The Chemistry of Enones
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CHAPTER **10**

Nucleophilic attacks on enones

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*We dedicate this chapter to our fathers

I. INTRODUCTION

A knowledge of the parameters that govern chemical reactions and their control is of paramount importance to the chemist striving to devise synthetic strategies, and aiming at the synthesis of the desired product, with the best possible yield and with the correct stereochemistry.

This chapter treats the vast field of nucleophilic attacks on enones. Our purpose is not to give an exhaustive account of the numerous reactions between nucleophilic agents and enonic systems, nor to discuss the advantages of the alternative models of the reaction mechanisms. Rather we review the most recent works on the subject, with the aim of defining the parameters that govern both the regio- and stereochemistry of nucleophilic attacks, in the widest sense, on typical ambident electrophiles: enones and enals.

II. FORMATION OF A CARBON–CARBON BOND FROM NUCLEOPHILIC ADDITIONS OF ORGANOMETALLIC COMPOUNDS

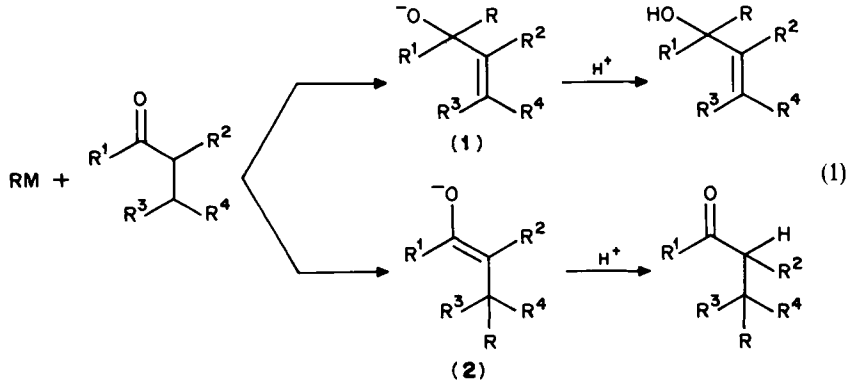
The most frequently met nucleophilic attack, and the synthetically most useful, on α,β-unsaturated aldehydes (enals) and ketones (enones) or quinones, is the addition of organometallic compounds in the widest sense, in which a new carbon–carbon bond is formed.

Considering the multiplicity of substrates and reagents, we will discuss the preparative aspects only to a minor extent and shall emphasize the mechanistic aspects, particularly the regioselectivity of these reactions, that has been developed in the last few years. Enals and enones behave as ambident electrophiles, as a consequence of the delocalization of the electron density in the C=C—C=O system. The additions of organometallic reagents (RM) can therefore proceed via two pathways: addition to the carbon atom of the carbonyl group $C_{(1)}$ [$C_{(1)}$ attack] or to the carbon involved in the double bond $C_{(3)}$ [$C_{(3)}$ attack]. This results in the formation of either oxy-anions of alcoholate type **1** or of enolate type **2**, which then generally leads to the addition of a proton (equation 1) and/or to an elimination (Knoevenagel, Darzens and Wittig type reactions, cyclopropanation or 2,3-dihydrofuran formation[1]).

The stabilization of oxy-anions of type **1** results in the formation of the products of the 1,2-addition to enals or enones (to the carbonyl group), while stabilization of oxy-anions of type **2** results in the formation of 1,4-addition (to the ethylenic bond) (Michael-type addition).

Regioselectivity of nucleophilic additions to enones and enals has been extensively studied[2], and theoretical interpretations have been proposed in terms of the Klopman theory[3]. Simply stated, reactions at $C_{(1)}$ are under charge control (hard site), while reactions at $C_{(3)}$ are under frontier control (soft site)[4–7]. Indeed, examination of the wide field of experimental results obtained with nucleophilic reagents RM under kinetic control reveals general trends[8]. Organometallic reagents can be divided into two classes:

(i) Those in which the metal is directly bound to the nucleophilic centre: (a) organoalkali



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metal derivatives (particularly organolithium reagents) in which M^+ is a hard cation prefer 1,2- over 1,4-additions[9,10]; (b) organocadmium, cuprates and palladium compounds lead to the attack of $C_{(3)}$; (c) organomagnesium and organoaluminium compounds show an intermediate behaviour and undergo both 1,2- and 1,4-additions.

(ii) Those in which the metal is not bound to the nucleophilic centre but in which the nucleophile reacts with enals or enones through its carbon atom (e.g. alkaline enolates): (a) loose enolate–M^+ ion pairs, in which the cation is free to be eventually complexed by the α-enone, imply a major attack on the carbon of carbonyl group; (b) tight enolate–M^+ ion pairs give an intermediate behaviour.

In fact, a delicate balance exists between the different interactions which favour 1,2- versus 1,4-addition. The nature of the products formed and the ratio of the $C_{(1)}$ and $C_{(3)}$ adducts depend on: (a) the nature and geometry of the organic part of the organometallic compound (number, nature and bulkiness of the substituents on the carbanionic centre), (b) the nature of the cationic counterpart, (c) the nature of the electrophilic partner (enals, enones or quinones) and particularly the relative steric hindrance around the carbonyl carbon and the β-ethylenic carbon, and (d) the experimental conditions used (solvent, temperature, presence of additives).

Any interpretation and predictions are all the more difficult, because reversibility of some of the reactions makes it difficult to assess whether the products are formed directly or after equilibration.

