NOVEL APPROACHES TO ALKYLATIONS

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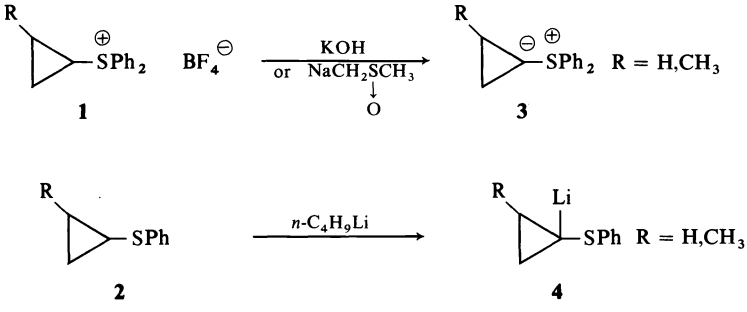
ABSTRACT

Use of sulphur-stabilized cyclopropyl anions has led to novel ways of forming carbon–carbon bonds, including spiroannelation, cyclopentane annelation, geminal alkylation and secoalkylation. Direct sulphenylations alpha to a carbonyl group have also led to useful structural modifications, including introduction of a double bond in conjugation with a carbonyl group, carbonyl transposition and alkylative elimination. A new method to introduce carbon–carbon bonds specifically alpha to a double bond under mild conditions based on organopalladium chemistry is developed and holds special promise in chiral syntheses.

Elaboration of molecular architecture involves creation of carbon skeletons for which the most elementary reactions require formation of carbon–carbon bonds. Such methods may be broadly classified as alkylation reactions. The continuing evolution of new structural types requires a continuing development of approaches to carbon skeletons. Our work has focused on new reactions and new reagents that form such bonds in novel ways.

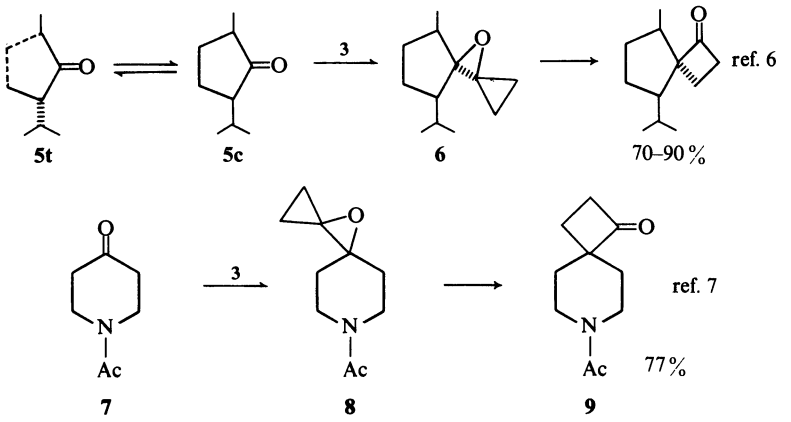
REAGENTS BASED ON SULPHUR-STABILIZED CYCLOPROPYL ANIONS

The cyclopropyl anions **3** and **4** are readily available from their hydrocarbon precursors **1** and **2** by base treatment [1–4]. These reagents add to carbonyl derivatives to give adducts of high potential energy as a result of high ring strain. Ylide **3** adds to the carbonyl group of both aldehydes and



1 **3** **2** **4**

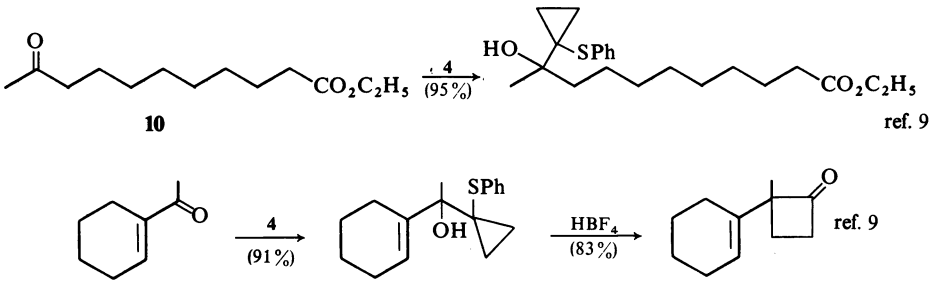
ketones that are not susceptible to conjugate addition[5]. The latter type of system undergoes conjugate addition with formation of spiropentanes[8]. The



5t 5c 6 7 8 9

carbonyl addition with formation of oxaspiropentanes is highly stereoselective with addition occurring from the less hindered face. With a ketone such as 2-isopropyl-5-methylcyclopentanone (**5**) and utilizing potassium hydroxide to generate **3**, epimerization of the carbonyl partner occurs faster than condensation of the ylide. Furthermore, of the two isomers, **5t** and **5c**, **5c** is more reactive. The net result is formation of a single oxaspiropentane whose stereochemistry is tentatively assigned as shown in **6**.

Adducts chemically equivalent to the oxaspiropentanes are obtained by addition of **4** to carbonyl groups[3]. In this case, even α,β-unsaturated carbonyl systems react by simple 1,2-addition. The addition of both **3** and **4** are chemospecific, as illustrated by the exclusive ketone condensation of both **7** and **10**.



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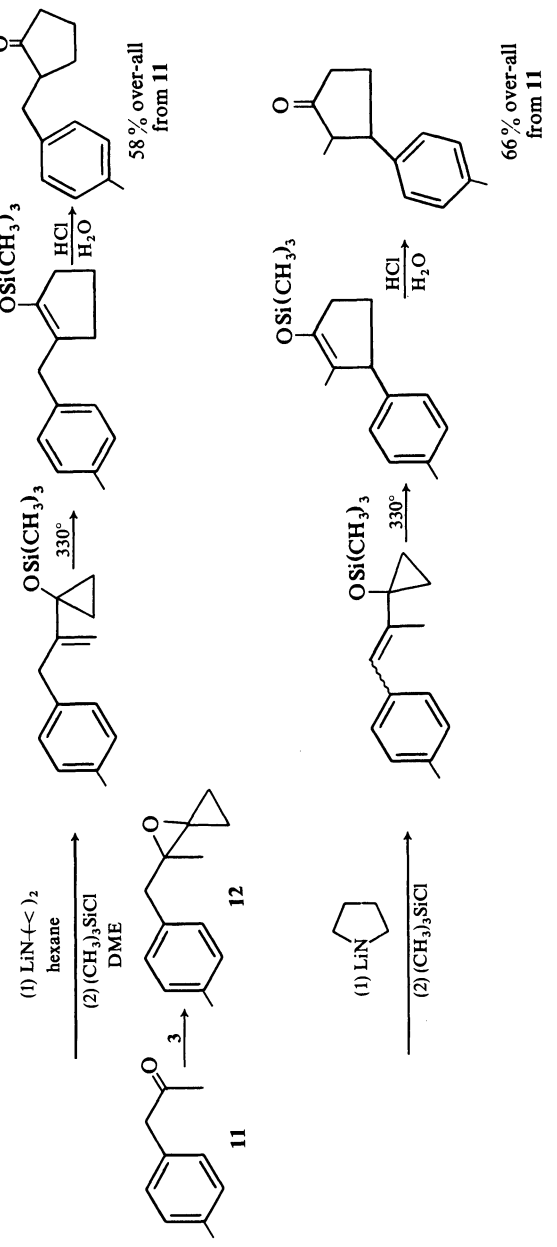
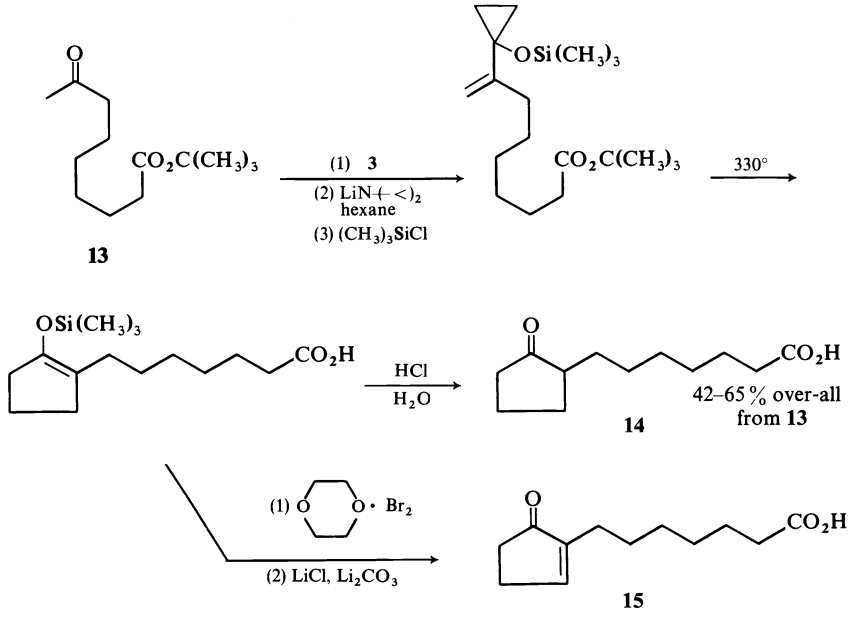
The high reactivity of these initial adducts generates real enthusiasm for their application in synthesis. Thus, the oxaspiropentane **12** from *p*-tolylacetone (**11**) undergoes regioselective epoxide ring-opening depending upon the choice of base[10]. A hindered base, lithium diisopropylamide, for short reaction times (30 min) eliminates by proton abstraction from the methyl group (kinetic control); wheras a less hindered base, lithium pyrrolidide, for longer reaction times (120 min) eliminates exclusively by proton

