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Organic Synthesis Using the Migrating Functional Groups Ph_2PO and PhS

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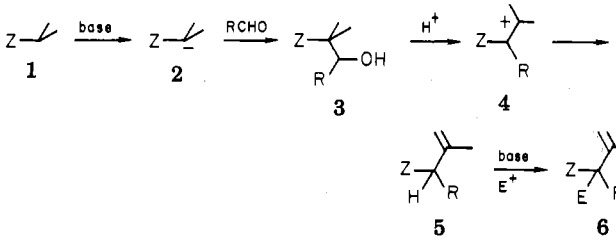
Alkyl migrations have long been used in organic synthesis.[1] One common strategy in the synthesis of compounds with fused five- and seven-membered rings is to set up the correct decalin and then reorganize the carbon skeleton by a pinacol rearrangement.[2] The migration of functional groups serves a different purpose. If a group, Z, which stabilizes a carbanion, **2**, can also migrate, we might use it to form one C–C bond in making **3**, and then, after rearrangement **3** → **4** → **5**, use the same group Z to form more C–C bonds, e.g., **5** → **6**.



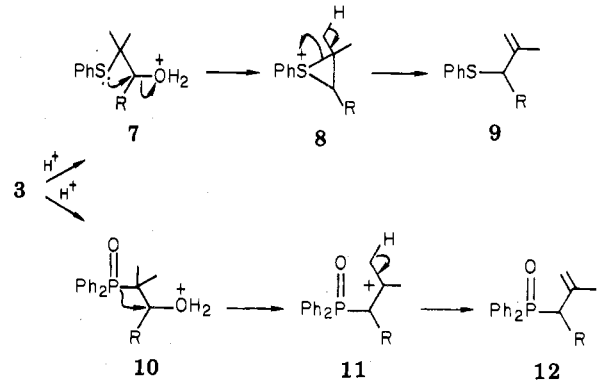
1 **2** **3** **4** **5** **6**

For schemes like this to be successful, we must have unambiguous answers to three questions about the rearrangement **3** → **5**. Will rearrangement be the only course taken by the reaction? If rearrangement does occur, will Z alone migrate, or will alkyl shifts compete? If migration of Z alone occurs, will a single product having a hydrogen atom next to Z (as in **5**) be formed in high yield?

Of the various groups we have studied, only phenylthio (PhS) and diphenylphosphinoyl (Ph_2PO) meet these requirements. We believe that PhS migrates because it participates so well[3] (**7**), whereas Ph_2PO migrates to give the stable tertiary cation **11** rather than the unstable cations next to the Ph_2PO group which would result from alkyl shifts.[4] Other groups such as carbonyl or nitro lead to other reactions in these circumstances.[5]

Ph_2PO Migrations in Synthesis

Making the Organophosphorus Compounds. Everyone knows that triphenylphosphine, the cheapest



7 **8** **9** **3** **10** **11** **12**

starting material, can be alkylated and the phosphonium salts **13** made into ylides for Wittig reactions. Not so familar is the "hydrolysis" of the phosphonium salts **13** in aqueous base: benzene is expelled, giving the phosphine oxides **14**.[6-14] The new group R^1CH_2 must

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(1) I. Fleming, "Selected Organic Synthesis", Wiley, London, 1973.
(2) C. H. Heathcock in "The Total Synthesis of Natural Products", Vol. 2, J. ApSimon, Ed., Wiley–Interscience, New York, N.Y., 1973, pp 395–424.
(3) P. Brownbridge and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1131 (1977).
(4) F. H. Allen, O. Kennard, L. R. Nassimbeni, R. G. Shepherd, and S. Warren, *Nature (London)*, 248, 670 (1974); *J. Chem. Soc., Perkin Trans. 2*, 1530 (1974), and references therein to earlier work.
(5) P. Brownbridge, P. K. G. Hodgson, R. G. Shepherd, and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 2024 (1976).
(6) H. R. Hays and D. J. Peterson in "Organophosphorus Compounds", Vol. 3, G. M. Kosolapoff and L. Maier, Ed., Wiley–Interscience, New York, N.Y., pp 349–354.
(7) A. H. Davidson, C. Earnshaw, J. I. Grayson, and S. Warren, *J. Chem. Soc., Perkin Trans 1*, 1452 (1977).
(8) A. H. Davidson and S. Warren, *J. Chem. Soc., Perkin Trans 1*, 639 (1976).
(9) A. H. Davidson, I. Fleming, J. I. Grayson, A. Pearce, R. L. Snowden, and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 550 (1977).
(10) D. Howells and S. Warren, *J. Chem. Soc., Perkin Trans 2*, 1472 (1973).
(11) A. H. Davidson and S. Warren, *J. Chem. Soc., Chem. Commun.*, 148 (1975).
(12) J. I. Grayson, H. K. Norrish, and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 2556 (1976).
(13) C. Earnshaw, C. J. Wallis, and S. Warren, *J. Chem. Soc., Chem. Commun.*, 314 (1977); submitted to *J. Chem. Soc., Perkin Trans. 1*.
(14) P. F. Cann, D. Howells, and S. Warren, *Chem. Commun.*, 1148 (1971); D. Howells and S. Warren, *J. Chem. Soc., Perkin Trans. 2*, 1645 (1973).