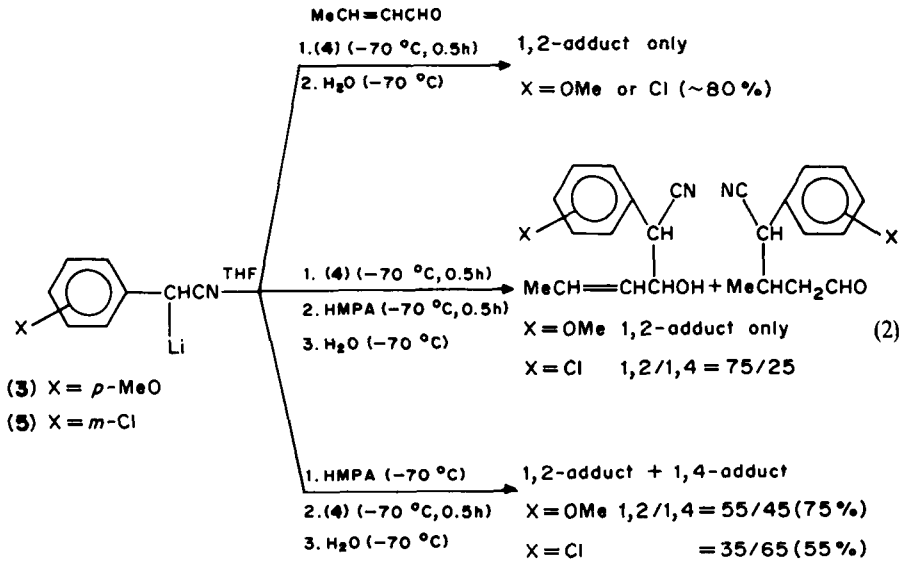
For each class of 'organometallic reagents', we collected typical examples from the large variety of experimental and theoretical results described in the literature in the last 10–15 years and discussed them from the standpoint of the influence of the above factors on the mode of addition.

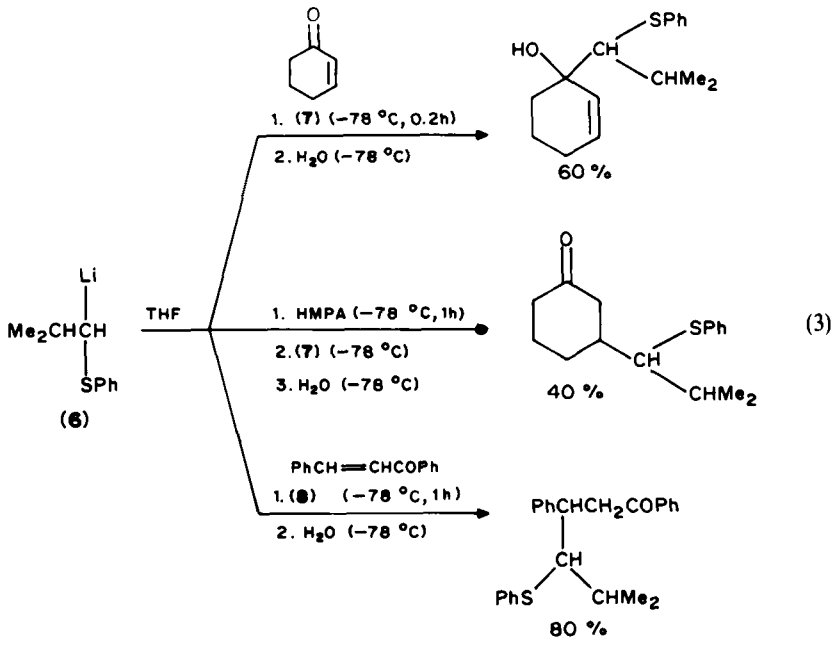
A. Organo Alkali Metal Reagents

A large variety of organo alkali metal reagents, mainly organolithiums, react with enals, enones and quinones and, as expected, all possibilities, including formation of the pure $C_{(1)}$ or $C_{(3)}$ adduct to a mixture of both, have been encountered, depending on the nature of the reactants and the reaction conditions[11–13].

Among organometallics, organo alkali metal reagents are perhaps those for which the regioselectivity of addition is the most dependent upon the above factors. This is exemplified by some results of Seyden-Penne and coworkers[14,15]. Whereas 1,4-addition is observed only under kinetic control between lithiated *p*-methoxyphenylacetonitrile (**3**) and crotonaldehyde (**4**) (equation 2), 1,4-addition is observed under thermodynamic

control when the closely related lithiated *m*-chlorophenylacetonitrile (**5**) is substituted for the *p*-methoxy substituted reagent (equation 2). In contrast, 1-lithio-1-phenylthio-2-methylpropane (**6**), which needs HMPA to add 1,4 to cyclohexenone (**7**) at − 78 °C, reacts 1,4 with chalcone (**8**) in THF at the same temperature (equation 3).





The theory of generalized perturbation applied to reactivity has been important for the development of the understanding of the regioselectivity of additions of organoalkali reagents to enals and enones.

Assuming that the transition state is reactant-like and that complexation phenomena do not exist, 1,2-addition should result from charge control (predominant coulombic term), whereas 1,4-addition results from frontier orbital control (energy gap control or matrix element control interaction). Under charge control, 1,2-addition is favoured as the total charge on the nucleophilic centre is greater. Under frontier energy gap control, dominant 1,4-addition is expected when the HOMO energy level of the reagent is high. Under matrix element (overlap control) ($H^2_{LU,HO}$) a large proportion of 1,4-adduct is expected if this term has a high value. For a given reagent, an increase of frontier orbital control is expected if the $C_{(1)}$ positive charge on the substrate and/or the LUMO energy level decreases and/or the $C_{(3)}$ coefficient in LUMO increases[16]. These considerations provide an interpretation for the differences between the modes of reaction of charge-localized anions **9**[17-20] and charge-delocalized anions **10**–**12**[16,20-26] with α-enones.