Scheme 1. Cyclopentane Annelation of *p*-Tolylacetone

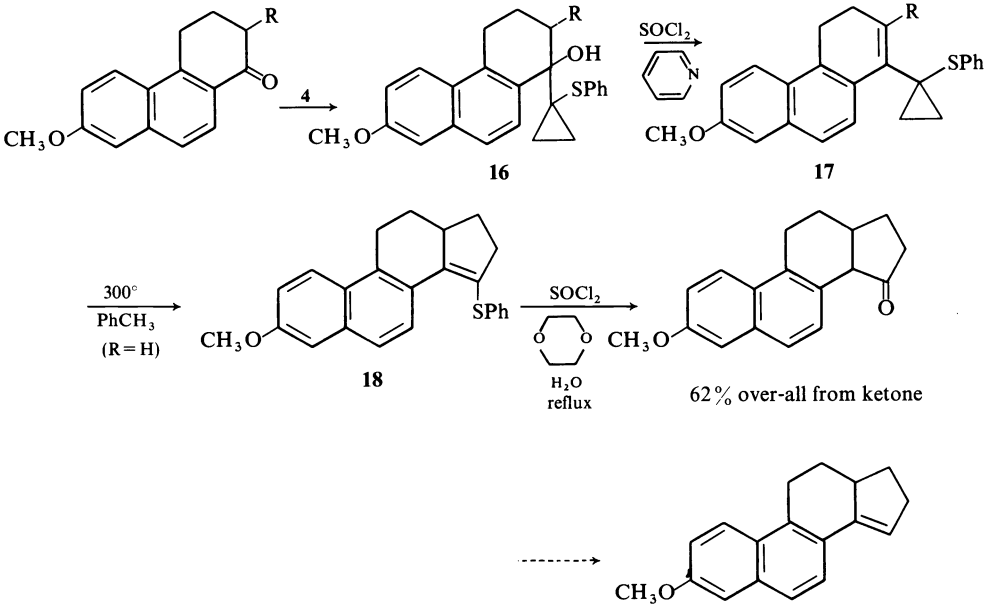


abstraction from the benzylic position (thermodynamic control). Dropping a solution of the resultant vinylcyclopropane through a conditioned hot tube (330°) effects smooth conversion to the cyclopentene[10,11]. The presence of the trimethylsiloxy group on the double bond makes this cyclopentene a masked cyclopentanone. Unmasking can be achieved by mild acid hydrolysis. The ability to cleave enol silyl ethers to enolates with methyllithium allows further regioselective functionalization at the α-carbon atom[12].

The method is not limited to monofunctional compounds. Thus, the keto-ester **13** can be converted to the cyclopentanone **14** without interference from the *tert*-butyl ester[10]. Bromination of the enol silyl ether followed by dehydrobromination allows direct regioselective formation of a cyclopentenone. Compound **15** has been utilized as a prostanoid precursor[11]. In this case, the vinylcyclopropane rearrangement is accompanied by loss of isobutylene from the *tert*-butyl ester.

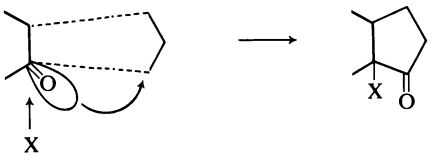


The methodology is not limited to volatile partners since the rearrangements may be effected in sealed tubes. An alternative approach based upon the carbonyl adduct of **4** illustrates the sequence[9]. Dehydration of **16** (R = H or CH_3) with thionyl chloride in pyridine at room temperature creates the requisite vinylcyclopropane **17** (R = H or CH_3). Heating a solution of **17** (R = CH_3) in toluene does not lead to rearrangement at any temperature up to 500°. Alternatively, heating a solution of **17** (R = H) in toluene at 300° leads to smooth rearrangement. Once again, the cyclopentene **18** is special in that the double bond bears a phenylthio substituent. Thus, the vinylthioether represents a masked carbonyl. Hydrolysis with either mercuric chloride in refluxing aqueous dioxane or titanium tetrachloride in



aqueous acetic acid forms the cyclopentanones. In principle, desulphurization with Raney nickel would allow a regioselective cyclopentene annelation.

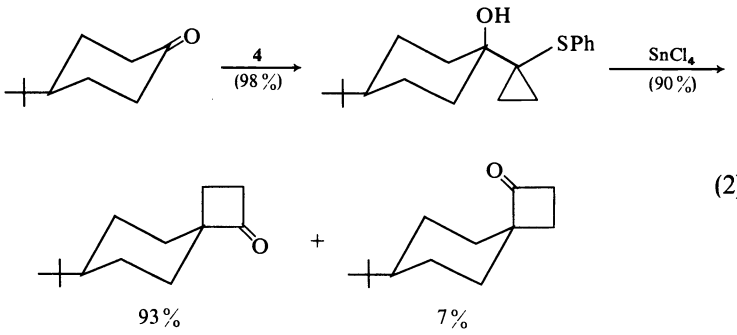
This approach to cyclopentane formation allows annelation of a three-carbon unit to a carbonyl group and an α-methyl or methylene unit. The



(1)

original carbonyl group migrates to one of the carbons of the three-carbon unit to allow for further elaboration. Furthermore, the nature of the intermediates allows for additional regioselective functionalization at the former carbonyl carbon atom. Thus, the method should prove to be an unusually versatile and regioselective cyclopentene, cyclopentanone or cyclopentenone annelation.