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Table I
Alkyldiphenylphosphine Oxides 15

entry	R^1	R^2	method	yield, %	ref
1	$PhCH_2$	H	a	90	12
2	*i*-Pr	Me	b	80	9
3	MeO	H	a	90	13
4	Me	Me_3SiCH_2	b	80	9
5		$(CH_2)_4$	c	82	7

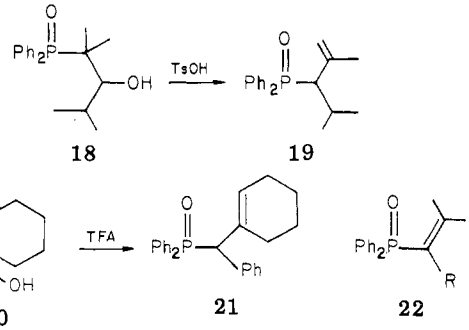
Table II
Adducts 17 of Phosphine Oxides 15 and Carbonyl Compounds

	phosphine oxide		carbonyl compound		yield of 17,	
entry	R^1	R^2	R^3	R^4	%	ref
1	H	$PhCH_2$	Ph	H	71	12
2	H	MeO	*p*-$MeOC_6H_4$	H	85	13
3	H	Me_3SiCH_2	$(CH_2)_5$		69	9
4		$(CH_2)_4$	Me	H	83	7
5	Me	Me	Me	Et	70	9

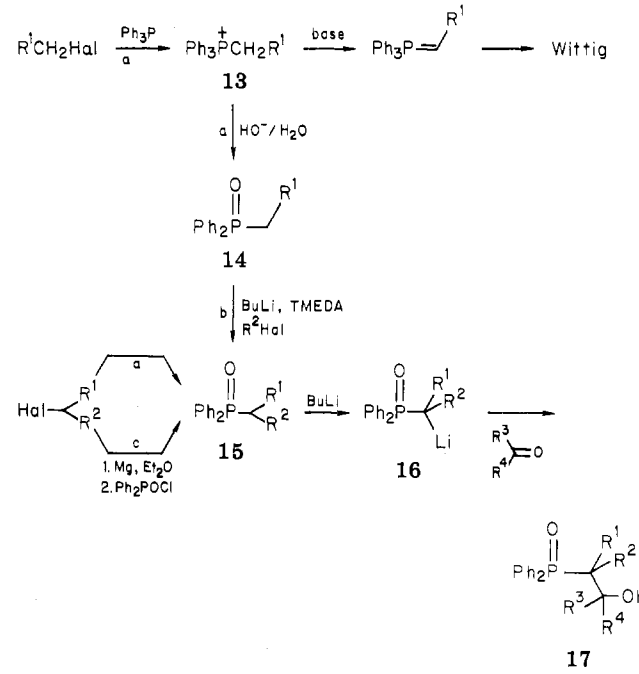
be a simple alkyl group: if R^1 stabilizes an adjacent anion, R^1CH_3 will be expelled instead. Secondary alkylphosphine oxides **15** can be made in the same way (Scheme I), or from the same halide via the Grignard reagent and the acid chloride Ph_2POCl.[7,8] If the preformed alkyl fragment is not available, either branch (R^1 or R^2 in **15**) can be added by alkylation of **14**, using TMEDA as cosolvent.[9] These phosphine oxides are highly crystalline white solids, as are all the Ph_2PO-containing compounds we have made except vinylphosphine oxides. Some examples are given in Table I.

