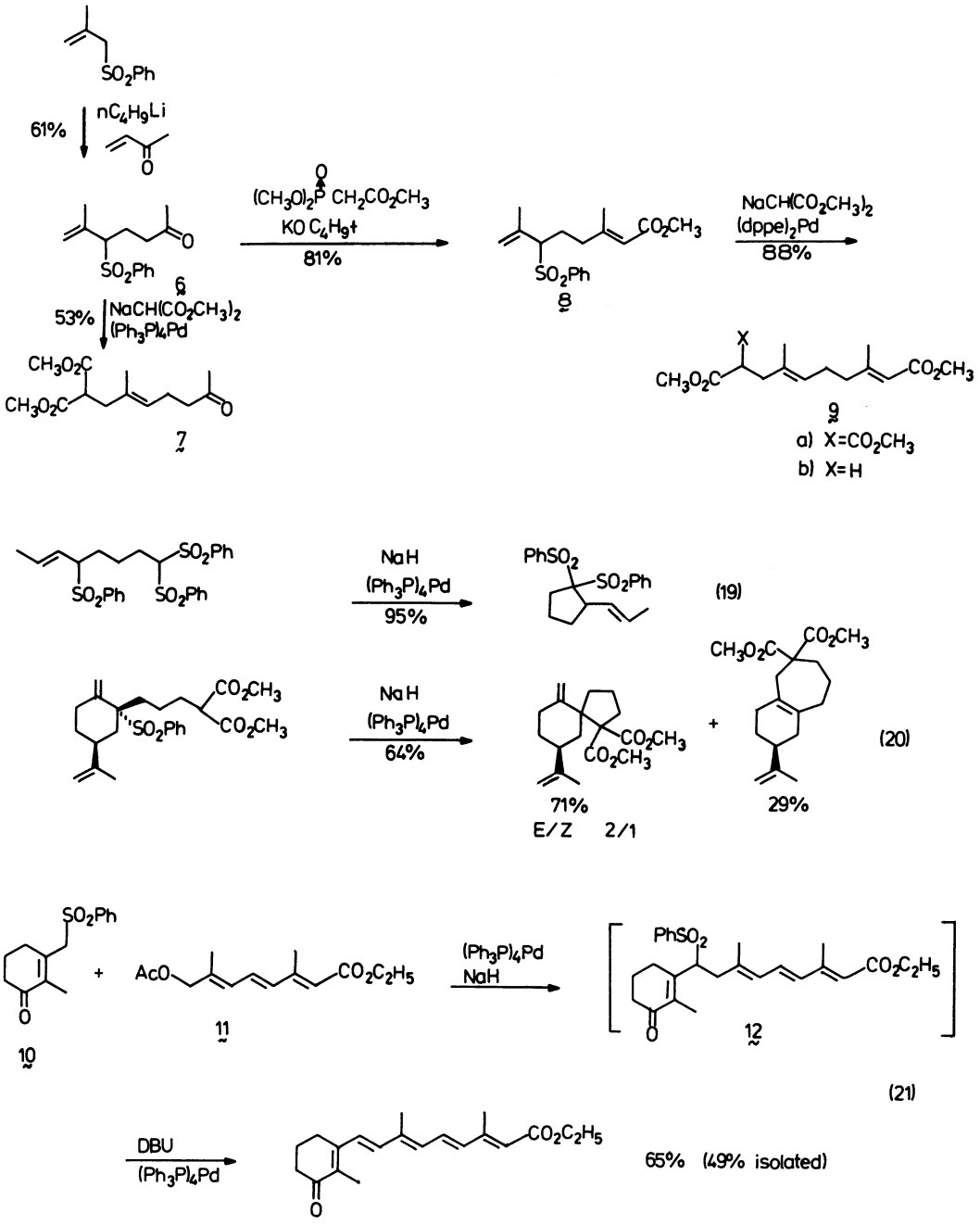
The elimination of the elements of arenesulfinic acid to form olefins relies upon the leaving group ability of sulfones. Although a phenylsulfonyl group has been estimated[21] to be a poorer leaving group than chloride by 10^9, it still functions viably in such a role. We became intrigued with the question of substituting the sulfone—a type of reaction which was



almost unprecedented. The earliest documented case involved formation of a cyclopropane[22] which evolved into a practical synthesis of methyl chrysanthemate according to Eq. 14.[23] Such a cyclopropanation proves to be rather limited and no other types of rings have been produced.

Transition Metal Promoted Substitutions. The poor leaving ability of an arylsulfonyl group has led to the exploitation of the trifluoromethylsulfonyl group which is 10^7 times better as a leaving group.[24] An alternative approach to overcome this lack of reactivity is to use a transition metal to activate the sulfone. The excellent ability of low valent palladium complexes to facilitate displacements of poor leaving groups at allylic positions led us to explore the reactions of allyl sulfones. Diastereoselective alkylation of allyl sulfone **4** leads predominately (88:12) to **5**.[25] Subjecting sulfone **5** to dimethyl sodiomalonate in the presence of a catalytic amount of a Pd(0) complex leads to regio- and diastereoselective substitution as depicted in Eq. 15. Since Pd(0) catalyzed alkylations involves initial substitution of the leaving group by palladium followed by displacement of the palladium by the nucleophile, the overall stereochemistry is net retention of configuration (Eq. 16). In principle, attachment can occur at either terminus of the allyl system independent of the original location of the sulfone. While formation of the new C–C bond at the less substituted position as depicted in Eq. 15 is most common, unhindered nucleophiles like malonate anion preferentially form the new C–C bond to the more substituted carbon when the competition is between a primary and a tertiary center or between a secondary and a tertiary center in an acyclic case (Eq. 17). This method has been employed to introduce a steroid side chain in a stereocontrolled manner (Eq. 18).[26]

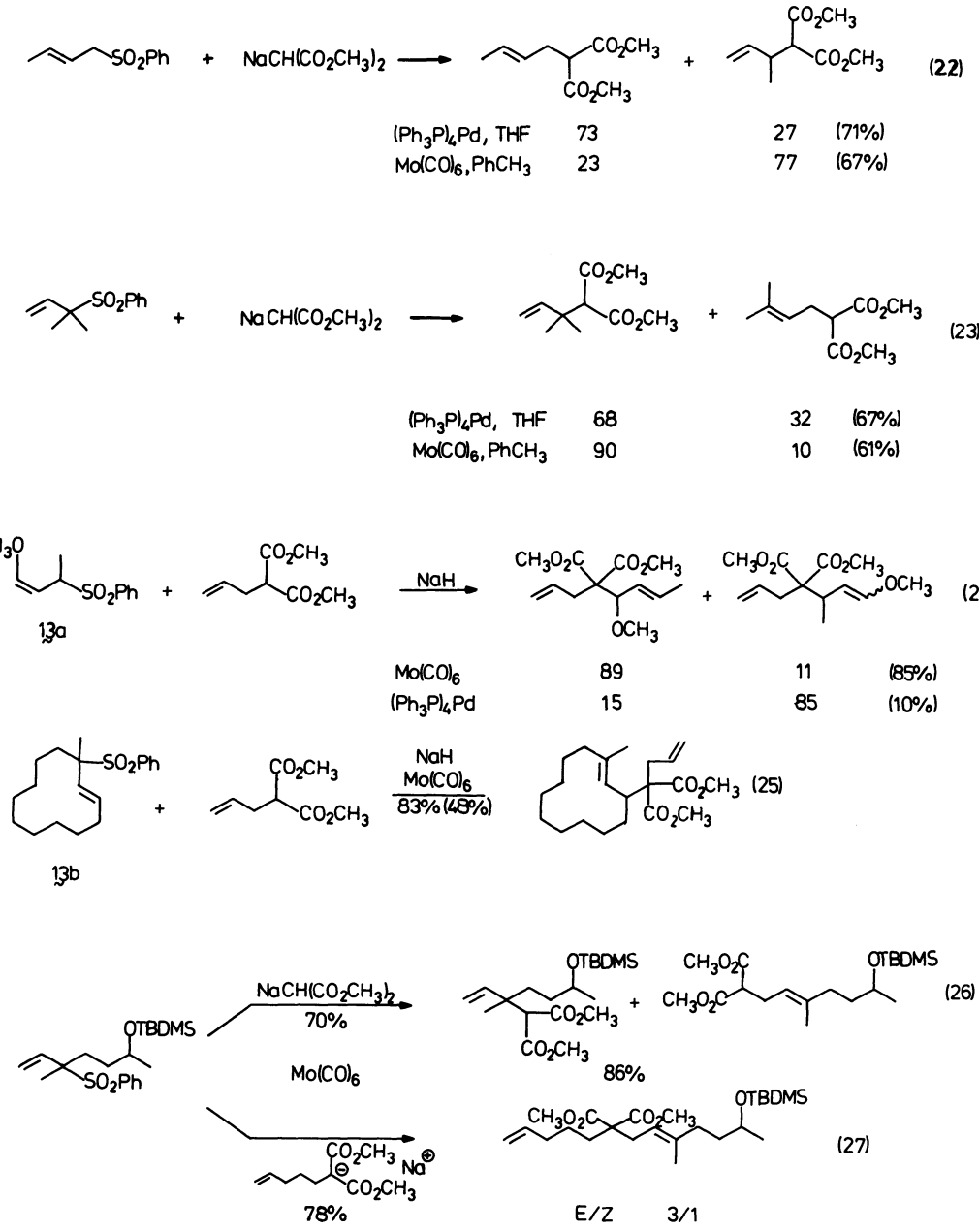
The chemoselectivity of this approach for C–C bond formation is highlighted by a short synthesis of the dimethyl ester of the sex pheromone of the Monarch butterfly (**9b**).[25] The keto sulfone **6** was a substrate for the palladium reaction, without the need to protect the carbonyl group, to give **7** with excellent regioselectivity. On the other hand, use of a typical carbonyl reagent, a phosphonate anion, led to the olefination product **8** without complications from the allyl sulfone. Addition of the sterically less demanding catalyst, $Pd(dppe)_2$, and dimethyl sodio-