$R\bar{C}XY$ (**9**) $Ph\bar{C}XY$ (**10**) $X\bar{C}HCO_2R'$ (**11**) $(EtO)_2PO\bar{C}RX$ (**12**)

R = H or Me, X = CN or CO_2R', Y = H or Cl

For instance, when a comparison is made between the calculated parameters of chalcone, *p*-methoxychalcone and benzalacetone, and the proportions of 1,2- and 1,4-adducts formed after 30 min reaction at 20 °C and *t*-BuOK as base under kinetic control with phosphonoester **13**, phosphononitrile **14** and phosphine oxide **15** (Table 1)[24], it appears that the greater the charge delocalization on the anionic reagent, the greater the frontier control and the more favoured $C_{(13)}$ attack: the ester reagent **13** gave more $C_{(3)}$ attack than nitrile **14**; the phosphine oxide **15** gave more $C_{(3)}$ attack than **14** and, in fact, even more than **13**. Only benzalacetone has a relatively high total charge q_1 on the carbon of the carbonyl group. It is also the only ketone which gave substantial amounts of dienes resulting from a Wittig-type reaction. Chalcone and *p*-methoxy chalcone both have lower carbonyl q_1 and LUMO levels: carbonyl attack is less favoured and $C_{(3)}$ attack is more important.

$(EtO)_2POCH_2CO_2Et$ (**13**) $(EtO)_2POCH_2CN$ (**14**) Ph_2POCH_2CN (**15**)

TABLE 1. Certain characteristics of enones and experimental results obtained with the anions derived from **13**–**15**[24]

Enone	E_{LUMO}[a]	q_1[a]	$C_{(3)}$[a]	Reagent	Yield (%)	
					1,4-adduct	1,2-adduct
PhCH=CHCOPh	−0.132	+0.30	0.513	**13**	90	< 2
				14	70	< 5
(*p*-$MeOC_6H_4$)CH=CHCOPh	−0.183	+0.25	0.503	**13**	90	< 2
				14	60	10
PhCH=CHCOMe	−0.226	+0.38	0.563	**13**	35	15
				14	30	55
				15	40	< 2

[a]Calculation by the Hückel method.

TABLE 2. Characteristics of anionic reagents α to nitrile and experimental results obtained with 2-cyclohexenone[21,23,28]

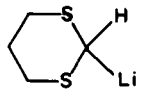
Anion	Geometry[a]	$q_c^{tot\,a}$	E_{HO}(eV)[a]	$C_c^{2p\,a}$	$C_c^{2s\,a}$	$C_{(1)}$ attack	$C_{(3)}$ attack
$[CH_2CN]^-$	pyramidal	−0.398	2.50	0.801	0.403	⩾95	5
	planar	−0.391	2.94	0.823	—		
$[ClCHCN]^-$	pyramidal	−0.240	0.95	0.753	0.471	⩾95	5
	planar	−0.252	1.69	0.814	—		
$[PhCHCN]^-$	planar	−0.251	1.66	0.709	—	⩽5	95
$[PhC(Cl)CN]^-$	planar	−0.130	0.90	0.708	—	⩽5	95
$[(HO)_2P(O)CHCN]^-$	planar	−0.461	1.20	0.787	—	⩽5	95[b]

[a]Total charge density (σ + π) and HOMO parameters (energy level E_{HO} and orbital atomic coefficients on anionic carbon C_c) calculated for the more stable geometry of anions, from a STO-3G basis set[28].
[b]Experimental results for $[(EtO)_2P(O)CHCN]^-$ [24-26]

Reactions with phosphorylated anions are also a good example of the limits of the use of Klopman's theory to rationalize the regioselectivity. When the additions of anions derived from **13** and **14** are extended to other 3-aryl and 3-alkyl substituted α-enones such as crotonophenone, 3-buten-2-one, cyclohexenone or 3-methylcyclohexenone, it is not possible to correlate $C_{(3)}$ reactivity with the LUMO characteristics of these α-enones. This has been interpreted in terms of the relative position of the transition states, which should involve rehybridization of the α-enone moiety with π energy loss of the system associated with steric factors for $C_{(3)}$ disubstituted compounds[25,27]. In the same way, all attempts to correlate the characteristics obtained by *ab initio* calculations for anionic reagents α to the nitrile group and experimental results of their attacks on cyclohexenone under kinetic control in conditions where electrophilic participation of the cation or ion pairing with the anion are not important, are at the least hazardous as is shown in Table 2.

The proportions of 1,2- and 1,4-additions cannot be interpreted (at least for these reagents) by taking into account only the attractive charge and frontier interactions. The repulsive terms between nucleophile and electrophile occupied orbitals must be considered. If the nucleophile contains many occupied orbitals and if the carbanion centre is sp^2 hybridized, 1,4-addition will be strongly favoured. If the carbanion centre is pyramidal, 1,2-addition predominates in spite of the fact that calculations show only a trend towards this process[28].