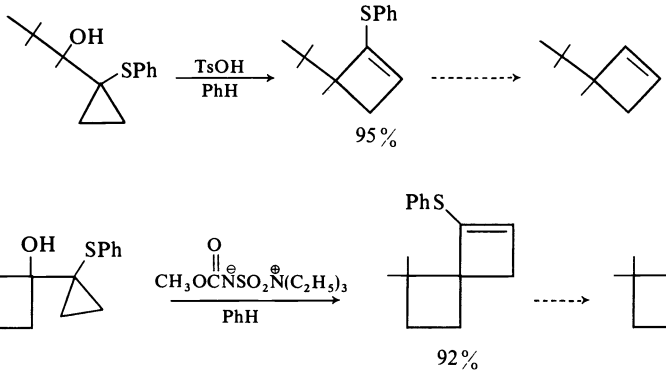
Alternatively, treatment of the oxaspiropentanes or 1-phenylthiocyclopropyl carbinols with acid produces the corresponding cyclobutanones by ring enlargement (*vide supra*)[3,14]. For the oxaspiropentanes, aqueous fluoroboric acid, oxalic acid in acetonitrile, lithium perchlorate or lithium fluoroborate has been used. For the 1-phenylthiocyclopropyl carbinols, aqueous fluoroboric acid or stannic chloride in methylene chloride has been used. As illustrated for oxaspiropentane **6**, the rearrangement is stereospecific. On the other hand, the rearrangement of the cyclopropyl carbinols



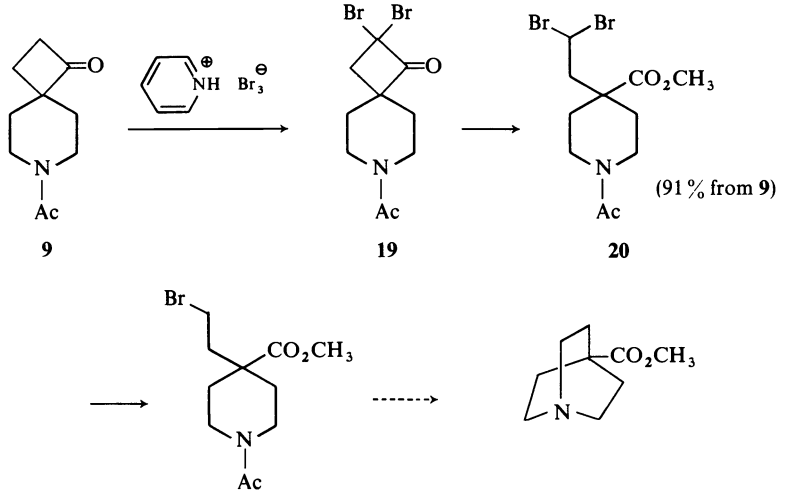
(2)

is stereoselective (e.g. equation 2)[15]. In general, spiroannelation with the ylide **3** produces the cyclobutanone possessing the carbon–carbonyl carbon bond on the more hindered face of the starting ketone; whereas spiroannelation with the anion **4** produces a complementary stereochemical result—the cyclobutanone possessing this bond on the less hindered face of the initial substrate. The important conclusion is that the methodology allows the replacement of the two carbon–oxygen bonds of a carbonyl group with two carbon–carbon bonds in a highly stereoselective fashion.

Rearrangement of the carbonyl adducts of **4** under anhydrous conditions produces enol thioethers rather than cyclobutanones[9,15]. While these enol thioethers may be hydrolysed to the cyclobutanones, more interestingly they should be easily convertible into the olefin by desulphurization.

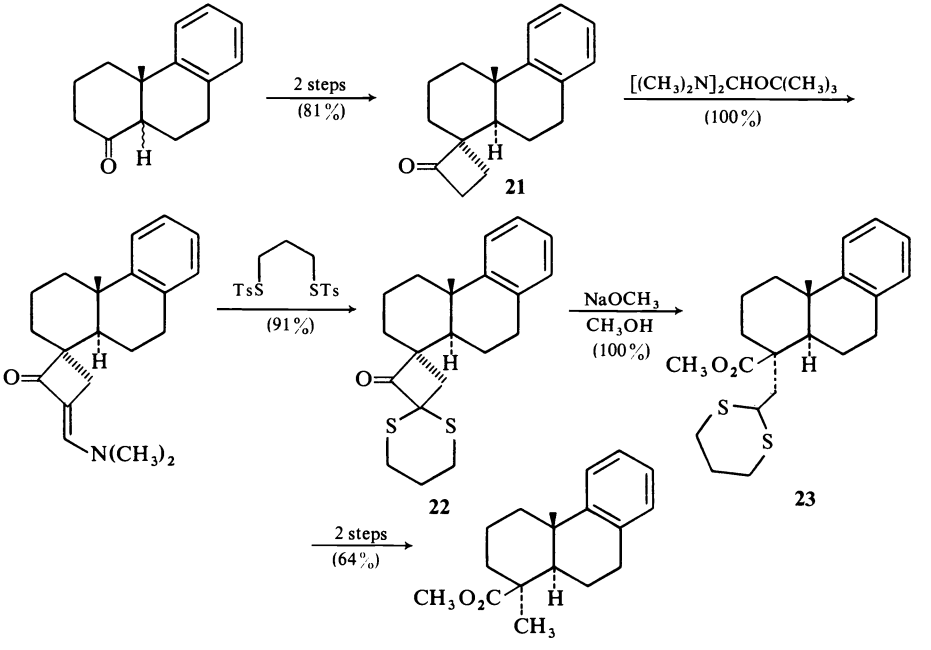


Cleavage of the cyclobutanones obtained in this fashion allows stereoselective geminal alkylation—a special example of secoalkylation. Even with facilitation of this cleavage by the release of the approximately 26 kcal/mol of ring strain, base-induced ring cleavage requires the presence of anion-stabilizing groups. Bromine serves as such an anion-stabilizing group [16]. The cyclobutanone **9** (*vide supra*) is geminally brominated with molecular bromine in refluxing carbon tetrachloride but preferably with pyridinium bromide perbromide essentially quantitatively[6]. Dissolution of **19** in methanolic sodium methoxide induces almost instantaneous



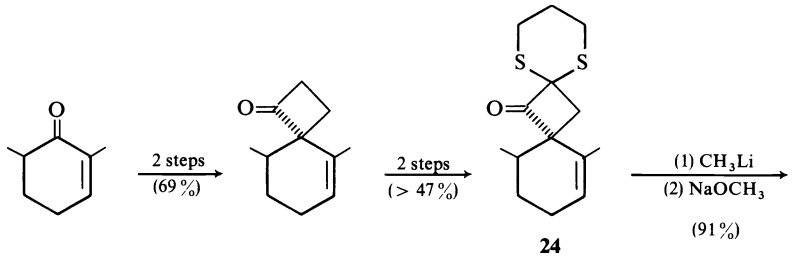
fragmentation to give **20**. Such geminal bromine substitution is quite versatile. While it can be recognized as a masked carbonyl group, the bromines can be sequentially removed with tri-*n*-butyltin hydride. In the case of **20**, this route serves as an entry into quinuclidines.

Sulphur is also an excellent anion-stabilizing group. Condensation of the cyclobutanone **21** with bis-dimethylamino-*tert*-butoxymethane produces the vinylogous amide which reacts with trimethylenedithiotosylate under solvolytic conditions to produce the α-dithianyl ketone **22**[17]. Refluxing **22**



in methanolic sodium methoxide effects complete ring cleavage. The lack of cleavage of α-dithianyl derivatives of larger ring ketones demonstrates the effect of ring strain. Note that the stereoselectivity of the spiroannelation (**21** is a single isomer even though the starting ketone is a *cis–trans* mixture) translates into stereoselective geminal alkylation.