malonate led in a regioselective alkylation to **9a** which has been previously decarbomethoxylated to the pheromone ester **9b**.

Whereas, all of the foregoing examples involve intermolecular alkylations, intramolecular alkylations also succeed as shown in Eqs. 19 and 20.[27] The choice of nucleophile may determine the regioselectivity. Thus, as Eq. 20 shows, the sterically undemanding malonate prefers to attack the sterically congested tertiary carbon although the selectivity is only moderate. In the absence of a nucleophile, eliminations to dienes occur. The ability of sulfone stabilized anions to serve as nucleophiles in palladium catalyzed alkylations of allylic acetates combined with the palladium catalyzed eliminations of allylic sulfones has led to a useful one pot alkylative elimination to polyenes according to Eq. 21.[25] In a model to vitamin A metabolites, the anion derived from allyl sulfone **10** is smoothly alkylated by allylic acetate **11** in the presence of a Pd(0) catalyst in DMSO at room temperature to give the intermediate **12**. DBU is added directly to the reaction mixture and the temperature raised to 80 °C to complete the sequence. Both steps, alkylation and elimination, require Pd(0) activation.

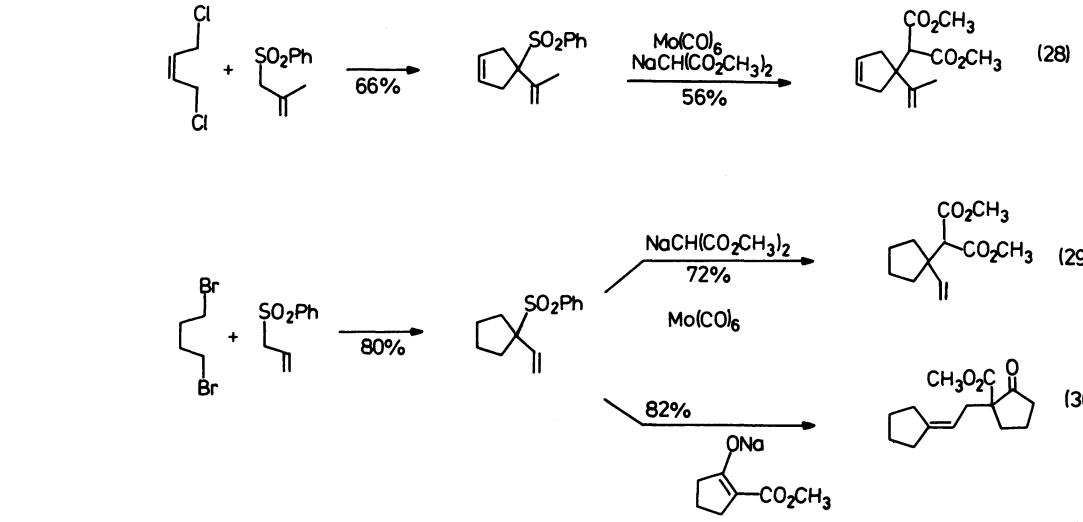
Molybdenum catalysts also activate allylic sulfones

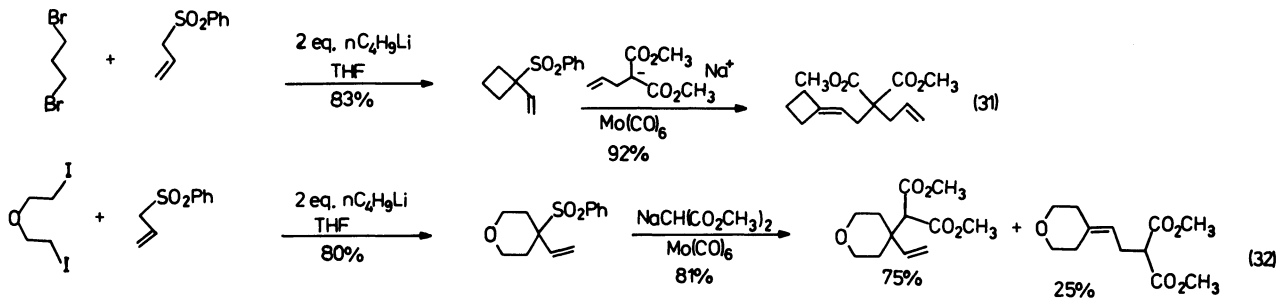


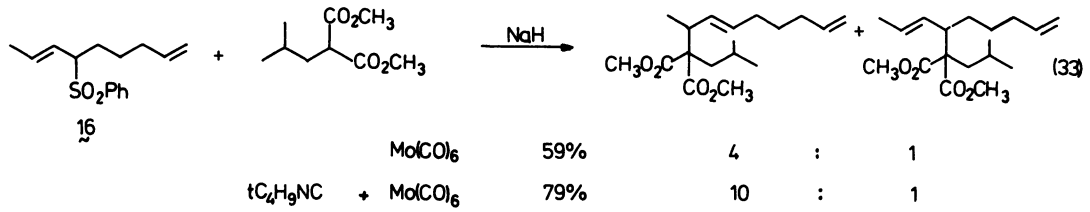
for alkylation.[27] Such catalysts usually complement the regiochemistry of the palladium catalyzed reactions as shown in Eq. 22. In the case of α,α-dimethylallyl phenyl sulfone, the propensity for alkylation at the tertiary position shown by the palladium catalyst is further enhanced by the molybdenum catalyst. In some cases, an allylic sulfone participates poorly in a Pd(0) catalyzed reaction but quite well in the Mo(0) version as in the case of **13a** and **13b** (Eqs. 24 and 25). In the case of Eq. 25, no reaction was observed with the Pd(0) catalyst; whereas, the Mo(0) catalyst gave an 83% yield at about 50% conversion. Normally, however, the Pd(0) catalyzed reaction is the more general.

Good diastereoselectivity may accompany these reactions as shown in Eq. 26 where only one diastereomeric product was observed although we have no basis for making an assignment of stereochemistry as yet. Increasing the steric bulk of the nucleophile by simply switching from the anion of dimethyl malonate (Eq. 26) to that derived from an alkylated malonate (Eq. 27) changes the regioselectivity from one dominated by the electronic distribution in the intermediate π-allylmolybdenum system to one dominated by the steric demands of the attacking nucleophile.