All the simple alkylphosphine oxides **15** form deep-red lithium derivatives **16** with butyllithium (BuLi) in ether or THF,[8-13] and these add cleanly to aldehydes or ketones to give the alcohols **17** (Table II). Additions to acetaldehyde and cyclopentanone show that enolization of the carbonyl compound is not a problem, though it does help to use solvent saturated with LiBr in these cases.[7,9,12]

Rearrangement of the Ph_2PO-Containing Alcohols. Almost all the secondary alcohols with neighboring Ph_2PO groups on tertiary carbon rearrange in acid by Ph_2PO migration (**10**).[7-14] Those with a symmetrical migration origin having two methyl groups, e.g., **18**, or a cyclohexyl group, e.g., **20**, give the allyl phosphine oxides **19** and **21** as the only products. Benzaldehyde adducts, e.g., **20**, react in hot trifluoroacetic acid (TFA), the less reactive alkanal adducts, e.g., **18**, in boiling benzene containing *p*-toluenesulfonic acid (TsOH). Under these conditions the allylphosphine oxides **12** slowly isomerize to the useless vinylphosphine

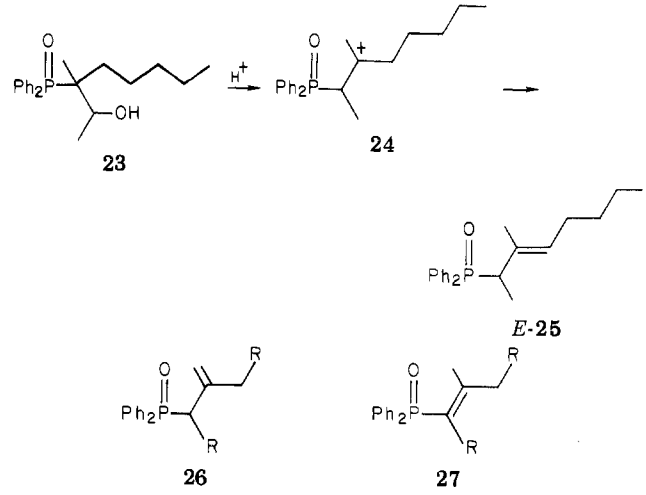


Scheme I



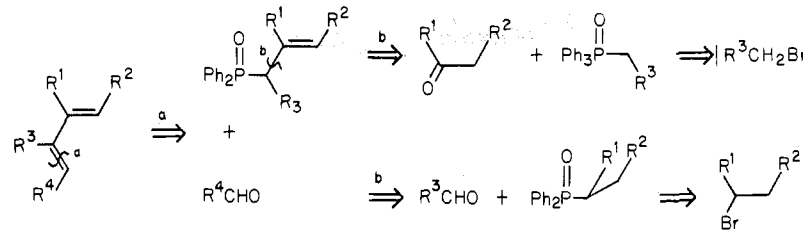
oxides **22**, particularly when R = Ph. This does not happen to **21**.

Alcohols with an unsymmetrical migration origin,[9] e.g., **23**, could rearrange to either allylphosphine oxide **25** or **26**. The methylene compound **26** is the first-formed kinetic product, but it never accounts for more than 30% of the reaction mixture. By the time the starting material has gone, only the more substituted olefin **25** is present: this is stable under the reaction conditions. The reaction is therefore totally regioselective. It is also reasonably stereoselective: *E*-**25** is favored over *Z*-**25** by >8:1. Pure *E* isomers are easily isolated by chromatography, if necessary, and recrystallization.

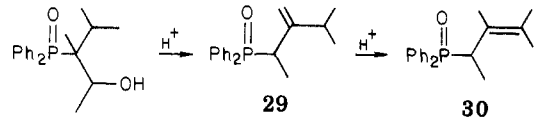


Regioselectivity between products (e.g., **12** vs. **22** and **25** vs. **26** or **27**) depends very much on the relative stabilities of the compounds as olefins, regarding Ph_2PO simply as a rather large alkyl group. Conjugation between P=O and C=C is very weak, if it is there at all. The thermodynamic order of stability seems to be: tri- > 1,2-di- > tetra- > 1,1-di- > monosubstituted olefins. The kinetic order (rates of formation from and return to the corresponding cation) is probably: 1,1-di- > tri- > tetra- >> mono- and 1,2-disubstituted. So,

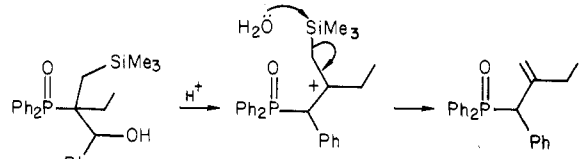
Scheme II



when we have a secondary alkyl substituent at the migration origin as in **28**, one product, **30**, is now tet-



28 **29** **30**

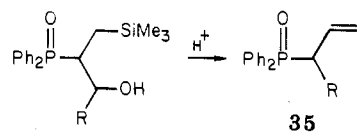


31 **32** **33**

rasubstituted and is both slowly formed and only slightly more stable than the 1,1-disubstituted alternative **29**. We can isolate **29** in 55% yield as the kinetic product or let it slowly form **30** in 90% yield as the thermodynamic product. Similarly the kinetic product **12** slowly forms the vinylphosphine oxide **22**. The trisubstituted olefin **25**, on the other hand, is both rapidly formed and very stable and is *not* transformed into **26** or **27**. The Ph_2PO group, because of its size, exaggerates the normal discrimination between the various olefins to the extent that single regioisomers can be isolated.[9]