The importance of the repulsive terms and steric factors is exemplified by results obtained under kinetic control with the lithiated derivatives of 1,3-dithiane (**16**) and 2-substituted-1,3-dithiane (**17**) with enals and enones (Table 3). In THF or THF–HMPA, conjugate addition is more favoured for **17** (R = Ph) than for **16** due to repulsive interactions between occupied orbitals of the nucleophiles and electrophiles: these interactions, more important for **17** than **16**, and on $C_{(1)}$ more than on $C_{(3)}$, lead to an increase of $C_{(3)}$ addition for **17**. When the substitution on $C_{(3)}$ increases, the proportion of 1,4-adduct decreases, and even in THF–HMPA the 1,4-addition of **17** to 3-methylbutenal is low[29,30]. On the other hand, repulsive interactions on $C_{(1)}$ should be weaker for enals than for α-enones. Hence, the 1,2-addition is favoured in the former case[9].



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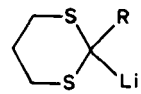


R = Me, $SiMe_3$, Ph

(17)

TABLE 3. Addition of reagents **16** and **17** (R = Ph) to enals[29]

Enal	Solvent	Reagent	$C_{(1)}$ attack	$C_{(3)}$ attack
MeCH=CHCHO	THF	**16**	>95	<5
	THF	**17**	65	35
	80:20 THF–HMPA	**16**	55	45
	80:20 THF–HMPA	**17**	<5	>95
PhCH=CHCHO	THF	**16**	>95	<5
	THF	**17**	85	15
	80:20 THF–HMPA	**16**	75	25
	80:20 THF–HMPA	**17**	35	65
Me_2C=CHCHO	THF	**16**	>95	<5
	THF	**17**	>95	<5
	80:20 THF–HMPA	**16**	>95	<5
	80:20 THF–HMPA	**17**	65	35
CH_2=CMeCHO	THF	**16**	>95	<5
	THF	**17**	65	35
	80:20 THF–HMPA	**16**	45	55
	80:20 THF–HMPA	**17**	<5	>95

These results also show the major influence of media having large dissociating and basic powers upon the regioselectivity of organoalkali additions to enones and enals. Thus, under kinetic control, the presence of a cosolvent such as HMPA or DMPU (1,3-dimethyl-2-oxohexahydropyrimidine) generally promotes conjugate addition to a significant extent, as exemplified by results obtained with lithiated derivatives **16** and **17** and cyclohexenone (Table 4).

The very important influence of solvents on the mode of addition of nucleophiles to enals and enones has been frequently noted and efficiently exploited[11,13,22,34]. It has been explained only recently by considering the effect of the cation counterpart on the regioselectivity of addition[35]. Briefly, the reagent can exist in two forms according to the nature of the ions and the media: solvent-separated ion pairs (loose ion pairs) and close (contact) ion pairs (tight ion pairs). In the first case, the carbanion interacts only weakly with the alkali counterion, so that a complex can be formed between the cation and the

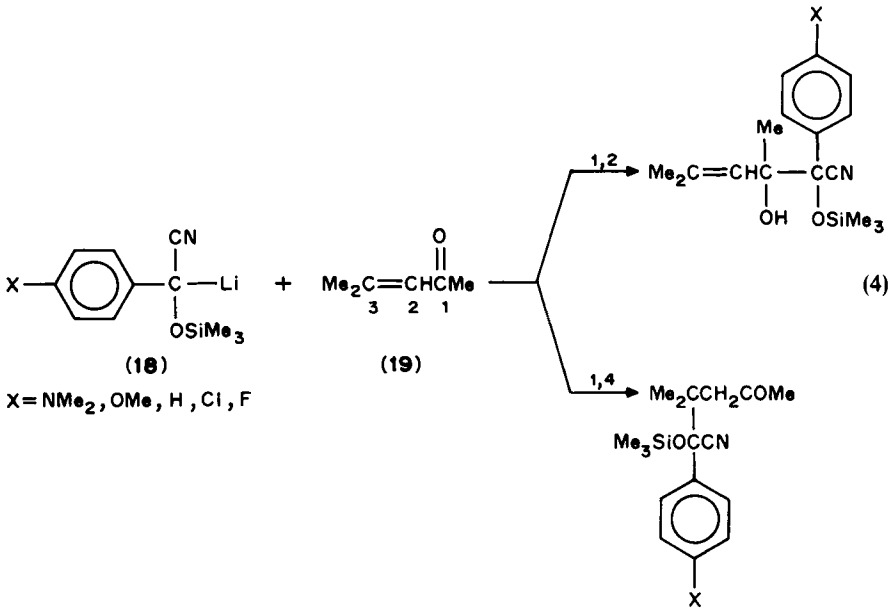
TABLE 4. Addition of 2-lithio-1,3-dithianes to 2-cyclohexenone in various media

Reagent	Solvent and additive (eq.)[a]	$C_{(1)}$ attack	$C_{(3)}$ attack	Overall yield (%)	Ref.
16	THF	98	2	90	31
16	THF–HMPA (1 eq.)	8	92	76	32
16	THF–HMPA (2eq.)	5	95	—	33
16	THF–DMPU (4eq.)	8	92	70	31
17 (R = Me)	THF–Hexane (1:1)[b]	>99	0	—	33
17 (R = Me)	THF–HMPA (1 eq.)	8	92	70	32
17 (R = $SiMe_3$)	THF–Hexane (1:1)[b]	>99	0	—	33
17 (R = $SiMe_3$)	THF–HMPA (2eq.)	3	97	—	33

[a]eq. = equivalent = mmol/mmol of dithiane.
[b](1:1) = 50% THF, 50% Hexane.