Combining alkylation of sulfone stabilized anions with molybdenum catalyzed reactions leads to a synthesis of 1,1-disubstituted cycloalkanes (Eqs. 28 and 29). As in all cases, use of a sterically more

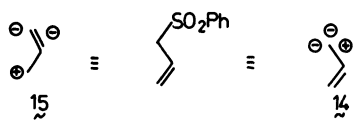






	$Mo(CO)_6$	59%	4	:	1
tC_4H_9NC	+ $Mo(CO)_6$	79%	10	:	1

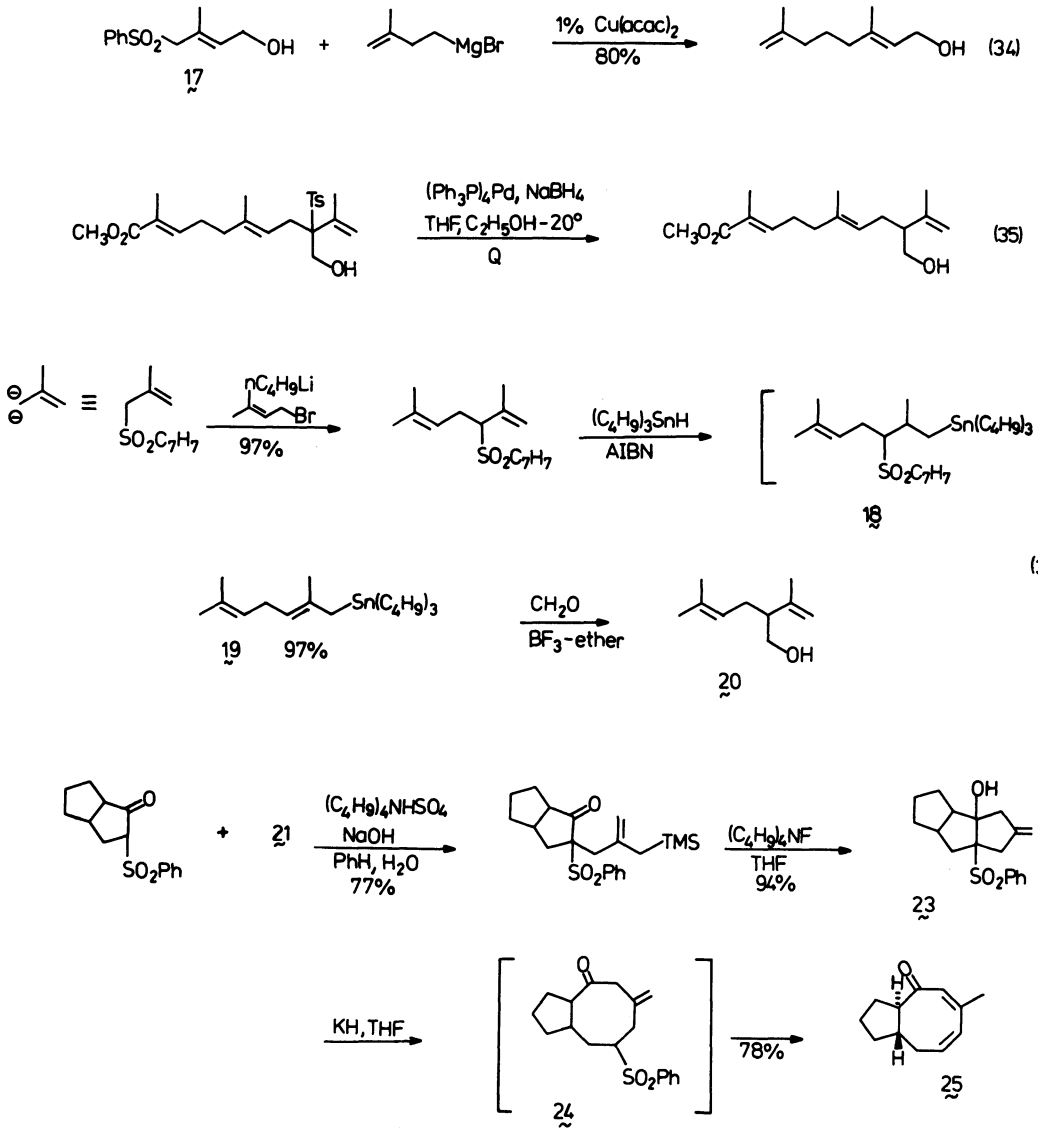
crowded nucleophile leads to attack at the primary carbon (Eq. 30). Both four membered rings (Eq. 31) and heterocycles (Eq. 32) can be made. Unlike other examples, dimethyl sodiomalonate gives poor regioselectivity in the four-membered ring case. This two step sequence illustrates the equivalency of an allyl sulfone to a 1,1,1-(i.e. **14**) or 1,1,3-(i.e. **15**) tripole.



The lability and volatility of the CO ligands limits the lifetime of the molybdenum hexacarbonyl catalysts. In a preliminary examination, we found that addition of a catalytic amount of *t*-butyl isocyanide indeed enhances the catalyst lifetime.[27] For example, the yield in the alkylation of allyl sulfone **16** increased substantially as did the degree of regioselectivity upon adding 3 eq. of *t*-butyl isocyanide per molybdenum.

Nickel catalysts also promote substitutions of allyl sulfones[28] but with lower regioselectivity than observed with either palladium or molybdenum catalysts. For example, the alkylation of α,α-dimethylallyl sulfone with dimethyl sodiomalonate gave a 91% yield of the two alkylation products depicted in Eq. 23 in almost a 2:3 ratio (with the major product derived from attack at the primary carbon) using $(dppe)_2Ni$.[27]

In all of the cases discussed, stabilized anions, were employed as nucleophiles. Substitutions by non-stabilized carbon nucleophiles occur smoothly using copper catalyzed additions of Grignard reagents. For example, a chemo- and regioselective displacement of

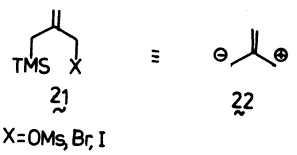


the sulfone moiety of the hydroxy sulfone **17** occurs as shown in Eq. 34.[29]

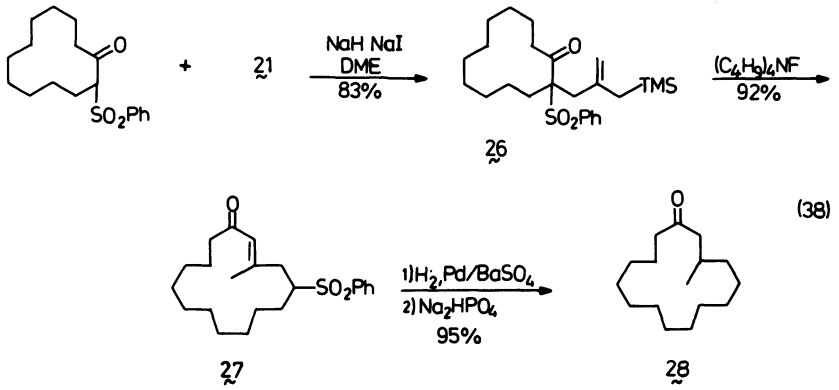
Reductive desulfonylations can also be achieved by using a hydride equivalent in metal catalyzed reactions. As shown in Eq. 35,[30] a synthesis of dehydrohelepuberinic acid ester took advantage of the sulfone stabilized anions to construct the carbon skeleton and then reductively cleaved the sulfone using Pd(0) catalysis in which the hydroxyl group dictated the regioselectivity.

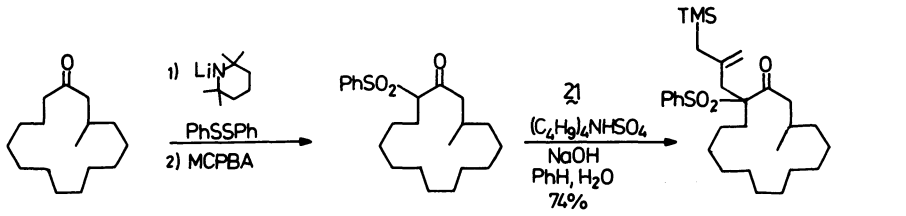
Radical Substitutions. An alternative way to overcome the sluggishness of sulfones to substitution takes advantage of the radicals bearing a β-sulfone. Thus, the allyl sulfone **18** undergoes radical substitution, presumably by an addition–elimination sequence, by tributyltin radical as depicted in Eq. 36.[31] The resulting allylstannane undergoes carbonyl addition to give the monoterpene lavandulol (**20**). In this case, the umpolung associated with converting an allyl sulfone **18** to an allylstannane **19** equates the starting methallyl phenyl sulfone to a 1,1-dianion.