The main problem, then, in controlling the reaction to give the interesting methylene compounds, e.g., **26**, is not that they are less stable than **25** but that they are rapidly transformed into **25** under the conditions of the reaction. Our answer to this was to use the trimethylsilyl group (Me_3Si).[9] The rearranged cation **32** should now be stabilized by its β-Me_3Si group,[15] and Ph_2PO migration should be faster. In addition an oxygen nucleophile (water) should attack silicon rather than a hydrogen atom. The benzaldehyde adduct **31** rearranged at room temperature in TFA to give **33** alone. Only at higher temperatures was **33** transformed into the vinylphosphine oxide.[9]

No rearrangement normally occurs when migration origin and terminus are both secondary,[9] but an Me_3Si group will drive this reaction too: **34**, R = Ph or Me, rearranges to **35**. The products, though thermody-

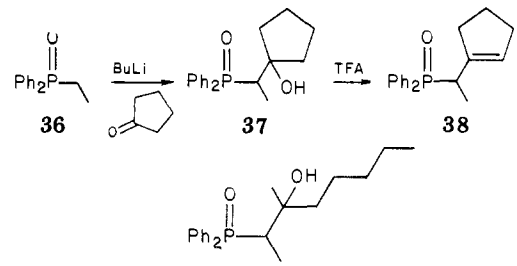


34 **35**

namically unstable, are protonated so slowly that they are stable under the reaction conditions.[9]

(15) I. Fleming, *Chem. Ind. (London)*, 449 (1975); I. Fleming, A. Pearce, and R. L. Snowden, *J. Chem. Soc., Chem. Commun.*, 182 (1976).

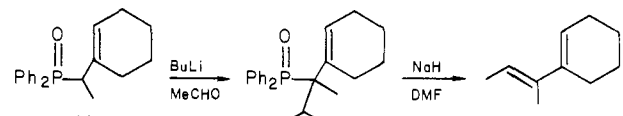
Synthesis of Allylphosphine Oxides without Rearrangement. I have so far assumed that the rearranged cation (e.g., **11**, **24**, **32**) is a genuine intermediate. One reason for this is that both diastereoisomers of, e.g., **23** give the same mixture of geometrical isomers of, e.g., **25**. It should follow that the same cation, e.g., **24**, should give the same mixture of products if formed directly from the tertiary alcohol without rearrangement. We therefore added lithium derivatives of primary alkylphosphine oxides, e.g., **36**, to ketones



36 **37** **38** **39**

and found that the alcohols, e.g., **37**, did indeed dehydrate in TFA to give the same products, e.g., **38**.[7-9] Again, either diastereoisomer of **39** gave the same mixture of geometrical isomers as before. This is often the quickest way to make, e.g., **25** and **38** providing that the ketone is readily available.

Synthesis of Dienes from Allylphosphine Oxides.[16] The single geometrical isomers of allylphosphine oxides (e.g., **40**) available from these reactions could be metalated with BuLi and combined with aldehydes to give alcohols **41**. These could again be



40 **41** *E*-**42**

separated by chromatography and recrystallization to remove traces of other diastereoisomers or geometrical isomers. Treatment with NaH and DMF then gives a single isomer of the diene **42**, usually characterized as its maleic anhydride adduct.[8,9] The diene needs to be separated only from $Ph_2PO_2^-$ as the elimination is stereospecific.

Strategy of the Diene Synthesis. The disconnections used in analyzing the diene synthesis are shown in Scheme II. The first disconnection (a) is a conventional one, giving an aldehyde and the allylphosphine oxide which acts as a regiospecific allyl anion synthon. The second disconnection (b) unconven-

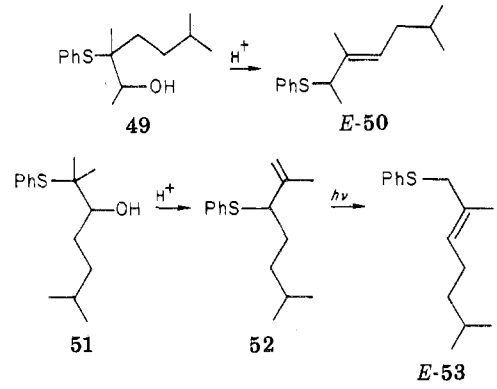
(16) A one-step version of this reaction has been reported by B. Lythgoe, T. A. Moran, M. E. N. Nambudiry, and S. Ruston, *J. Chem. Soc., Perkin Trans. 1*, 2386 (1976); M. Schlosser and H. B. Thuong, *Chimia*, **30**, 197 (1976).

tionally cleaves the single bond in the diene to give two alternative carbonyl compounds as starting materials depending upon whether Ph_2PO migration is or is not used. The strategy is to build the diene from at least three electrophilic fragments: one or more alkyl halides (for the phosphine oxides, see above) and two carbonyl compounds.