Other nucleophiles may be added to the α-dithianyl ketones. For example, addition of methyllithium to **24**, available from 2,6-dimethylcyclohexenone in a fashion analogous to the preparation of **22**, followed by methanolic sodium methoxide also leads to smooth fragmentation[18]. Hydrolysis of the



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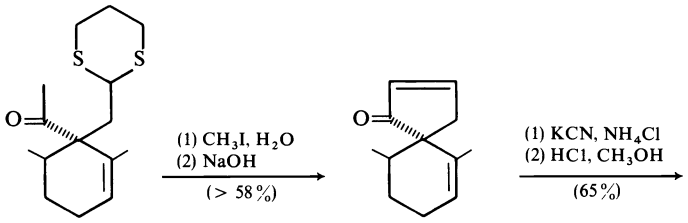

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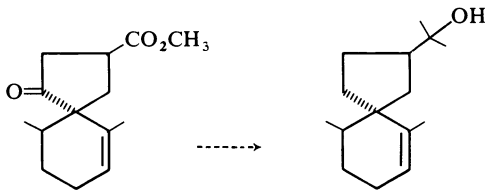

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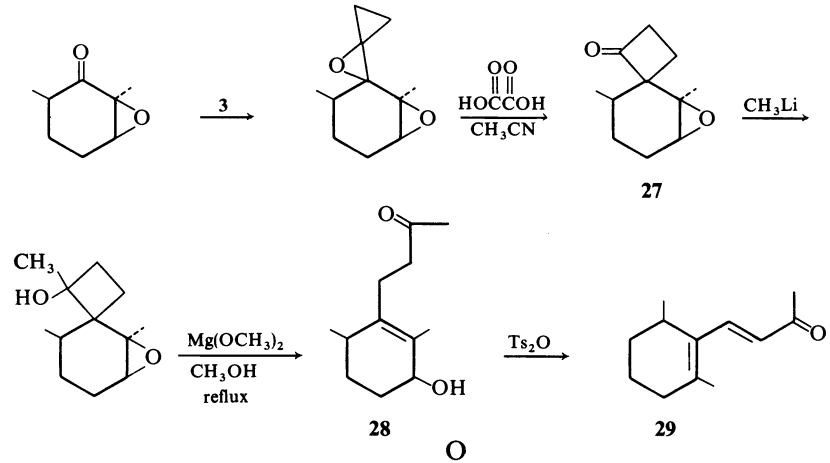
dithiane and aldol condensation creates completely stereoselectively a spiro [4.5]decane, **25**, a carbon system common in many spirosesquiterpenes. Indeed, conjugate addition of cyanide ion followed by hydrolysis produces **26**, a logical precursor to hinesol.

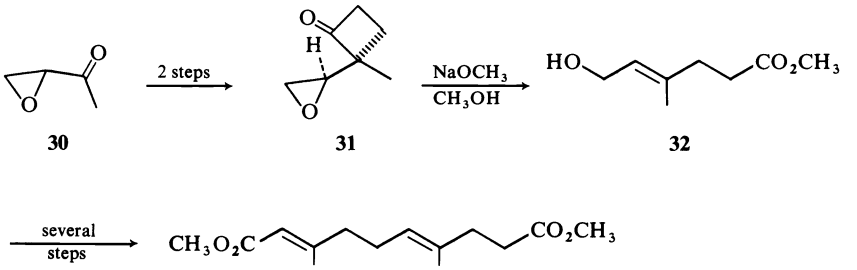
An alternative way to stabilize a developing negative charge in base-catalysed cyclobutane ring cleavage is to introduce a leaving group on a carbon β to the carbonyl group of the cyclobutane. A particularly interesting example employs an α,β-epoxyketone in the cyclobutane annelation[19]. Selective rearrangement of the oxaspiropentane can be achieved by use of lithium fluoroborate in benzene, aqueous fluoroboric acid or oxalic acid in

acetonitrile at room temperature. Thus, the cyclobutanone **27**, obtained in this way from 2,6-dimethyl-2,3-epoxycyclohexanone, can be cleaved after addition of methyllithium with magnesium methoxide in refluxing methanol



to yield **28**, the net addition of a $\overset{\ominus}{C}—C—\overset{O}{\overset{\|}{C}}—CH_3$ unit to a carbonyl group[20]. Dehydration of **28** produces desmethyl-β-ionone **29**, which may be utilized to synthesize modified retinals.

Starting with an acyclic epoxyketone **30**, a mixture of diastereomeric cyclobutanones from which diastereomer **31** can be separated was isolated[21].



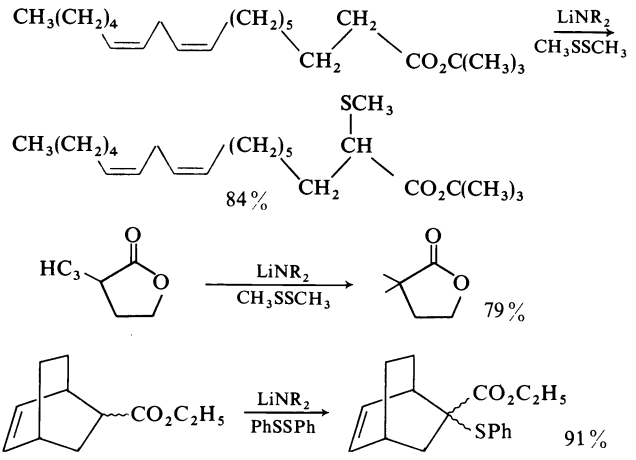
Fragmentation proceeds stereospecifically to produce the *trans* olefin **32**, which can be converted to the dimethyl ester of a sex pheromonal secretion of the monarch butterfly by standard methods. This example represents a net addition of a $\overset{\ominus}{C}—C—\overset{O}{\overset{\|}{C}}OCH_3$ unit to a carbonyl group. Such units can be considered as Michael acceptors of inverse electronic sense. The versatility of the Michael reaction (conjugate addition) in organic synthesis insures great promise for the electronically inverted system. One intriguing application has been the development of a cyclohexenone annelation that complements the Robinson annelation[19].

It is clear that the current investigations are merely pointing the way for further new reactions and applications. The premise that small rings offer

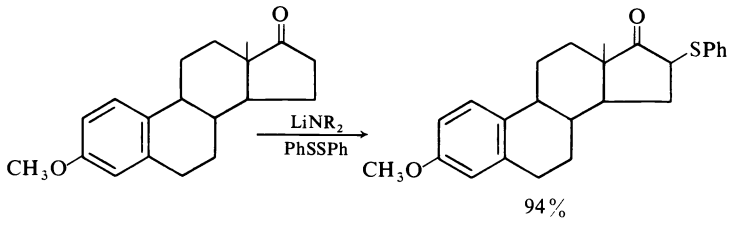
a source of potential energy for structural modification in synthetically useful ways has been vindicated.

SULPHENYLATIONS AND RELATED REACTIONS

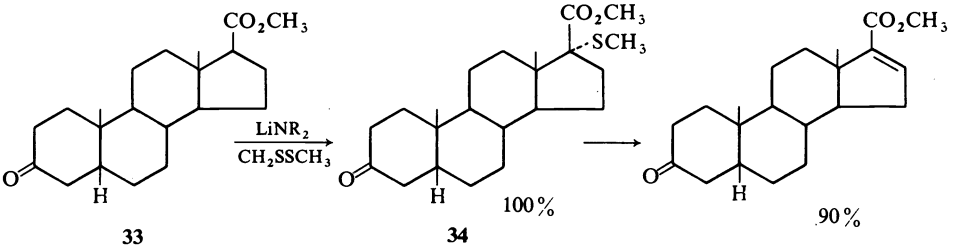
The utility of α-thiocarbonyl compounds to elaborate structures has led to many indirect methods to introduce a thioether unit[22,23]. The most direct method involves the treatment of an enolate derived from an ester or ketone with a suitable sulphenylating agent. While sulphenyl halides or other derivatives suffice, disulphides are more convenient. Thus, ester or lactone enolates react with dimethyl disulphide or diphenyl disulphide to produce the α-sulphenylated materials in excellent yields[24,25]. In contrast,



ketone enolates only react with the more reactive diphenyl disulphide in THF solution although both diphenyl and dimethyl disulphide do sulphenylate when a mixture of THF and HMPA is employed as solvent. The differential reactivity shown (a phenomenon termed chemospecificity) allows for



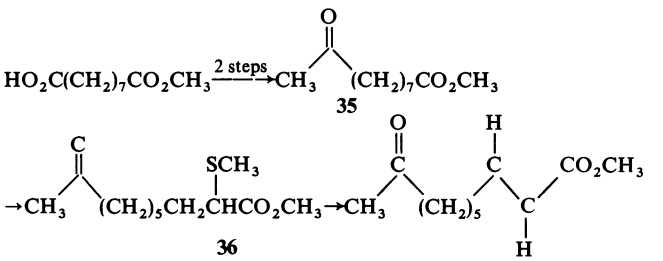
selective sulphenylation alpha to an ester in the presence of a ketone (e.g. **33** → **34**).