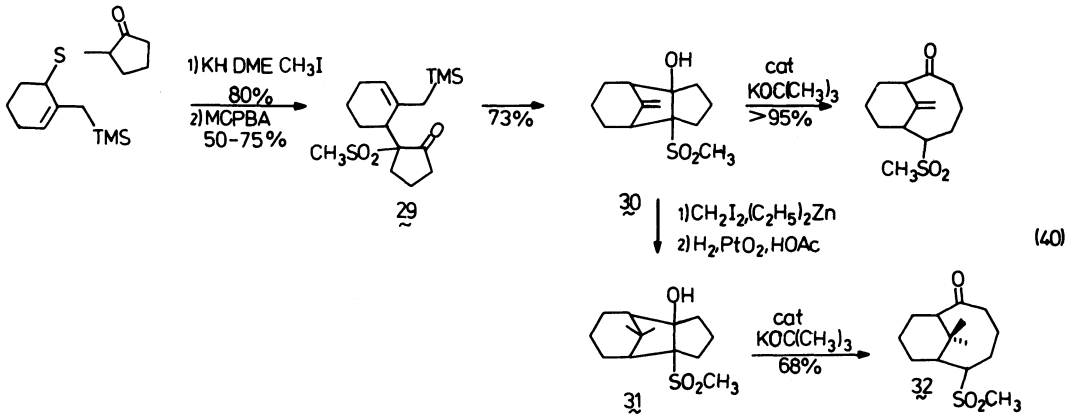
A Three Carbon Intercalation. The bifunctional conjunctive reagent **21** serves as a synthon for a 1,3-dipole **22**.[32] As depicted in Eq. 37, this zwitterionic



behavior allows straightforward methylenecyclopentane annulation.[33] By employing a β-keto sulfone as the starting meterial, the annulation creates a β-hydroxy sulfone **23**. Due to the anion stabilizing ability of the sulfone, converting the hydroxyl group into a "naked" alkoxide causes the common bond to cleave to create a ring enlarged β-keto sulfone **24**. Under the basic conditions for ring cleavage, the exocyclic double bond migrates into conjugation with the carbonyl group and, by so doing, facilitates the



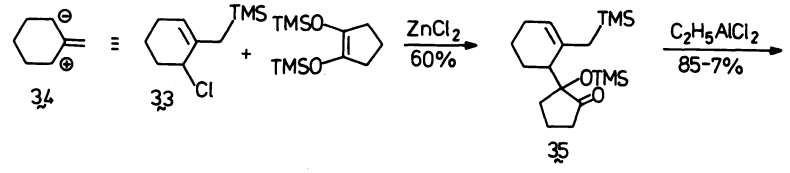




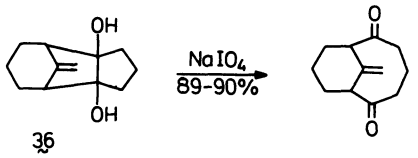
base catalyzed elimination of the elements of benzenesulfinic acid to produce the eight membered ring dienone **25**.

The facility of fragmentation of the β-hydroxy sulfone **23** is related to ring size. If the starting β-keto sulfone is either acyclic or a cyclic system of more than seven carbons, cyclization of the allylsilane to create the methylenecyclopentane is accompanied by fragmentation as depicted for the 12-membered case **26** (Eq. 38). Thus, fluoride promoted cyclization leads directly to the enone **27** whereby fragmentation of the methylenecyclopentane and double bond migration occur concomitant with initial cyclization. Catalytic hydrogenation and desulfonylation complete a synthesis of muscone in an outstanding 62% overall yield from cyclododecanone, the precursor of the β-keto sulfone. This sequence lends itself to an iterative process. As shown in Eq. 39, muscone has been grown to an 18-membered ring.[34]

This method can also be used to create bridged bicyclic systems. In a model directed toward the bridged bicyclic portion of taxanes, the keto sulfone **29** was prepared by a sigmatropic rearrangement followed by oxidation (Eq. 40).[35] Fluoride initiated cyclization of the allylsilane led to substantial protodesilylation. On the other hand, ethylaluminum dichloride induces cyclization to the bridged bicyclic hydroxy sulfone **30**. Fragmentation occurred most smoothly with a catalytic amount of potassium *t*-butoxide in DMSO. More pertinent, the gem-



34 33 35



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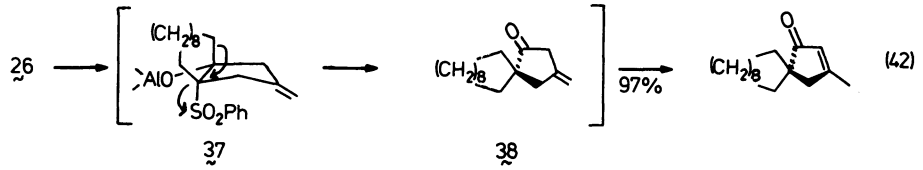
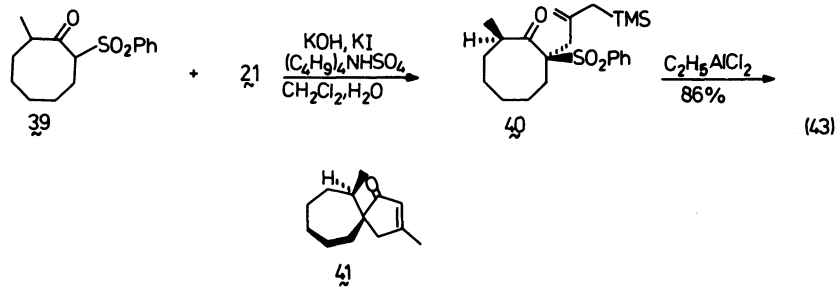
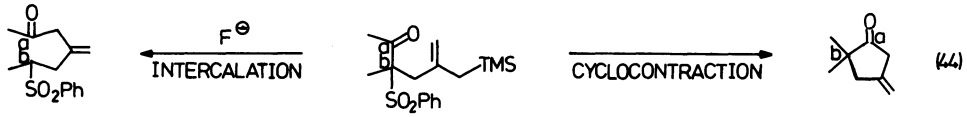


37 38 (42)



39 40 (43) 41



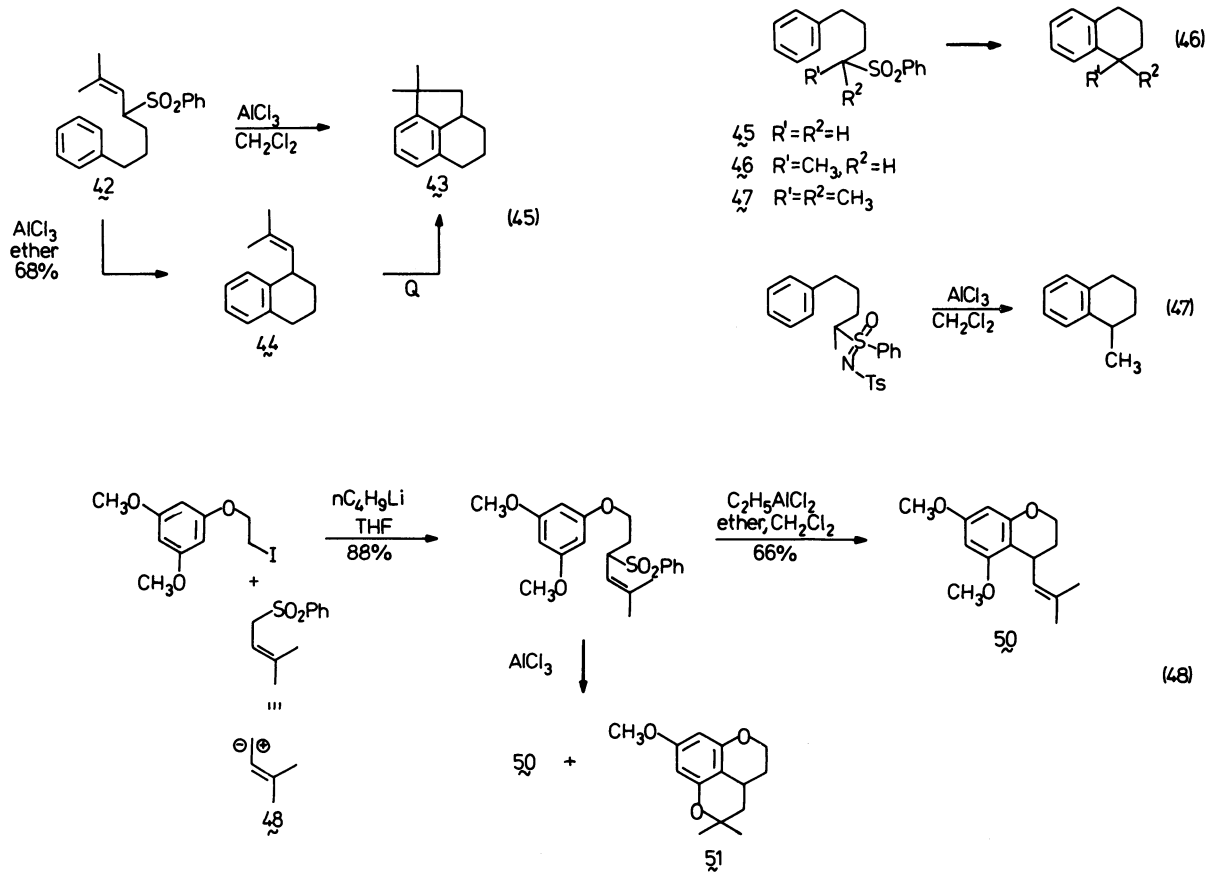
(44)

dimethyl compound **31**, available by hydrogenolysis of the cyclopropane derived from methylenation of the olefin of **30**, also fragments to the desired bicyclo-[5.3.1]undecane skeleton.[36]

In this version, the silyl chloride **33** serves directly as the 1,3-dipole synthon **34**. Lewis acids reveal both types of reactivity by, first, activating the allyl chloride **33** in its reaction with the enediol bis(silyl ether) and, second, by activating the carbonyl group of **35** towards addition by the allylsilane. Diol cleavage then completes the sequence.