PhS Migrations in Synthesis

Making the Organosulfur Compounds. PhS is a weaker anion-stabilizing group than Ph_2PO, and, at the time we started looking at PhS migrations, we believed that $PhSCHR^1R^2$ was metalated on the aromatic ring[17] and a general synthesis of α-phenyl thioketones **44** was not available.[18] We therefore built up the alcohols **45** in stages from the nitrile **43** and the available ketones **48**, R^3 = Me, Ph and **47**, $R^1 = R^3$ = Me, always using the PhS group to control C–C bond formation[3] (Scheme III).

Rearrangement of the PhS-Containing Alcohols. PhS migration in **45** is very fast—a few minutes in refluxing benzene with TsOH are enough.[3,21] The allyl compound, as in the Ph_2PO series, is the only product, but the mechanism is presumably **7**. With an unsymmetrical migration origin, e.g., **49**, only the trisubstituted olefin **50** is formed, and stereoselectivity is



again high (*E*:*Z* = 9:1). The reaction time is so short that there is never any question of vinyl sulfide formation.

The compounds with two methyl groups at the migration origin, e.g., **51**, proved particularly interesting as the first formed allyl sulfides, e.g., **52**, isomerized to, e.g., **53**, by a [1,3] PhS shift both photochemically and thermally (100–110 °C, no solvent). We have presented evidence that this is an associative radical chain reaction (Scheme IV),[22] but Kwart[23] prefers a concerted mechanism for the [1,3] shift in similar compounds. The photochemical reaction is extremely efficient, occurring even with English sunlight filtered through the window and the Pyrex flask. Control is therefore easy: wrapping the flask in foil stops the [1,3] shift, and the allyl sulfides, e.g., **52**, can be isolated in high yield.

(17) A recent report suggests that it may be possible to metallate $PhSCHR^1R^2$ on the aliphatic side after all: T. M. Dolak and T. A. Bryson, *Tetrahedron Lett.*, 1961 (1977).

(18) We have since developed one. See ref 19 and 20.

(19) P. Blatcher and S. Warren, submitted to *J. Chem. Soc., Perkin Trans 1.*

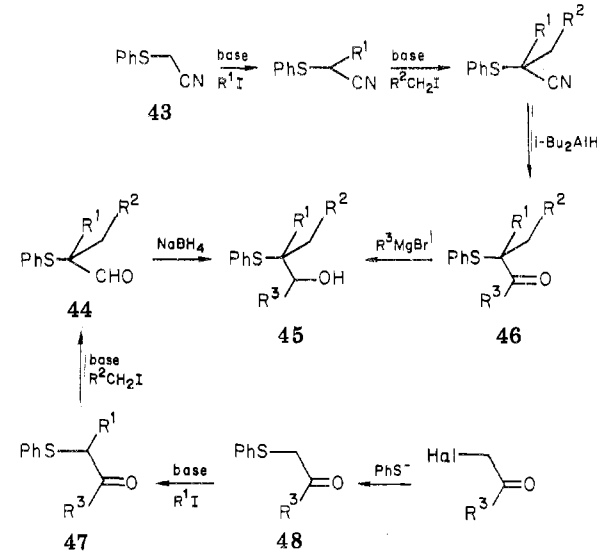
(20) P. Blatcher and S. Warren, *J. Chem. Soc., Chem. Commun.*, 1055 (1976).

(21) P. Brownbridge and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 2272 (1977).

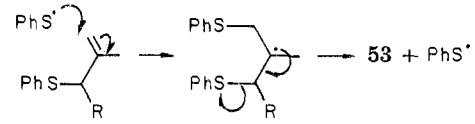
(22) P. Brownbridge and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 2125 (1976).

(23) H. Kwart and T. J. George, *J. Am. Chem. Soc.*, **99**, 5214 (1977).