33 34

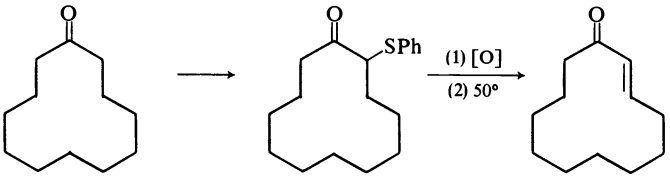
A new application of these sulphenylated esters and ketones is a two-step elimination. Oxidation of the thioethers with sodium metaperiodate, *m*-chloroperbenzoic acid, *N*-chlorobenzotriazole or *tert*-butylhydroperoxide-vanadyl acetylacetonate produces the sulphoxide, which suffers smooth thermal elimination between room temperature and refluxing toluene. Thus, in the case of **34**, oxidation with sodium metaperiodate followed by thermolysis in refluxing toluene introduces a double bond in conjugation with the ester in 90 per cent over-all yield from **33** in a completely chemospecific fashion.

This method lends itself to a facile synthesis of the methyl ester of queen

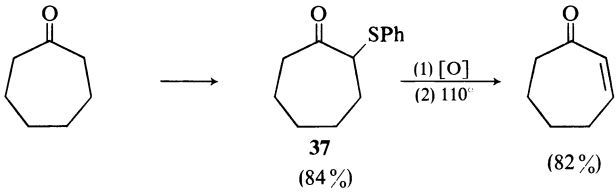


substance[26,27]. While the keto ester **35** can be directly sulphenylated, the low yields (~ 30 per cent) made protection of the ketone prior to sulphenylation desirable. Ketalization, sulphenylation, deketalization produced **36** in 69 per cent yield. Oxidation with *m*-chloroperbenzoic acid followed by thermolysis produced only the desired *trans* unsaturated ester. This stereochemical result is general for creation of a disubstituted double bond; whereas formation of trisubstituted olefins normally leads to mixtures of *cis* and *trans* isomers.

Thermal elimination of the sulphoxides of α-phenylthio or α-methylthio ketones also proceeds smoothly. The temperature for elimination in cyclic



(93%) (88%)

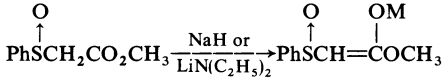


37
(84%)

(82%)

ketones is dependent upon ring size. Whereas a six-membered and twelve-membered ring underwent elimination in 10–15 h at 50°[24], the seven-membered ring compound required refluxing toluene for several hours to avoid side reactions[26]. It is interesting to note that the selenium derivative corresponding to **37** could not be converted into the enone in more than a few per cent yield[28].

The facility of the elimination suggested alternative direct routes to α,β-unsaturated esters utilizing the anion of methyl 2-phenylsulphinylacetate[29]. The anion **38** condenses with reactive alkylating agents in HMPA



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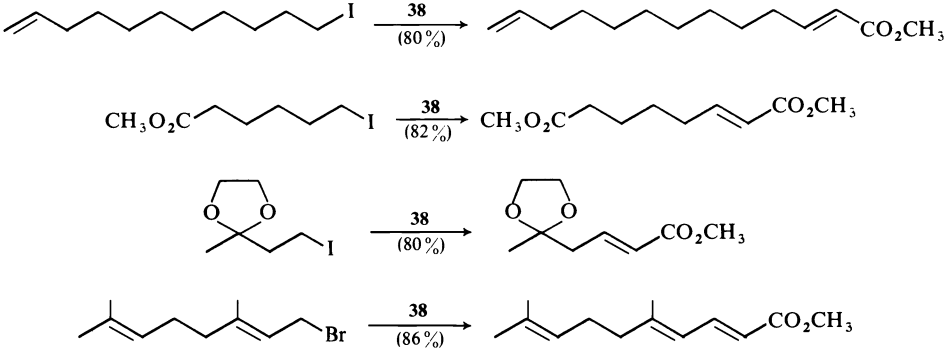
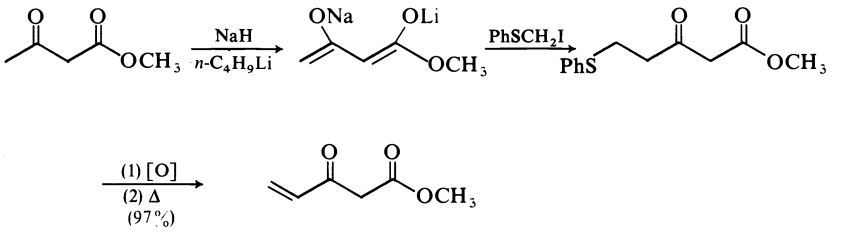
at room temperature. Raising the temperature to approximately 80° effects elimination. The accompanying equations illustrate the utility of the method

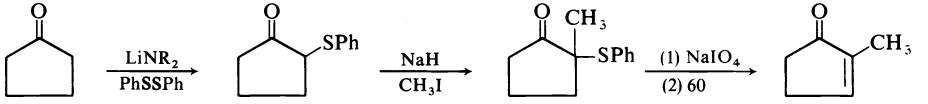


and the compatibility with an olefin, ester and ketal. Formation of disubstituted double bonds occurs with *trans* stereochemistry, as indicated by the 16 Hz coupling constant in the proton n.m.r. spectra of products.

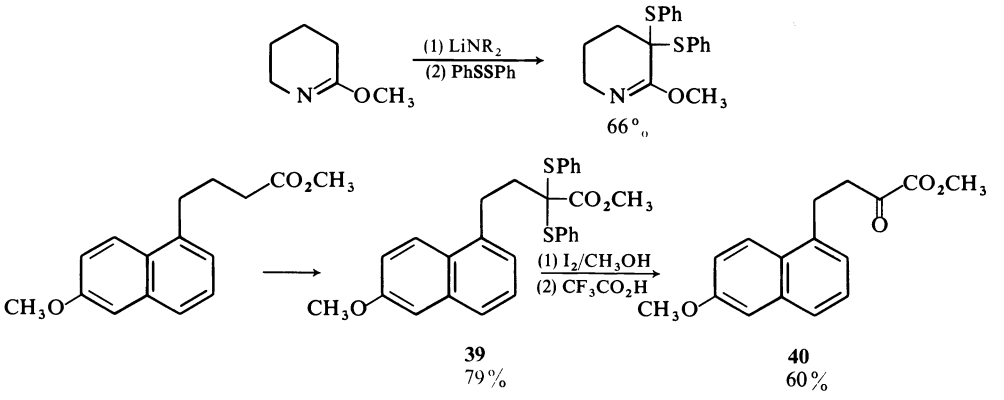
An alternative alkylative elimination employs iodomethyl phenyl sulphide and is illustrated by the preparation of methyl 3-oxo-4-pentenoate[30,31]. Alkylation of the dianion of methyl acetoacetate with this reagent produces methyl 5-phenylthio-3-oxopentanoate in 63–80 per cent isolated yield. Oxidation with sodium metaperiodate at room temperature to the sulphoxide



and thermolysis in refluxing carbon tetrachloride produced the annelating agent in 97 per cent yield (60–76 per cent over-all). In general, this sequence represents a novel approach to the introduction of a methylene group alpha to a carbonyl group. An additional alkylative elimination takes cognizance of the ease of regiospecific monoalkylation of α-sulphenylated ketones[23]. The synthesis of 2-methylcyclopent-2-enone illustrates the sequence.