The use of ethylaluminum chloride to cyclize the allylsilanes as in the cases of **29** and **35** proved limited. Applying the reaction to substrate **26** led to a totally different process as shown in Eq. 42.[37] In the presence of the Lewis acid, the initial cyclization product **37** apparently suffers a pinacol-type rearrangement to produce the ring contracted spiro ketone **38**. Isomerization of the exocyclic double bond into conjugation completes the sequence of this cyclocontraction-spiroannulation.

Excellent diastereoselectivity accompanies this novel approach to form spirocycles. Alkylation of the eight-membered ring keto sulfone **39** gives a single diastereomer **40** (Eq. 43). Ethylaluminum dichloride leads to cyclization and ring contraction to give the spirocycle **41** in which the migrating carbon completely retains its stereochemistry. Thus, depending upon the nature of the catalyst, two quite disparate reactions reflecting the multifaceted properties of sulfones can occur. As summarized in Eq. 44, a nucleophilic trigger promotes intercalation and an electrophilic trigger diverts the intermediate via a pinacol type rearrangement to a 2,2-disubstituted 4-



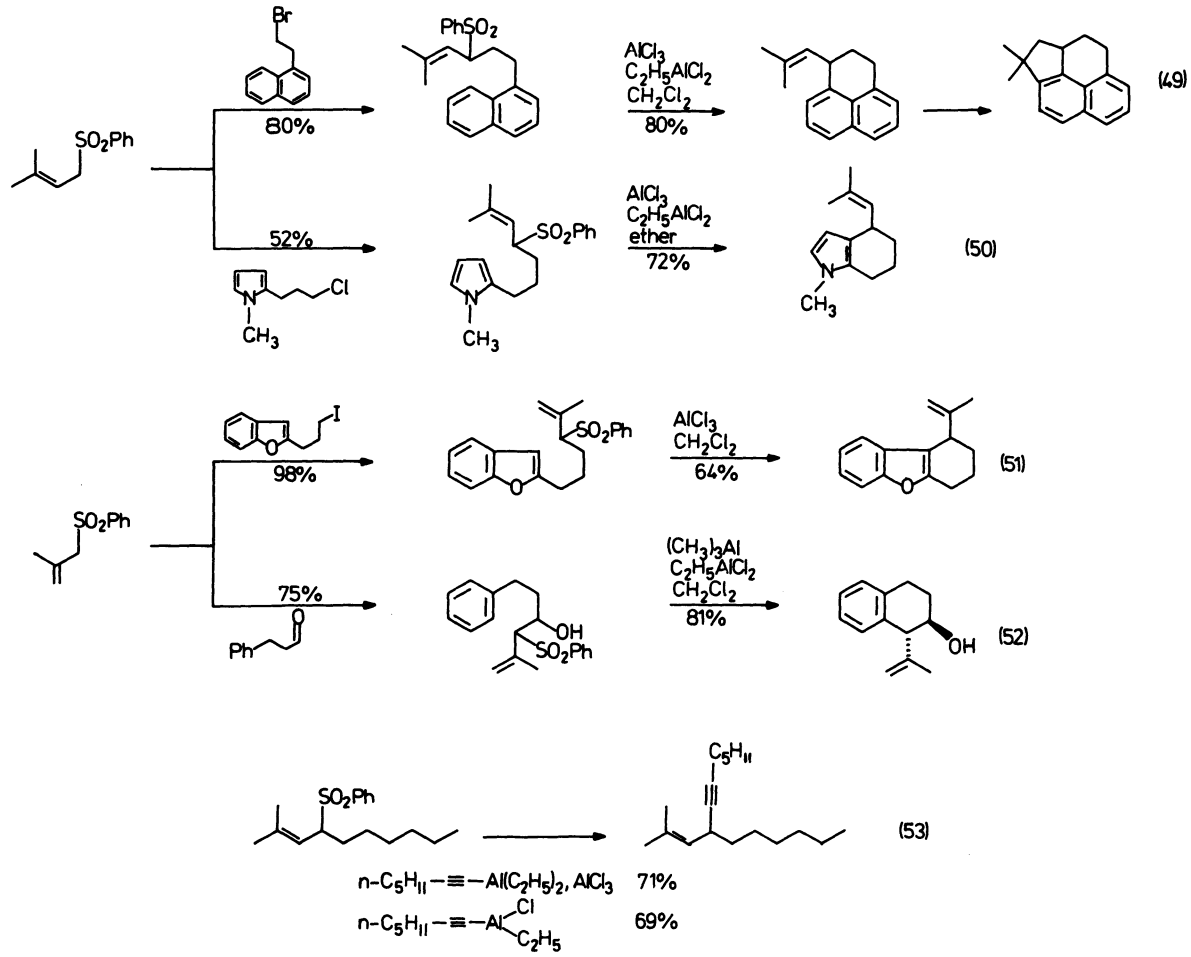
methylenecyclopentanone. The sensitivity of the β-hydroxy sulfone toward Lewis acid promoted rearrangement is quite remarkable considering the absence of any prior indication that Lewis acids induce ionization of organosulfones.[38]

Lewis Acid Induced Cyclizations. The ability to effect a pinacol-type rearrangement in which a phenylsulfonyl group ionizes in the presence of as weak a Lewis acid as ethylaluminum dichoride led to an investigation of the ionizing ability of simple organosulfones. Strikingly, the allyl sulfone **42** cyclized to the tricycle **43** even at −78°C in the presence of aluminum chloride in methylene dichloride.[39] Attenuating the reactivity of the aluminum chloride by using ether as a solvent requires 35°C for reaction, but the product is cleanly that of the simple cyclization **44**. Subsequent treatment with either aluminum chloride in methylene dichloride or trifluoroacetic acid quantitatively cyclizes the latter to the tricycle **43**.

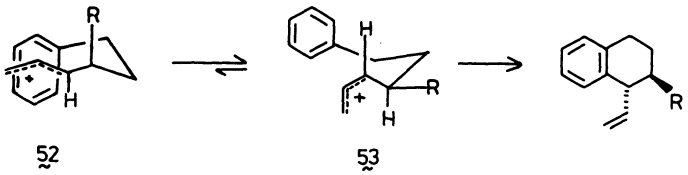
To determine how good a cation is necessary for ionization, the substrates **45**—**47** were treated with aluminum chloride (Eq. 46). Neither **45** nor **46** satisfactorily cyclizes; however, the tertiary sulfone **47** smoothly produces 1,1-dimethyltetralin in 70—80% yield with aluminum chloride in methylene dichloride. Increasing the Lewis basicity of the sulfone by using the sulfoximine extends the cyclization to secondary carbon centers (Eq. 47).[40] Competition studies indicate the sulfoximines are about twice as reactive as the corresponding sulfones.

The chameleon-type behavior of sulfones is readily apparent by the source of the cyclization substrates as revealed by a model study related to robustadials[41] and euglobals[42] (Eq. 48). The first step takes advantage of the nucleophilic properties of sulfone stabilized anions and the second step utilizes the propensity of allyl sulfones to ionize to the corresponding cations. In this way, prenyl sulfone serves as a synthon for the 1,1-dipole **48**. The choice of Lewis acid and solvent may be important. For example, aluminum chloride effects a second cyclization to **51** in competition with formation of the simple cyclization product **50**. By using ethylaluminum dichloride and further attenuating the Lewis acidity by using ether as a cosolvent, the second cyclization can be suppressed. Eqs. 49 and 50 reveal some of the generality of this cyclization strategy for both carbo- and heterocyclic cases. Equation 49 illustrates the further cyclization of the initial tricyclic product. Equation 50 reveals that the acid labile pyrrole ring survives when a HCl scavenger, ethylaluminum dichloride, is also employed although the benzofuran system of Eq. 51 does not require it.