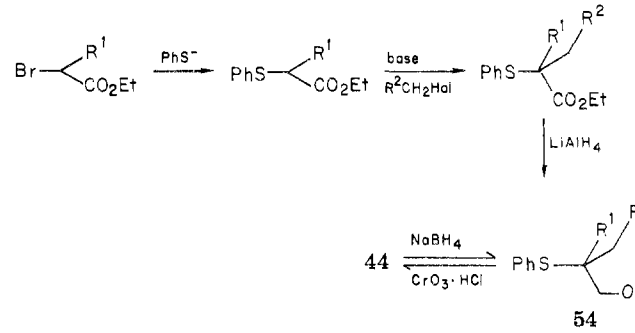
Scheme III



Scheme IV



Scheme V

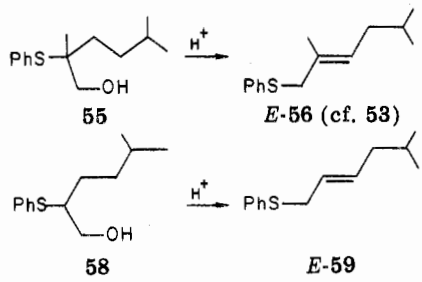


If the [1,3] shift is wanted, it is best to expose the solution to direct sunlight or to add a trace of PhSH.[22]

The sequence **51** → **52** → **53** gives allyl sulfides in which the PhS group has moved one atom along the chain in either direction. The [1,3] shift can be used only when the final product **53** has a more stable C=C bond than the first formed allyl sulfide **52**, using the thermodynamic hierarchy of olefin stability mentioned above.

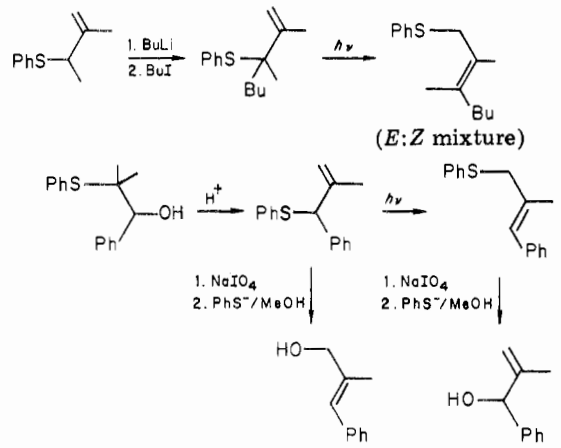
So far, except for the [1,3] PhS shift, PhS has done nothing that Ph_2PO could not do. Yet, if PhS is a better migrating group it ought to migrate in less favorable circumstances. We escaped from the necessity to have a substituent on each carbon atom of the allyl system in the Ph_2PO series only with the help of silicon, but the primary alcohols **54** made by the routes summarized in Scheme V rearranged cleanly, e.g., **55** → **56**, to the allyl sulfides with the same pattern of substitution as in **53**.[24] In one example (Scheme VI) we use the PhS group to build a five-membered ring and then migrate PhS out of the ring to give the allyl sulfide **57**. Migrations from secondary to primary centers (e.g., **58** → **59**) also occur, and with an Me_3Si group to control

(24) P. Brownbridge, I. Fleming, A. Pearce, and S. Warren, *J. Chem. Soc., Chem. Commun.*, 751 (1976).



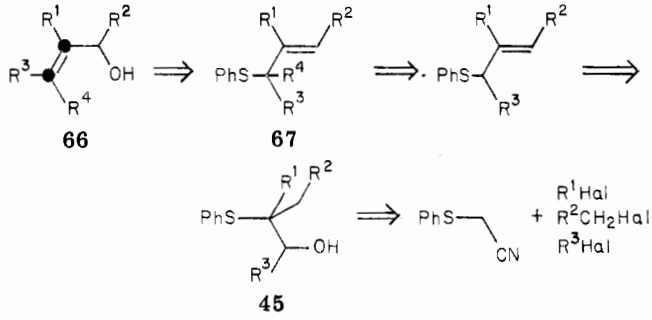
the reaction we can get secondary to secondary (**60** → **61**) and even secondary to tertiary (**63** → **64**) PhS migrations.[24] These products all give the photochemical [1,3] PhS shift.

Use of Allyl Sulfides in Synthesis. Perhaps the most important of the many uses of allyl sulfides in synthesis[25] are the reactions of their anions with electrophiles and their conversion into allyl alcohols via sulfoxides. Here is an example of anion formation from



an allyl sulfide followed by alkylation and [1,3] shift to form a new allyl sulfide, and an example to show how the [1,2] followed by the [1,3] shift can be used to make two isomeric allylic alcohols.[3]

Strategy of the Allyl Alcohol Synthesis. The basic strategy is to disconnect one alkyl group from the allyl sulfide **67**, reverse the rearrangement, and make