oxygen of the carbonyl group. The stability of the complex increases as the Lewis acid character of the cation increases ($Li^+ > Na^+ > K^+$). Thus, the reactions involving Li^+ seem to be the most interesting ones, because the cation is able to give stable complexes with the carbonyl group as well as to interact more or less strongly with the nucleophile. The complex formation increases the electrophilicity of the carbonyl group by increasing the charge on the $C_{(1)}$ atom and by decreasing the energy level of its LUMO, which favours regioselective attack at $C_{(1)}$ under charge control as much as under frontier orbital control. The complexation control also implies electrophilic assistance by the cation for both attacks at $C_{(1)}$ and $C_{(3)}$ depending on the nature of nucleophile and substrate. In the case of tight ion pairs, the nucleophile interacts strongly with the counterion (lithium) and the latter, which interacts only weakly with the oxygen of the carbonyl group, forms an associated species. Ion-pair association reduces the nucleophilicity of the carbanion by decreasing the charge on the nucleophile and the energy level of its HOMO, and then promotes the attack by nucleophiles on the $C_{(3)}$ atom.

The influence of solvation is strikingly manifested in the reactions between the trimethylsilyl ethers of *para*-substituted benzaldehyde cyanohydrins **18** and mesityl oxide (**19**)[36–38] (equation 4).



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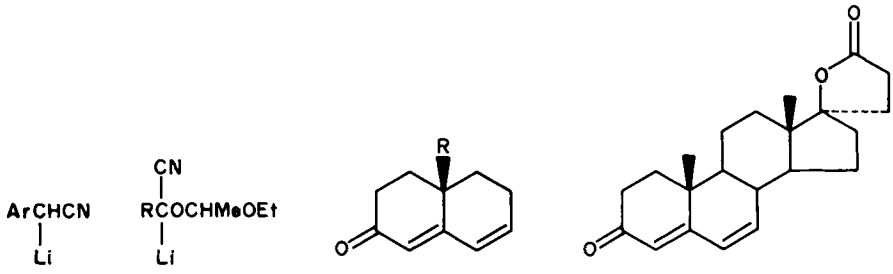
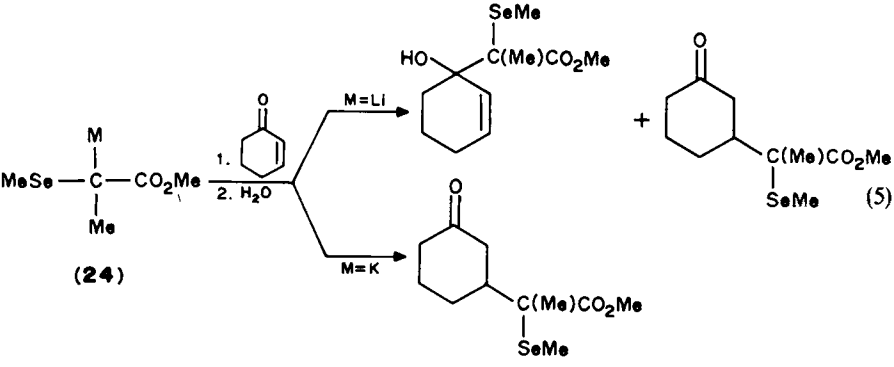
Regioselectivity depends upon the nature of the *para*-substituent and consequently upon the 'hardness' of nucleophiles in a given solvent; it also depends on the solvent. For instance, with **18** (X = H), under conditions of kinetic control a mixture of products of addition to $C_{(1)}$ and $C_{(3)}$ is formed rapidly and irreversibly in THF, in DME or in a mixture of these solvents whereas, in ether, only the addition to the C=C bond is observed. This was explained by assuming that ether promoted the conversion of the loose ion pairs of the reagent into tight ion pairs[36–39]. The accompanying decrease of the negative charge on the carbanionic centre is responsible for the preferential attack on the $C_{(3)}$ atom, despite the decrease in the energy of the HOMO of the nucleophile[13].

An interesting example of cation counterpart effect associated with the solvent effect is the change of rates of conjugate addition of lithiated arylacetonitriles (**20**) or of cyanohydrin ethers **21** to α-enones[21,23,40–43] and bicyclic α,γ-dienones[44]. For instance, the addition of **20** (Ar = Ph) to 3, 5, 5-trimethyl-2-cyclohexen-1-one (isophorone) for 1 min at −70 °C gives 45% of 1,4-addition in THF and 10% in 4:1 THF–HMPA[21,23]. By contrast, the conjugate 1, 6-addition of **20** and **21** to α,γ-dienones **22** or **23** is performed in considerable yield only in the presence of HMPA. In the former case, complexation between Li^+ and the carbonyl group of isophorone in THF induces electrophilic assistance for $C_{(3)}$ attack, because $C_{(1)}$ attack is sterically inhibited due to the interaction between the phenyl ring and the *gem* dimethyl groups. In THF–HMPA, the complexation is unlikely, since Li^+ is strongly solvated in HMPA, therefore the electrophilic assistance is suppressed. In the latter case, the 1,6-addition requires anionic activation and the solvation of Li^+ allows the nucleophilic attack, owing to the decrease of anion–cation interaction[44].

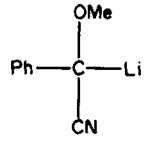


(20) Ar = Ph or *p*-$MeOC_6H_4$ **(21)** R = Ph or CH=CHMe **(22)** R = H or Me **(23)**

The complexation of the carbonyl group depends strongly on the Lewis acid character of the metallic cation. The methyl 1-lithio-1-methyl selenopropionate (**24**) (M = Li) reacted with 2-cyclohexenone in THF at −78 or −110 °C for 12 min to give after hydrolysis a mixture of both the $C_{(1)}$ and C(3) adducts in a ratio of 70:30 and in 75% overall yield. Under similar conditions the potassium derivative **24** (M = K) gives exclusively the $C_{(3)}$ adduct in 79% yield[45] (equation 5).