Equation 52 shows the utility of the adducts from the metalated sulfone and an aldehyde participating



in the cyclization.[43] The alcohol is first reacted with trimethylaluminum before subjecting it to the stronger Lewis acid. Cyclization proceeds in excellent chemical yield and diastereoselectivity with only the (E)-product produced. The excellent diastereoselectivity is not limited to the hydroxyl substituent since the substrate bearing a methyl group in lieu of the hydroxyl group shows similar stereocontrol.[44] View-



52 53

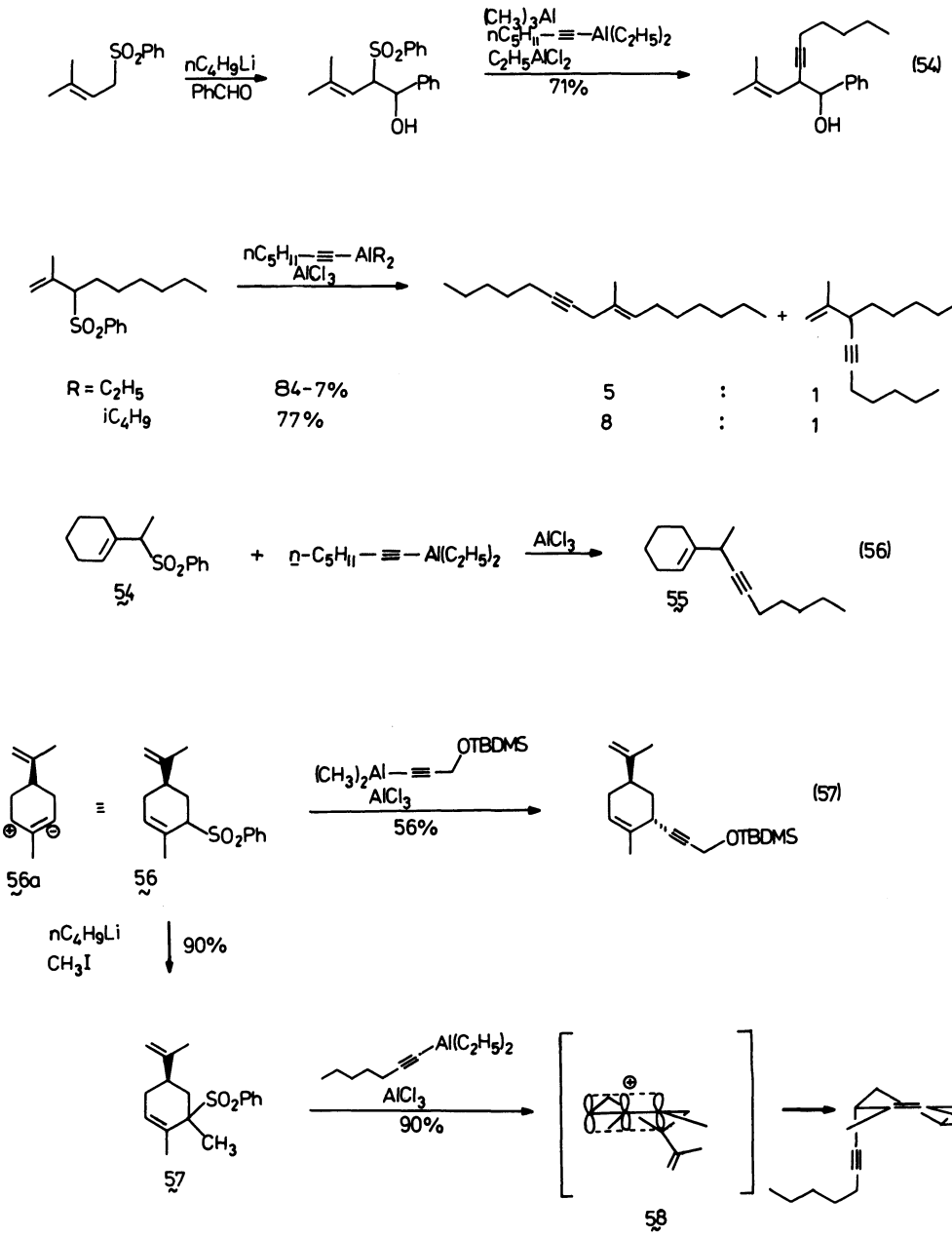
ing the cation generated upon ionization of the sulfone in a chair-type conformation suggests that placing this substituent in a pseudoaxial position as in **52** is less favorable than placing it in a pseudo-equatorial one as in **53**.

Lewis Acid Induced Condensations. The success of cyclization reactions led to a search of intermolecular condensations which require nucleophiles compatible with Lewis acids. Organoalanes have proven themselves as nucleophiles in the presence of Lewis acids and, in some cases, as both Lewis acid and nucleophile.[45]

Alkynylalanes, prepared by treating the lithiated alkyne with an appropriate chloroalane, smoothly condense with allyl sulfones. As shown in Eq. 53, use of a diethylalkynylalane requires aluminum chloride as a catalyst; whereas, an alkynylethylchloroalane serves as both the Lewis acid and nucleophile.[43] Unfortunately, the latter did not prove to be general and reactions frequently proceeded with only low conversions.

The high reactivity of the allyl sulfone is highlighted by the compatibility of the benzyl alcohol in the case of Eq. 54. As previously, smooth reaction requires initial treatment of the hydroxy sulfone with trimethylaluminum.

Even though the reaction proceeds through allyl cations, good regioselectivity normally accompanies this reaction. In the case of an unsymmetrical allyl system, competing a primary or secondary terminus with a tertiary one, very high selectivity for formation of the new C–C bond at the less substituted carbon occurs (cf. Eq. 53). In a primary versus secondary case, the selectivity for attack at the less substituted carbon

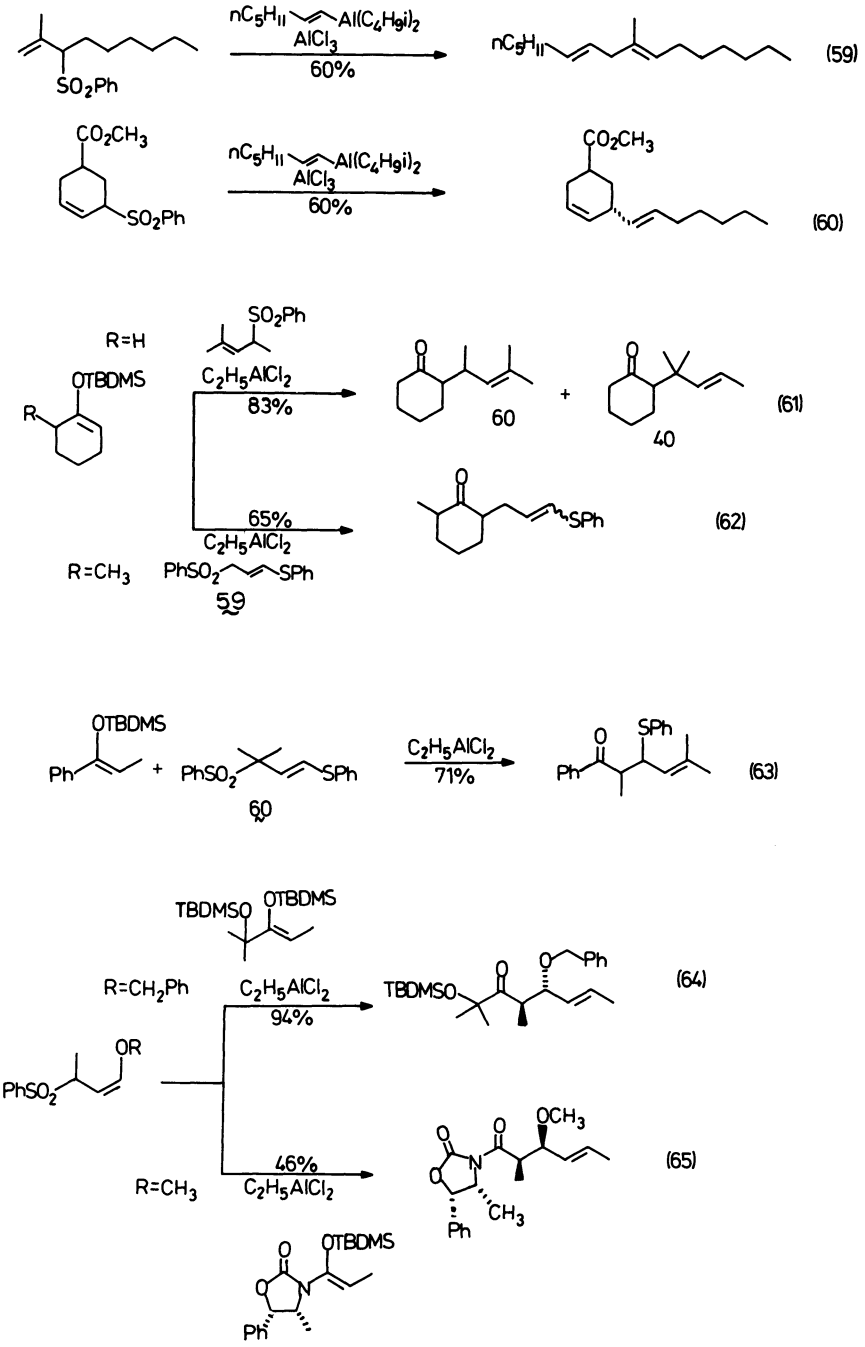


is somewhat lower (Eq. 55). By increasing the steric demands of the organoalane such as replacing ethyl by isobutyl, some improvement for attack at the primary terminus occurs. Allyl sulfone **54** competes two secondary carbons. The preference for the double bond to be endocyclic and the lower steric hindrance associated with attack at the exocyclic position leads to **55** as the dominant product (6:1, Eq. 56).