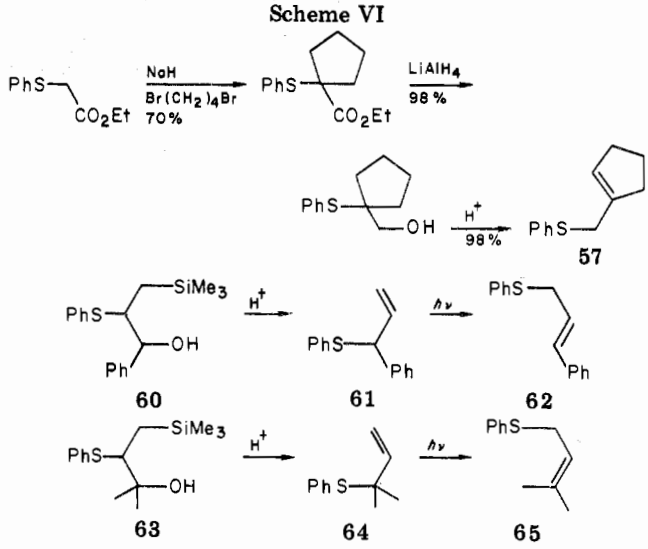
the alcohol **45** from a nitrile (Scheme III) or an ester (Scheme V and VI) which provides the core of the molecule (marked ● in **66**), the rest being added as alkyl halides.

Compounds with Two PhS Groups at the Migration Origin

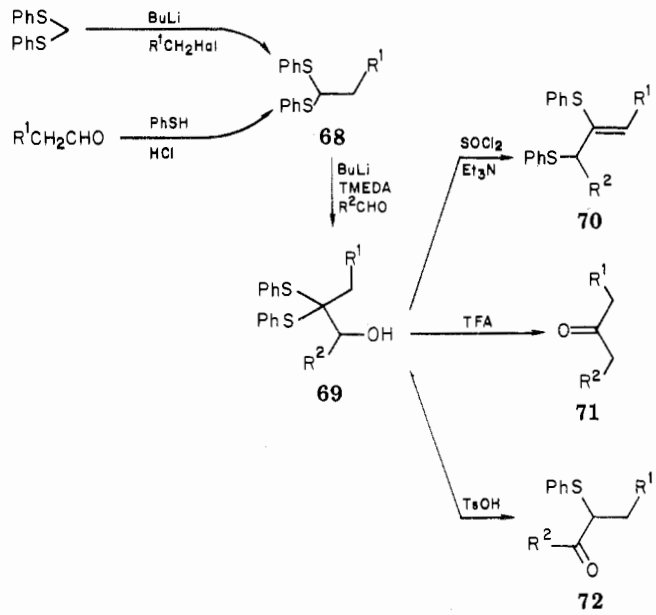
The synthesis of these adducts (**69**) of bis(phenylthio) acetals (**68**) and aldehydes is straightforward (Scheme VII), and treatment with $SOCl_2$ and Et_3N leads to **70**.

(25) D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).

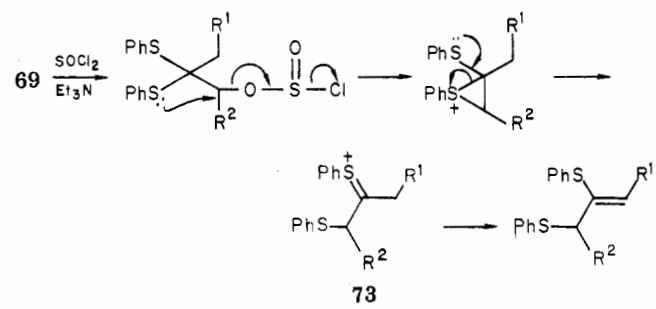
Scheme VI



Scheme VII



Scheme VIII

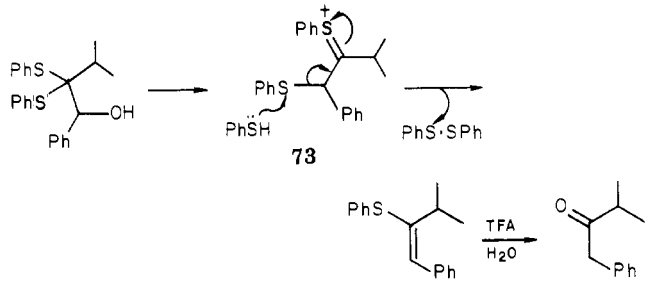


One PhS migrates to become an allyl sulfide in **70**; one stays behind to become a vinyl sulfide—a latent ketone (Scheme VIII).[26] We used these unusual reaction conditions because the normal acidic conditions gave different products.

In TFA, the simple ketone **71** is formed.[26] The other product of this remarkable redox reaction is PhSSPh. Such evidence as we have suggests a PhS migration (Scheme IX) to give an intermediate **73** (common to

(26) P. Blatcher, J. I. Grayson, and S. Warren, *J. Chem. Soc., Chem. Commun.*, 547 (1976).