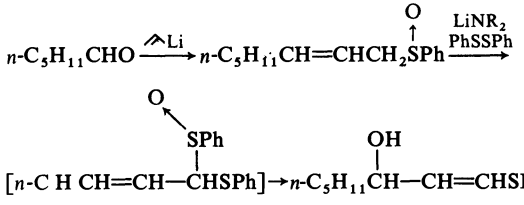


Sulphenylation of esters with 2 equivalents of diphenyl disulphide in THF–HMPA mixtures leads to bis-sulphenylations[26]. This reaction represents the net conversion of a methylene group to a ketone, since the thioketal



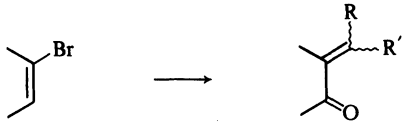
may be subsequently hydrolysed. A mild method to effect this hydrolysis involves initial transketalization to the methyl ketal by refluxing **39** in methanol containing iodine followed by ketal cleavage in trifluoroacetic acid at room temperature.

The sulphenylation of other anions has also led to the development of novel new alkylations. Treatment of the anion derived from **40**, readily available from hexanal, with diphenyl disulphide leads directly to enolthioether **41**[32]. The initial sulphenylation product undergoes sulphoxide–sulphenate rearrangement and desulphenylation *in situ*. Hydrolysis with



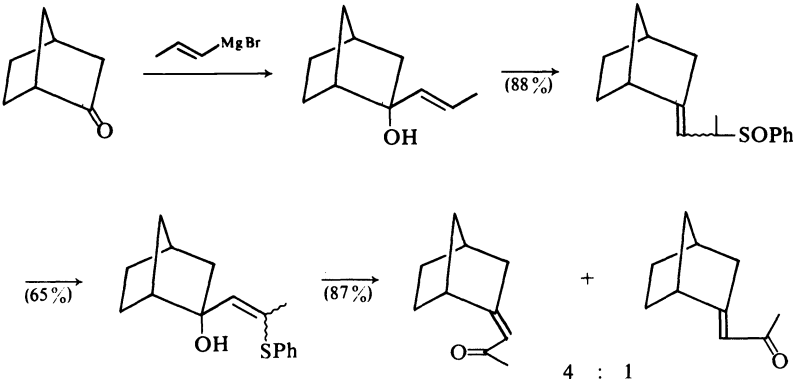
41

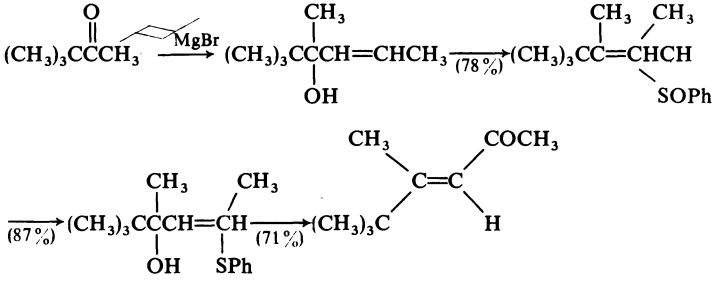
mercuric chloride in aqueous acetonitrile produces E-2-octenal in 79 per cent yield (over-all from hexanal). The over-all result, generalized in equation 3, allows conversion of a vinyl halide to an α,β-unsaturated carbonyl system.



(3)

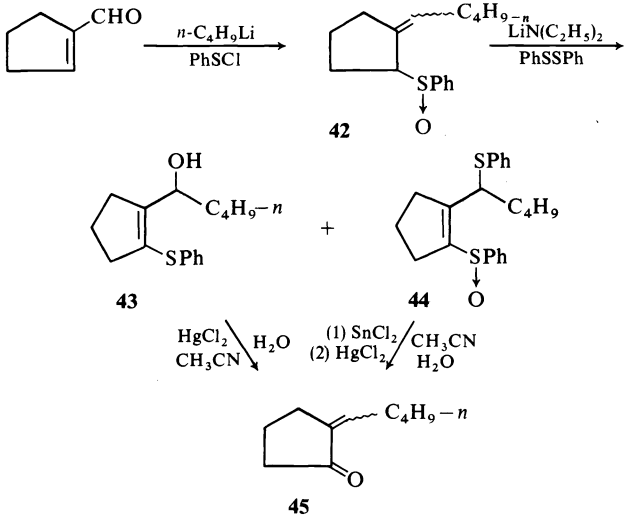
Alternatively, it may be considered as an alkylative carbonyl transposition similar to a directed aldol condensation. The accompanying equations provide further illustrations of the method as well as demonstrate the applicability to a hindered carbonyl.



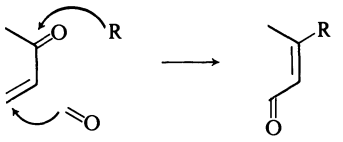


(4)

Such an alkylative carbonyl transposition may be achieved in an intramolecular sense if an α,β-unsaturated carbonyl system is employed as the carbonyl substrate. For example, addition of *n*-butyllithium to 1-cyclopentene-1-carboxaldehyde followed by phenylsulphenyl chloride produces **42**. Sulphenylation of the corresponding anion gives a mixture of α- and



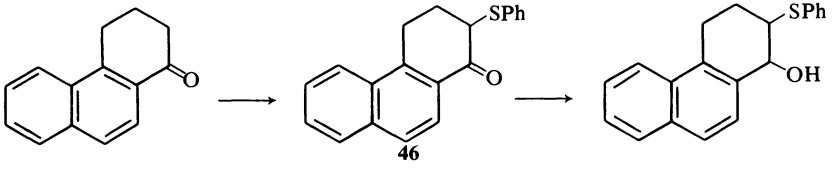
γ-sulphenylation products **43** and **44**. While **43** may be directly hydrolysed to 2-pentylidenecyclopentanone (**45**), **44** must be reduced with stannous chloride and then hydrolysed. The over-all result, summarized in equation

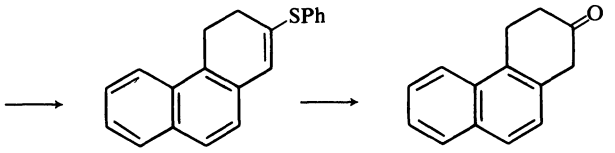


(4)

4 is allylic inversion of an α,β-unsaturated carbonyl system with specific carbon–carbon bond formation at the former carbonyl carbon atom.

In addition to the 1,3-carbonyl transpositions effected above, 1,2-carbonyl transpositions are possible through the sulphenylated ketones[33]. Reduction of **46** with sodium borohydride, dehydration with *p*-toluenesulphonic acid in benzene, and hydrolysis with titanium tetrachloride in aqueous acetic acid produces the β-ketone **47** from the corresponding α-ketone.