Good diastereoselectivity is obtained with cyclohexenyl phenyl sulfones (Eqs. 57 and 58). The preference for axial attack presumably derives from stereoelectronic factors.[46] Pseudoaxial attack on the intermediate allyl cation **58** allows the ring to directly distort toward the favorable half-chair conformation while maintaining good orbital overlap. Attack by the organoalane leading to the equatorial product requires distortion of the ring towards a boat—a less favorable process. The regioselectivity as shown in Eq. 58 demonstrates the preference for attack at the less hindered terminus of the allyl system regardless of the initial position of the sulfone. Since **57** arises by the methylation of the lithiated sulfone **56**, the latter is a synthetic equivalent to a 1,3-dipole **56a**.

Alkenylalanes, prepared by hydroalumination of acetylenes, behave in exactly analogous fashion as shown by Eqs. 59 and 60. Note that the intrinsically higher steric demands of an alkenylalane compared to an alkynylalane leads to higher regioselectivity (cf. Eqs. 55 versus 59).

The success of enol silanes as the nucleophilic

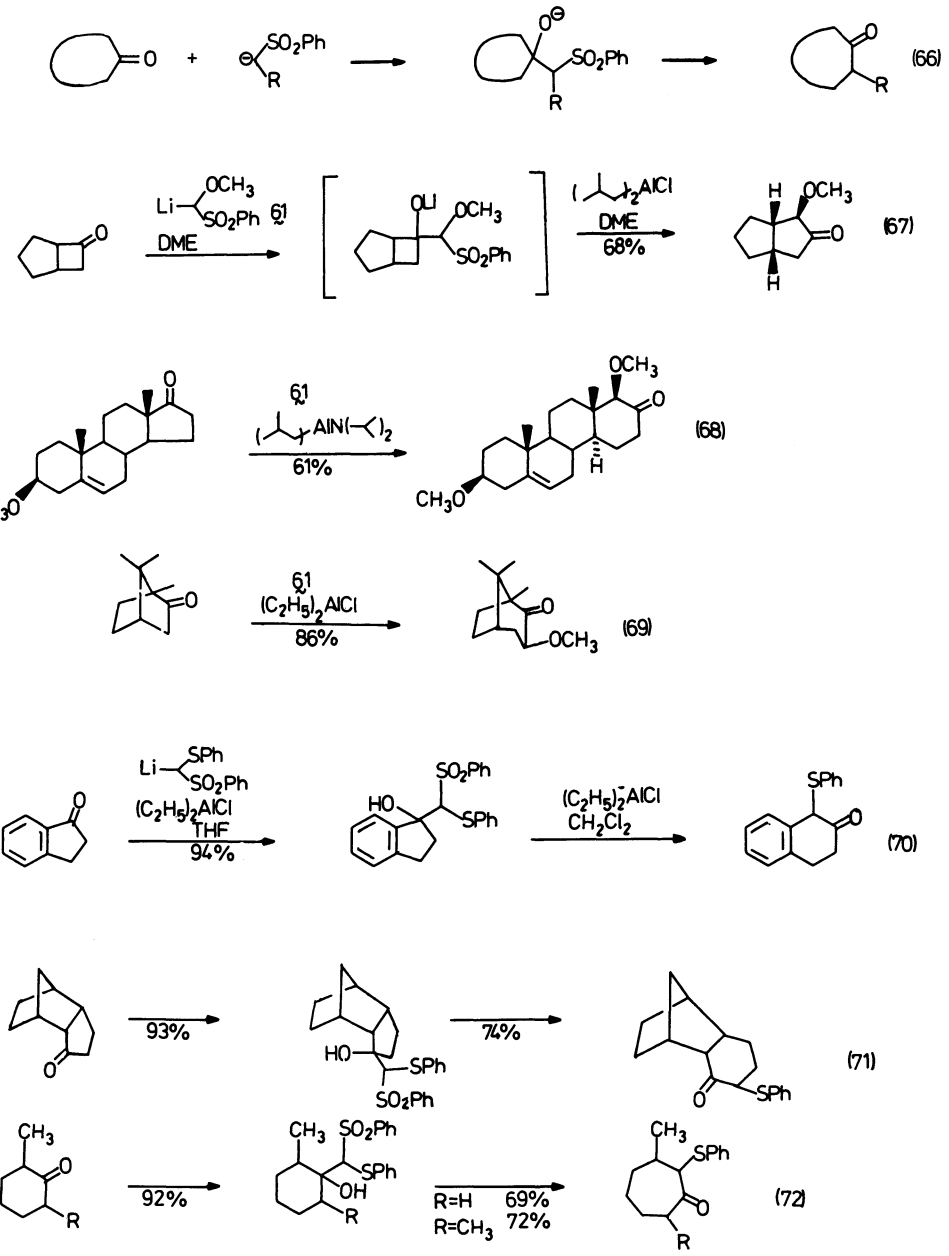


partners in Friedel–Crafts types of alkylations[47] led to their exploration as nucleophiles towards allyl sulfones. The most striking difference from the alkynyl- and alkenylalanes is the lower regioselectivity (cf. Eq. 61) unless the allyl sulfone has a strongly directing substituent (Eq. 62).[44] The regiochemistry in the latter case appears dictated by steric effects since the dimethyl analog **60** of the above sulfone **59** now proceeds by formation of the new C–C bond at the carbon bearing sulfur.

Modest diastereoselectivity accompanies this reaction. Whereas, the enol silyl ether of a ketone shows anti selectivity (Eq. 64, anti/syn 92/8); the enol silyl ether of an imide shows syn selectivity (Eq. 65, syn/anti 80/20).

The range of nucleophiles compatible with the conditions required for ionization of a sulfone remains yet to be defined. The success of organoalanes and enol silyl ethers indicated that we have reason to be optimistic that a rather broad variety will be feasible.

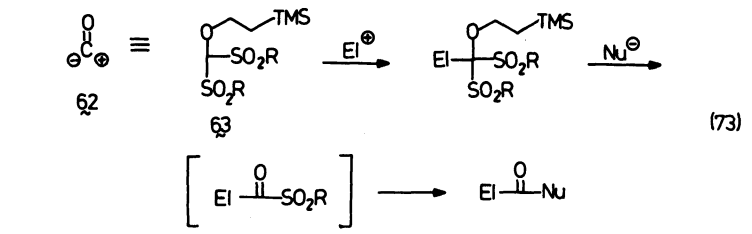
Lewis Acid Induced Ring Expansion. The duality of function of organosulfones corresponds to the type of reactivity necessary for ring expansions according to Eq. 66. The excellent acidifying properties of the sulfone should make this process feasible for



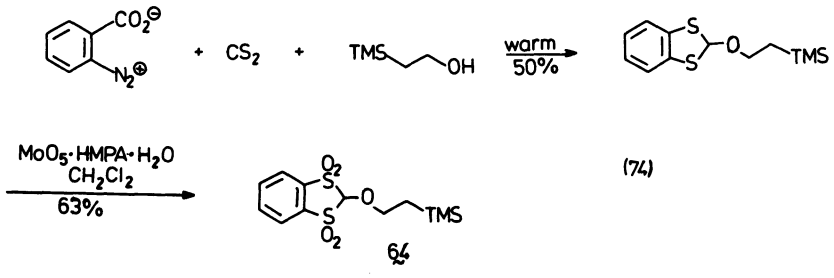
substrates in which R is a very poor anion stabilizing group or even anion destabilizing. Since few methods exist to expand rings directly to α-heteroatom substituted cycloalkanones, use of R=SPh and OCH_3 were first considered.[48]

As Eqs. 67—69 show, four- and five-membered ring ketones smoothly add methoxy(phenylsulfonyl)-methyllithium (**61**) in DME. Direct addition of a dialkylaluminum chloride to the lithium alkoxide effects ring enlargement in a one pot operation. While dialkylaluminum chlorides are normally employed (Eqs. 67 and 69), the steroid example required a milder Lewis acid which turned out to be diisobutylaluminum diisopropylamide (Eq. 68). As a carbonium ion process, the carbon α to the original carbonyl group that can best stabilize positive charge normally preferentially migrates (Eqs. 67 and 68). The case of camphor is an exception. Since migration of the bridgehead tertiary carbon would involve a boat-type transition state, the normally less favorable methylene group migrates since a favorable chair conformation can now be accomodated.[49]