Scheme IX



Scheme X

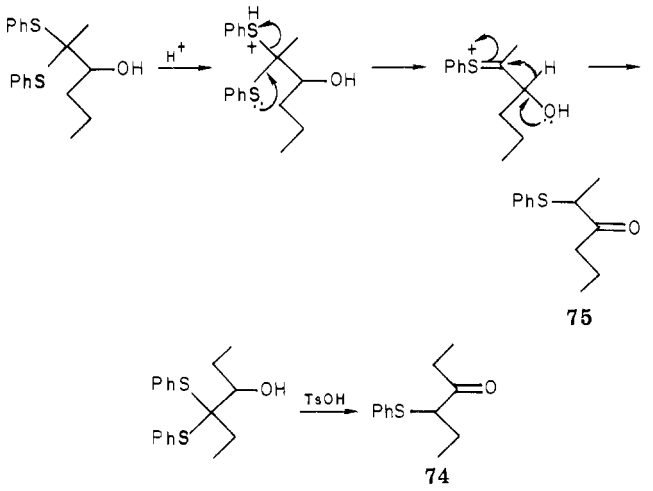


Table III
Products[19] from Bis(phenylthio) Acetals 69

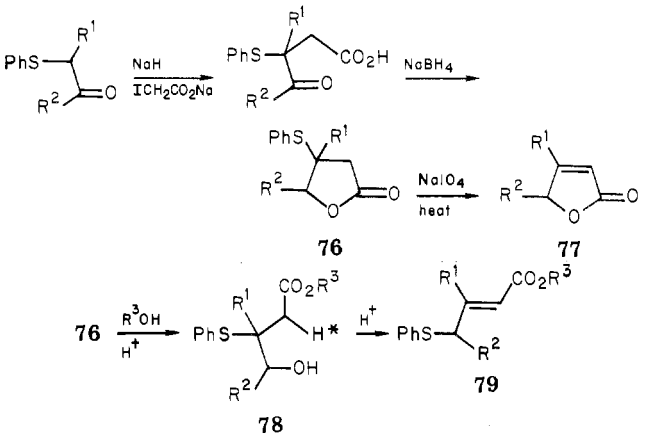
			yield, %			
entry	R^1	R^2	69	70	71	72
1	H	Et	84	a	90	84
2	H	*n*-Pr	70	a	b	81
3	Me	Et	76	83	b	72
4	Me	Me	73	90	90	80
5	*n*-Pr	Me	62	91	80	78

[a] When R^1 = H, this reaction gives a mixture of other products. [b] Not carried out.

Schemes VIII and IX) which is deprotonated by Et_3N in Scheme VIII but dethiated by PhSH in Scheme IX to give a vinyl sulfide.[19] Vinyl sulfides readily give ketones in TFA.[26] As a ketone synthesis this sequence uses an acyl anion equivalent (the anion of **68**) and is an alkylative carbonyl transposition on the aldehyde R^2CHO.

With TsOH in benzene yet another product is formed,[20] the α-PhS ketone **72**. Under these more vigorous conditions, protonation on sulfur is possible (Scheme X) and loss of one PhS group assisted by the other is followed by a "backward" hydride shift. The carbonyl groups in **71** and **72** are on different atoms: the TsOH reaction restores the carbonyl group of the

Scheme XI



aldehyde R^2CHO without transposition.

We had hoped to use the anions of **70** as specific enol equivalents[27] but, as in other cases where there were substituents on each atom of the allyl system, we were unable to make the anions satisfactorily. However, we have already used α-PhS ketones **72** in this way when we made compounds **45** for PhS migration, and this new reaction allows us to make both specific enol equivalents, e.g., **74** and **75**, of a ketone regiospecifically by using different starting materials.

Our butenolide **77** synthesis[28] (Scheme XI) uses α-PhS ketones in this way, but our real interest in this sequence was in the possibility of rearranging the lactone **76**. Direct rearrangement in acid does not work because PhS cannot displace the carboxylate group in what amounts to a 6-endo-tet[29] reaction. However, the small amount of ring-opened **78** formed with an alcohol and TsOH in benzene is enough for rearrangement to **79** to be rapid and complete. The products are interesting as *extended* enolate equivalents.[30]

The rearrangement **76** → **78** contains the most sophisticated control we have yet achieved. Only the enoate ester **79** is formed when the alternative side chain (R^1) is ethyl. The migration even occurs when R^1 is absent (=H) so that PhS migrates from one secondary center to another. This control comes from the preferential loss of the enolic proton H* which behaves rather like the Me_3Si group.

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