The structure of the reagent can itself affect the complexation effect of cations when a chelation between the cation and a basic group of the reagent is possible. This is the case of the lithiated cyanohydrin ether **21** (R = Ph) in which the two oxygens can chelate the lithium cation, unlike its homologue **25**. So, **25** leads to a mixture of 1,2- and 1,4-adducts with isophorone in THF under kinetic control, whereas only 1,4-addition is observed with **21**. The greater bulk of **21** also favours the conjugate addition[46].



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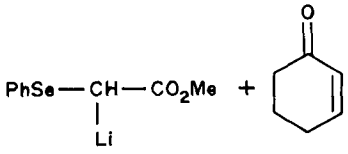
In conclusion, except for rare particular cases of reverse effect[9,47], 1,4-additions to enals and enones are favoured under kinetic control by using highly polar aprotic solvents such as HMPA. Moreover, 1,4-additions can also be realized with or without HMPA at higher temperature under thermodynamic control[11,21,46,48–51] as exemplified by the reaction of methyl 1-lithio-1-selenophenyl acetate (**26**) with 2-cyclohexenone (equation 6)[51].



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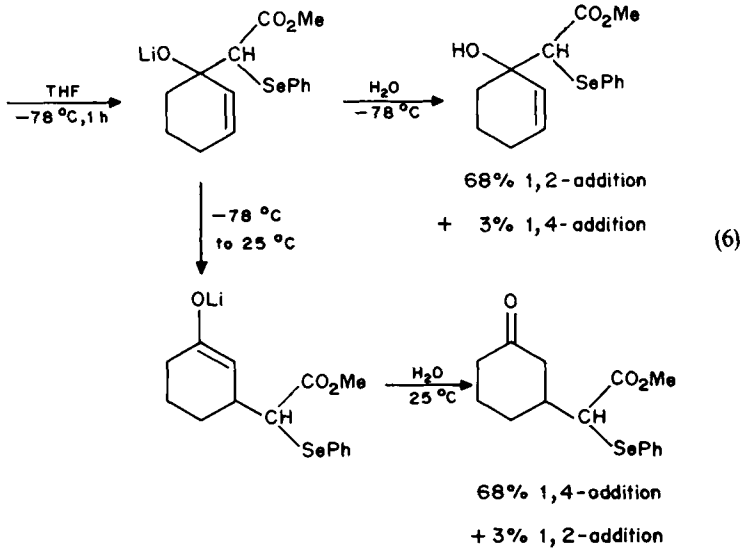


(6)

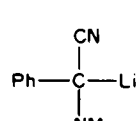
This equilibration, due to the reversibility of the 1,2-adduct formation, is observed with carbanions quite well stabilized and/or delocalized (high HOMO) and can formally occur

TABLE 5. Influence of temperature on the mode of addition of 1-lithio-1-phenyl-1,3-dithiane **17** to 2-cycloheptenone and 2-butenal

Substrate	Method	$C_{(1)}$ attack	$C_{(3)}$ attack	Overall yield (%)	Ref.
2-Cycloheptenone	THF, −78 °C for 10 min, quench	90	10	100	49
	THF, −78 to 25 °C for 1 h, quench	0	100	86	49
2-Butenal	THF, −70 °C for 30 min, quench	35	65	75	30
	THF–HMPA, −70 °C for 30 min, quench	95	5	80	30
	THF, −70 to 20 °C for 2 h, quench	35	65	70	30

in a cage of solvent or via the existence of two completely independent moieties[11]. Reversibility is highly substrate-dependent. For instance, the 2-lithio-2-phenyl-1,3-dithiane (**17**) (R = Ph) leads exclusively to the 1,4-adduct of cycloheptenone in THF when the temperature is raised from −78 to 25 °C[49], whereas no change of the 1,2/1,4 ratio is observed when the reaction is carried out at high temperature with enals[30] (Table 5). The latter case can be explained by the higher stability of secondary alcoholates versus tertiary ones[52–54]. In the other instances, when the metallated enolate formed by 1,4-addition is sterically hindered, an increase in temperature leads to a decrease in the yield of conjugate addition, due to retro-Michael reactions[46]. Lastly, an increase in the reaction temperature in order to favour the 1,4-adduct can also result in the decomposition of the starting reagent[55].