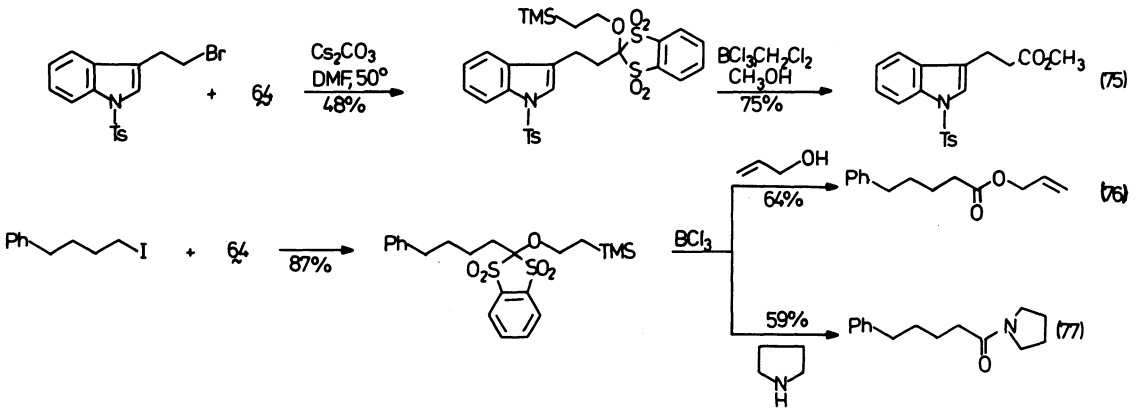
Extension of the above ring expansion to the phenylthio series proved problematic due to the fact that the equilibrium for carbonyl addition of phenylthiophenylsulfonylmethyllithium in THF was unfavorable. However, addition of diethylaluminum chloride to the THF solution resolves this problem and gives the simple carbonyl adducts without rearrangement (Eqs. 70—72). Subjecting the hydroxy sulfones to the same aluminum reagent but in methylene dichloride effects smooth rearrangement.



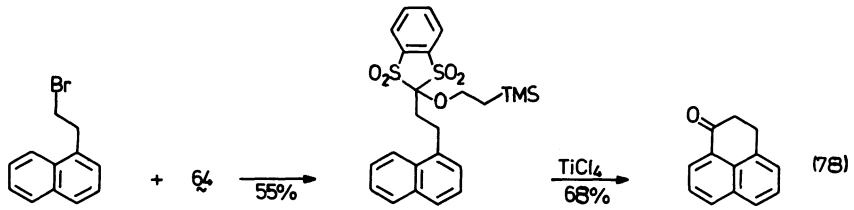
(73)



(74)



(75) (76) (77)

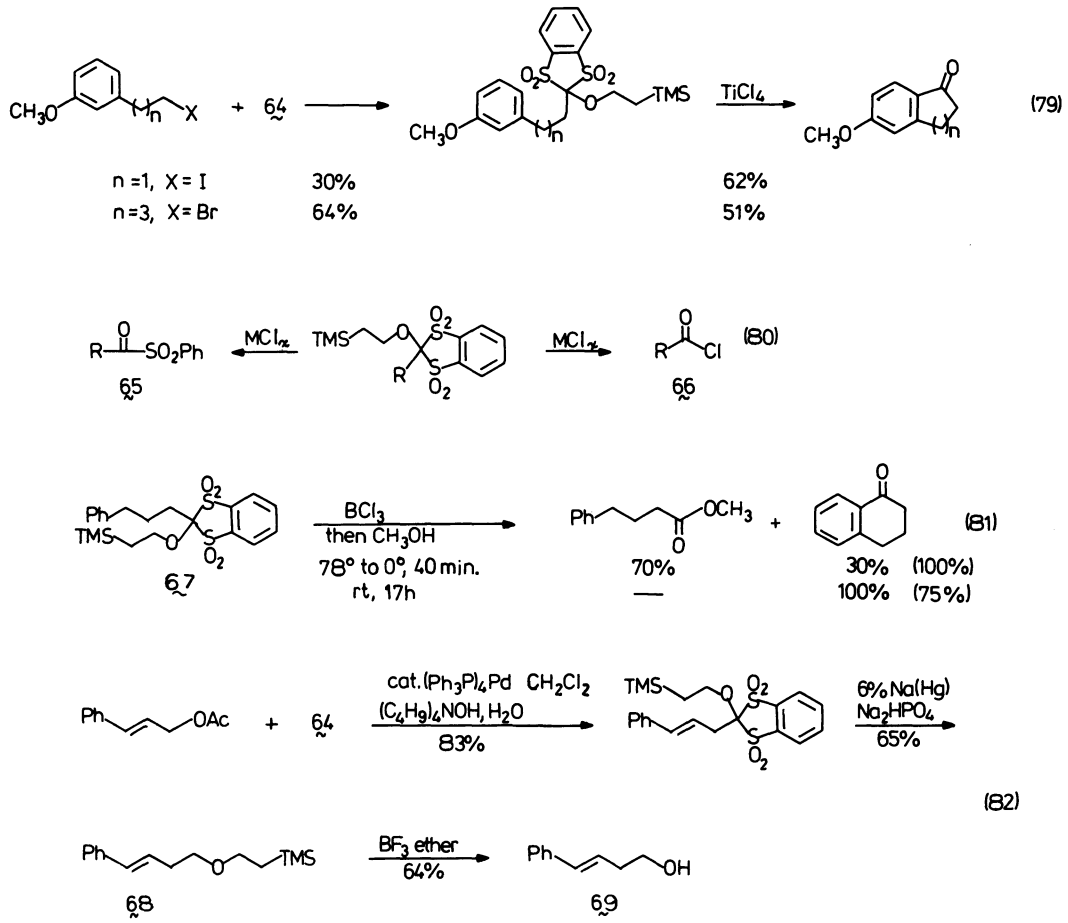


(78)

The migrating aptitude follows precisely the same pattern found for the methoxy reagent. The carbon that best stabilizes a positive charge normally migrates (Eqs. 70 and 72). On the other hand, conformational factors can overcome this electronic bias (Eq. 71). The ring expansion of the phenylthio reagent appears more general than that of the methoxy reagent **61**. Notably, ring expansion of six to seven (Eq. 72) occurs smoothly with the phenylthio reagent in contrast to the attempted reactions with **61**.

A Carbonyl 1,1-Dipole. The general importance of carbonyl compounds led to the extension of the above concepts to develop a controlled synthon for a carbonyl 1,1-dipole **62**. As revealed in Eq. 73, an alkoxy-bis(sulfone) **63** may be able to serve such a role. Such a reagent, **64**, was prepared as outlined in Eq. 74.[50]

The lability of the anion derived from **64** led to its formation in the presence of the appropriate electrophile. The examples of Eqs. 75—79 demonstrate that cesium carbonate in warm DMF best effects the alkylation. Exposure of the alkylation products to a Lewis acid such as boron trichloride followed by adding heteroatom nucleophiles such as an alcohol (Eqs. 75 and 76) or an amine (Eq. 77) completes the sequence. In these examples, a carbon group served as the electrophile and a heteroatom group served as the nucleophile. Thus, an ester and an amide synthesis is



available.

By using carbon groups as both nucleophile and electrophile, ketones are available. Equations 78 and 79 show how a carbonyl group can be stitched into place with appropriate arylalkyl halides. The demonstrated examples illustrate formation of five-, six-, and seven-membered rings.

The nature of the reactive electrophile in all of the above cases remains undefined. While it is tempting to speculate that acyl sulfones **65** may be involved, an acid chloride **66** may also be postulated (Eq. 80). That a reactive intermediate is indeed produced is strongly supported by treating **67** with boron trichloride at −78 to 0 °C followed by addition of methanol (Eq. 81) whereby the corresponding methyl ester and tetralone are both produced. Increasing the reaction time and temperature before adding methanol produces only tetralone.

The reductive desulfonylation of sulfones opens yet another avenue for application of this alkoxy-bis(sulfone) as shown in Eq. 82. The 2-(trimethylsilyl) ethyl group of **68** can be cleaved to produce the free saturated alcohol **69**. The overall transformation of Eq. 82 constitutes a homologation of an allyl alcohol to a homoallyl alcohol and corresponds to employment of the anion derived from **64** as a hydroxymethyl anion equivalent.

Conclusion

While it is always tempting to believe that a well explored path offers little opportunity for innovation, the tremendous subtleties that control reactivity undermine any such notion. Although the chemistry of sulfones extends back for over one hundred years, their utility as synthetic building blocks based upon their facilitation of carbanion formation strongly emerged in the 1960's. In spite of this extensive work, their high sensitivity to ionization to carbocations in the presence of Lewis acids, especially those derived from aluminum, had gone unnoticed. This reactivity of an inverse electronic sense opens new vistas. Their ability to function as nucleophiles in a basic environment and as electrophiles in a Lewis acidic environment aptly allows them to be called "chemical chameleons" from which many new applications and new synthetic reagents remain to be discovered.

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