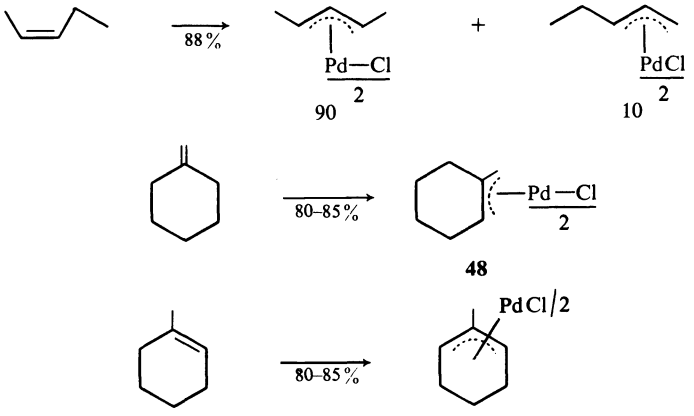


47

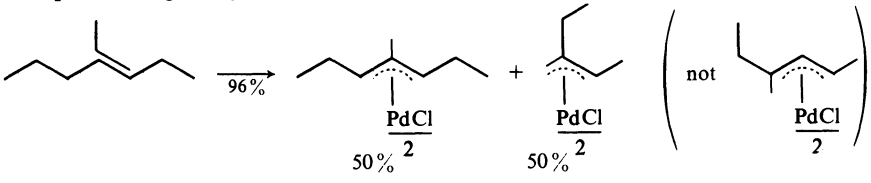
ALLYLIC ALKYLATION

The immense importance of the carbonyl group in organic synthesis stems from the activation of the alpha position to allow new bond formation at this site (via enols and/or enolates) as well as the ability to form new bonds to the carbonyl carbon. The isoelectronic carbon–carbon double bond allows additions to occur readily: however, reactions involving the allylic position mainly involve oxidations. Use of the double bond to activate the allylic position for alkylations has been exceedingly limited. Metallations employing exceedingly strong bases generate the allyl anions, which behave as typical organometallics[34,35]. The harshness of the conditions for metallation greatly restricts the applicability of such a method in complex molecules.

Palladium chloride, a rather mild reagent, has been shown to react with double bonds in the presence of weak bases to generate π-allyl palladium complexes[36]. Unfortunately, the conditions for this transformation were not general. In our hands, the best set of conditions involves utilization of a mixture of palladium chloride, sodium chloride, cupric chloride and sodium acetate in acetic acid[37]. In this way, mono-, 1,1- and 1,2-di- and trisubstituted

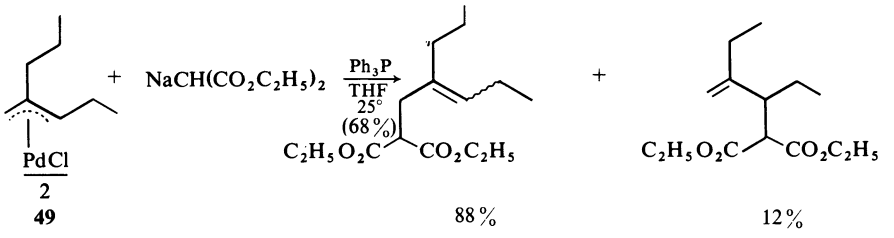


acyclic and cyclic olefins have been converted to their π-allyl palladium complexes in good yields. The formation of the complex follows Markow-



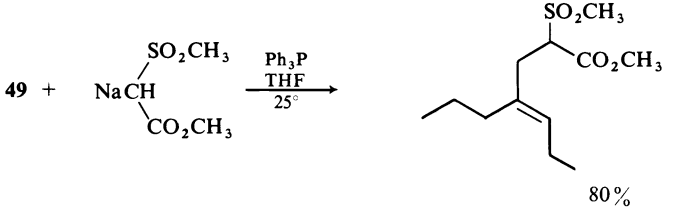
nikoff orientations. Thus, 4-methyl-3-heptene gives only the complexes involving deprotonation from the site allylic to the more substituted end of the double bond[38].

Such π-complexes have been invoked as intermediates in substitution reactions of allylic derivatives[39] and claimed to undergo coupling with malonic ester enolate[40,41]. The combination of these types of reactions with the above direct generation of π-allyl palladium complexes serves as an allylic alkylation. For smooth condensation in tetrahydrofuran, 4 equivalents of triphenylphosphine per mole of dimer is required[38]. Under



49 88% 12%

these conditions complex **49** reacted with diethyl sodiomalonate to give the adducts derived from preferential reaction at the less substituted carbon of the π-allyl complex. Trimethyl phosphite and *N,N,N',N'*-tetramethylethylenediamine also serve as ligands to effect similar reactions. Treatment of the same complex with the anion of methyl methylsulphonylacetate led to a single crystalline (m.pt, 78°) adduct. *In this case, the reaction proceeded completely regioselectively and stereoselectively.* The tentatively assigned

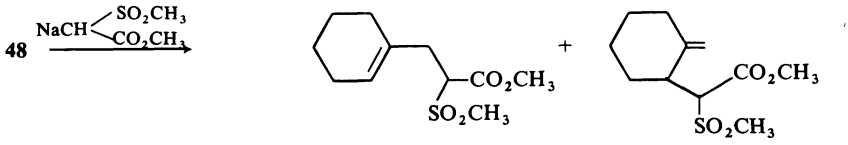


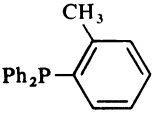
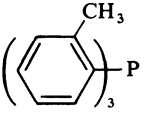
80%

stereochemistry of the double bond reflects the stereochemistry of the π-allyl palladium complex[42,43].

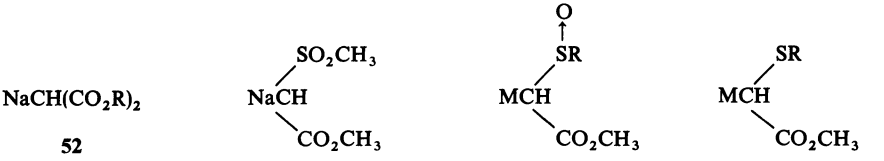
The orientational specificity is determined by the nature of activating phosphine ligand[44]. Reaction at the primary versus secondary carbon of complex **48** with the anion of methyl α-methylsulphonylacetate depends upon the steric bulk of the phosphine. Progressing from hexamethylphosphorus triamide to tri-*o*-tolylphosphine switches the relative amounts of **50/51** from 100/0 to 15/85. Unfortunately, the reasons for the selectivity can only be speculated upon at present.

The carbon nucleophiles that react with these π-allyl complexes must be stabilized. Utilizing triphenylphosphine as the activating ligand, anions

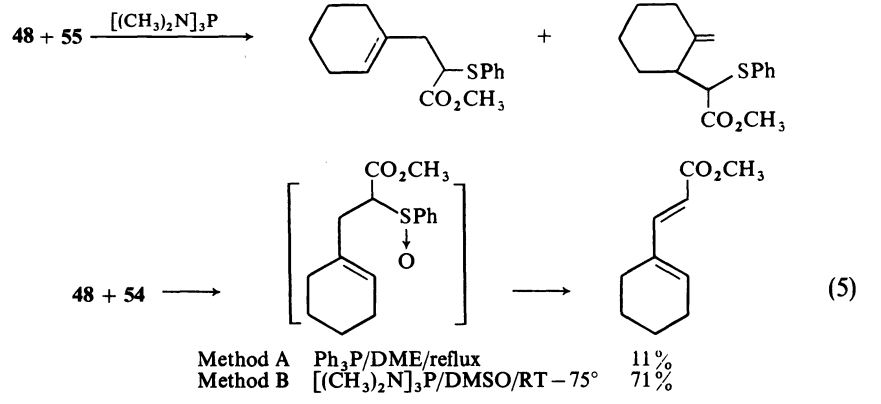


	50	51
$[CH_3]_2N]_3P$	100	0
Ph_3P	63	37
	54	46
	15	85

52–54 have been successfully employed. On the other hand, anion **55** failed to condense under these conditions. Use of hexamethylphosphorus triamide



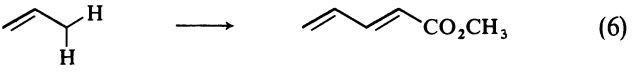
as the activating ligand did lead to successful alkylation of **55** with π-allyl palladium complex **48**. Thus, for less stabilized anions, phosphines which are weaker σ-donors but stronger π-acceptors are preferred.