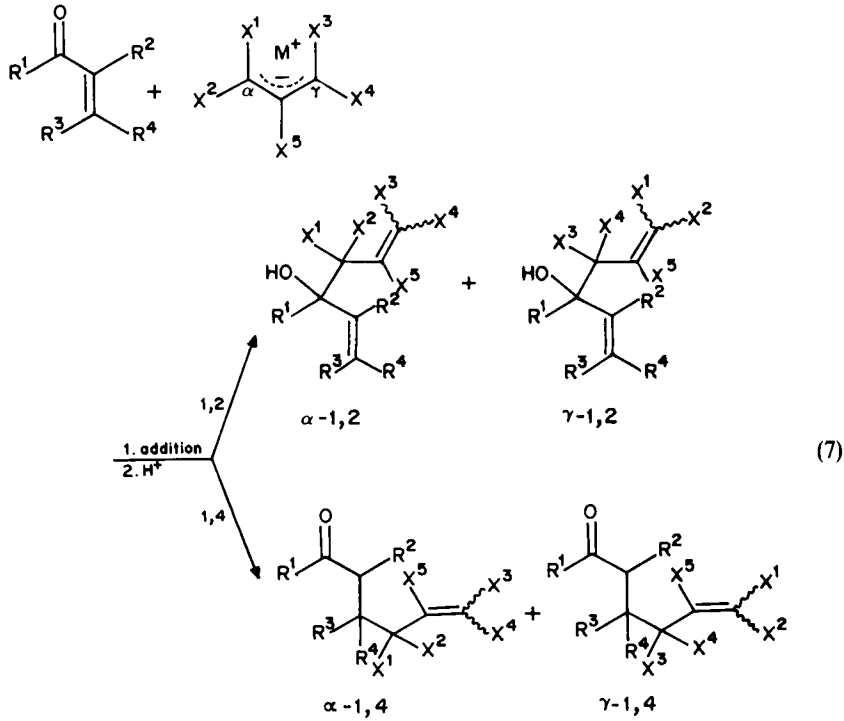
Because the carbonyl-counterion complexation effect can in principle participate in the mode of addition of organoalkali reagents to enones and enals[35], Lewis acids can be used when the nucleophilic additions are very sensitive to the degree of substitution of electrophiles. The changes in the yields and in the regioselectivity of additions depend upon the nature of the reagent and substrate and upon the experimental conditions[36,56–58]. For instance, both 1,2- and 1,4-additions of the lithiated derivative of α-dimethylaminophenylacetonitrile (**27**) to 3-methyl-2-cyclohexenone, isophorone[59] and mesityl oxide are accelerated in THF using BF_3–Et_2O, Ti(OPr-*i*)$_4$ and $ZnCl_2$ as additives; 1,2-addition and 1,4-addition are observed under kinetic control and thermodynamic control, respectively. The increase in 1,2-addition is easily explained if the carbonyl–Lewis acid complexation decreases the repulsive interactions due to the carbonyl lone pairs[28]. The strongly favoured 1,4-addition results from (i) a stabilization of the enolate species[60], (ii) structural modifications of the nucleophilic reagent and (iii) a decrease in the activation energy of the 1,4-addition[59]. With the same enones, LiBr is quasi-ineffective[59] suggesting the existence of a complexation between the carbonyl group and the lithium cation of the loose ion pair **27** in THF. On the other hand, adding $ZnCl_2$ to the reaction mixture of lithiated arylacetonitriles **20** and mesityl oxide results in a strong increase of 1,2-addition[56].



(27)

Predictions based on regioselectivity are more difficult when the organoalkali reagents are ambident nucleophiles. This is because anions not only present the usual concern for

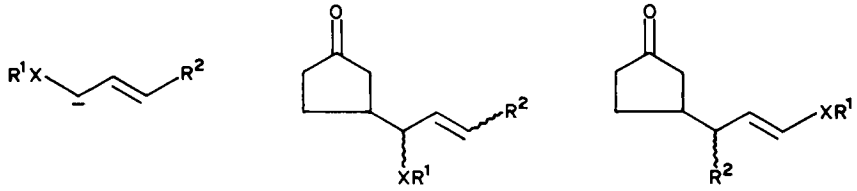
1,2- versus 1,4-reactivity, but also raise the added problem of α versus γ addition (equation 7).



(7)

A third aspect, namely the geometrical isomerism of substituents, comes into play simultaneously when the ambident nucleophile is highly substituted[61–64].

The mode of reaction is influenced by the nature of substituents bound to the allylic moiety. In a series of reagents containing sulphur, the carbanions **28** and **29** derived from allylic sulphides[65,66] and sulphones[67–70] undergo kinetically controlled conjugate addition to 2-cyclopentenone in THF at −78 °C in the presence of HMPA to give the allylic sulphides **31**[65,66] and sulphones **32**[63,69]. The sulphoxide derivative **30** gives the vinylic sulphoxide **33**[71–74], arising from reaction through the γ position of **30**. In addition, **33** was obtained as a single geometric isomer possessing the (*E*) configuration[63,71].



(28) X = S

(29) X = SO_2

(30) X = SO

α-1,4

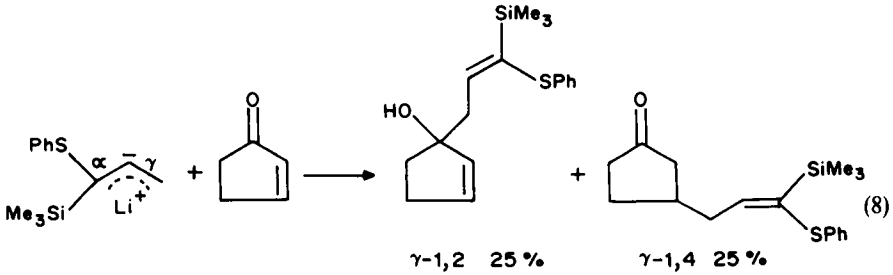
(31) X = S

(32) X = SO_2

γ-1,4

(33) X = SO

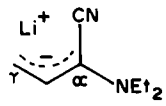
The addition of the 1-phenylthio-1-trimethylsilyl-2-propene lithiated derivative (**34**) to 1-cyclopentenone in THF–HMPA at − 78 °C furnishes a 50:50 mixture of γ-1,2 and γ-1,4 adducts, **35** and **36** respectively (equation 8)[75].