(5)

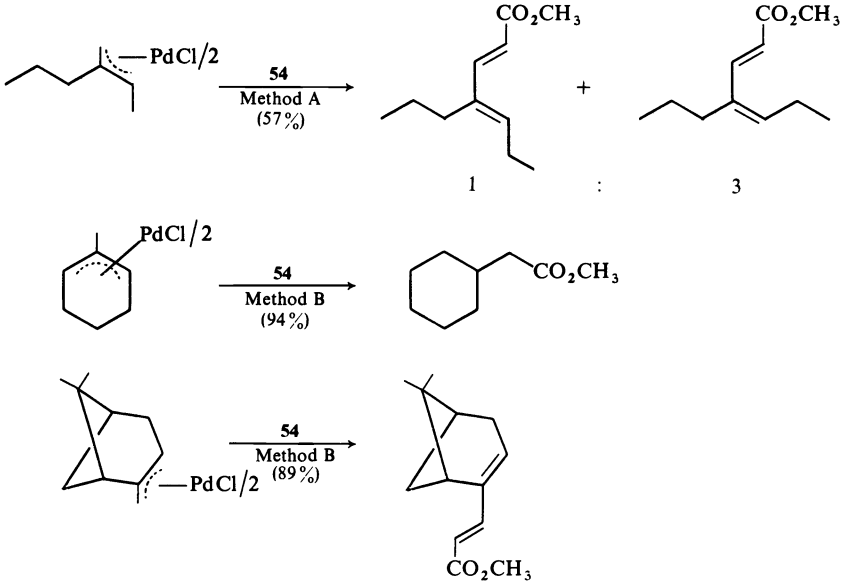
Method A Ph_3P/DME/reflux 11%
Method B $[(CH_3)_2N]_3P$/DMSO/RT – 75° 71%

For **54**, R = Ph, improved yields are obtained when hexamethylphosphorus triamide rather than triphenylphosphine or 1,2-bis-(diphenylphosphine) ethane is employed as the activating ligand (e.g. equation 5)[29]. The initial alkylated product undergoes *in situ* dehydrosulphenylation to generate the E-α,β-unsaturated ester. The net process (see equation 6) is an olefin equivalent of an aldol reaction. As the accompanying equations



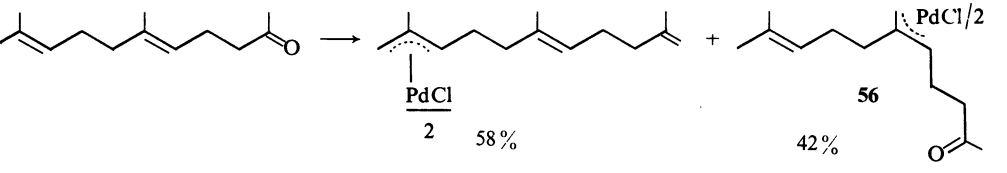
(6)

show, alkylation occurs at the less substituted end of the π-allyl system. The

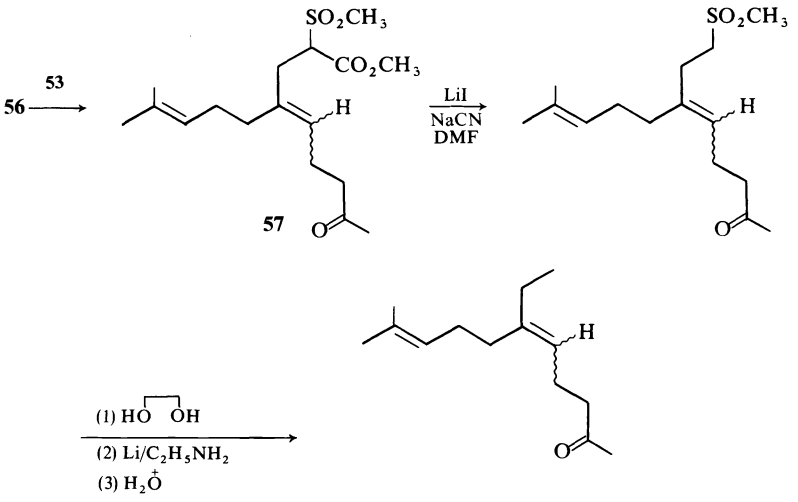


stereochemistry of the γ,δ double bond normally reflects the stereochemistry of the starting π-allyl palladium complex.

One unique aspect of this allylic alkylation procedure is its chemospecificity[45,46]. *trans*-Geranylacetone under the generalized conditions gave an approximately equimolar mixture of two π-allyl palladium complexes involving only deprotonation from the methyl branches. Either complex

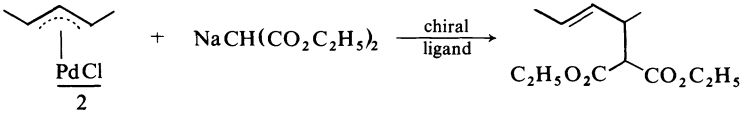


reacts with the anion of methyl methylsulphonylacetate (**53**) to give smooth alkylation. Again, rather high regiospecificity and stereoselectivity is observed



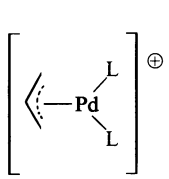
in which the resultant olefin mainly reflects the stereochemistry of the palladium complex. *This example demonstrates that a carbonyl group does not interfere in either stage of the sequence.* To illustrate the applicability of the method for the introduction of alkyl groups, **57** was decarbomethoxylated[47] and desulphonated[48]. The net result transformed a methyl-substituted olefin stereoselectively into an ethyl-substituted olefin.

The requirement of a ligand for alkylation suggested the potential of utilizing optically active phosphines and amines to achieve asymmetric induction. Treatment of syn, syn-1,3-dimethylallylpalladium chloride dimer with diethyl sodiomalonate in the presence of (+)-2,3-*o*-isopropylidene-

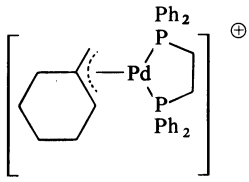


2,3-dihydroxy-1,4-bis(diphenylphosphine)butane, (+)-*o*-anisylcyclohexylmethylphosphine or (−)-sparteine led to allylic alkylation product in 20–25 per cent optical yields[49]. The asymmetric induction is among the highest known for such carbon–carbon bond formation[50]. The chemospecificity and the asymmetric induction make this process unique in the arsenal of alkylation reactions.

Although no definitive statements regarding the course of alkylation can be made, the requirement of 4 equivalents of ligand per mole of dimer and the use of a soft anion led us to suggest the ionic complex **58** as an intermediate[51]. Support for this interpretation arises from the utilization of preformed cationic complex **59** in the alkylation without additional phosphine[44]. Initial attack at either carbon or palladium[41] for this ambident

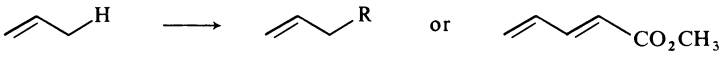


58



59

electrophile cannot be differentiated at this time. It is reasonable to anticipate that the over-all process of allylic alkylation can be made catalytic in pallad-



ium. Nevertheless, the recoverability and recycling of palladium makes it an attractive approach for carbon–carbon bond formation at present.

CONCLUSION

Specificity and selectivity are the keys in the development of new synthetic reactions. In addition to control of relative stereochemistry and regiospecificity, control of absolute stereochemistry and chemosopecificity are coming to the fore. Sophistication is evolving in such a fashion that the synthetic organic chemist will soon be able to carry out only the desired transformation in complex molecules; no more, no less. The above methods contribute to these goals.

ACKNOWLEDGMENT

I thank my co-workers and co-thinkers who are responsible for the evolution of our research programme. They are acknowledged individually in the cited references. I also thank the National Science Foundation and the National Institutes of Health for financial support.

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