(8)

(34) (35) (36)

Steric factors on the substrates also play a significant role. For instance, the anion **37** formed from the α-diethylamino-2-butenonitrile and LDA in THF gives products resulting from the attack of the γ-carbon atom of **37** on α-enones. 2-Cyclohexenone, 2-cyclopentenone or methyl vinyl ketone yields only γ-1,4 addition products, while α,β- or β,β-disubstituted enones such as isophorone or carvone lead to a mixture of γ-1,2 and γ-1,4 adducts. However, yields of 1,4-adducts can be increased by allowing the 1,2-kinetic products to equilibrate[76]. In the same way, the highly hindered reagent **38** also adds exclusively 1,4 (α to SPh, γ to CN) across the conjugate systems of cyclopentenone and cyclohexenone in THF when the temperature is raised from − 50° to 0 °C over a period of 2 h[77].



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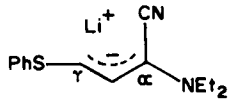


(38)

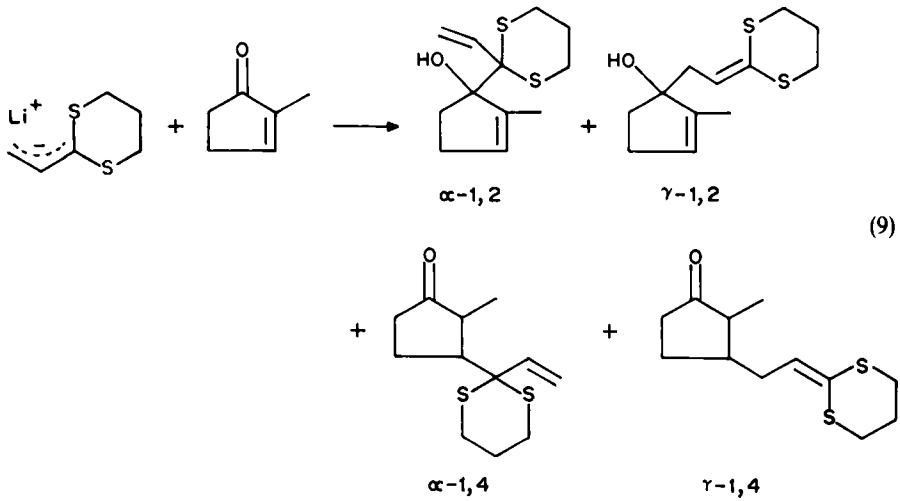
An interesting example of a change in regioselectivity of the reaction as the solvent composition is altered or the counterion modified is provided by the reaction of

TABLE 6. Addition of 2-ethylidene-1,3-dithiane anion to 2-methyl-2-cyclopentenone under various conditions[79]

Solvent and additive	Composition of reaction products (%)			Overall yield (%)
	α-1,2 + γ-1,2	α-1,4	γ-1,4	
THF	24	16	60	82
THF, CuI·$(MeO)_3P$[a]	0	98	2	54
THF, HMPA[b]	0	100	0	66

[a] 1.5 equivalent of CuI·$(MeO)_3P$.
[b] 3 equivalents of HMPA.

2-methylcyclopentenone with the carbanion generated by treating 2-ethylidene-1,3-dithiane with LDA (equation 9)[78,79]. The results are summarized in Table 6.



(9)

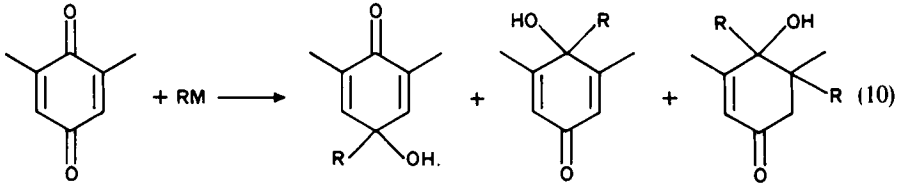
In this example, 1,4-addition predominates over 1,2-addition. Of the 1,4-addition products, γ-addition predominates when the lithium counterion is employed in THF. The increased amount of γ-1,4 adduct formed upon warming (from −78 to 25 °C) arises from an alkoxy-Cope rearrangement[61,80,81]. The preference for γ-1,4 selectivity can be effectively reversed by treating the lithium anion with 3.0 equivalents of HMPA or 1.5 equivalent of $CuI \cdot (MeO)_3P$ at −78 °C prior to the addition of the enone. Under these conditions, 10/1 to 50/1 α-1,4/γ-1,4 selectivity has been routinely obtained with other cyclenones without the appearance of 1,2-adducts[78,79]. We think that an oxy-Cope rearrangement could also explain the results obtained by Hirama[69], who observed that the reaction of lithiated derivative of allylsulfone on 2-cyclohexenone at −78 °C in THF without HMPA leads to the α-1,2 adduct as the major kinetic product. It is then transformed mainly to the γ-1,4 adduct, slowly at −78 °C or quickly at 0 °C.

With *p*-quinones, 1,2-additions of organoalkali reagents, mainly organolithiums, can be performed at low temperature to produce the corresponding quinols in high yield[82,83]. However, with unsymmetrical quinones these additions exhibit low regioselectivity, except in particular cases[83]. Indeed, the two carbonyl groups can be attacked. The regioselectivity is obtained by blocking one carbonyl group of the quinone with trimethylsilyl cyanide, followed by reaction of the other carbonyl group with the organometallic reagent, the protecting group being then removed with silver fluoride[84]. In fact, selective additions of carbanions to unsymmetrical *p*-quinones can be achieved at either carbonyl carbon by a judicious choice of reaction conditions without the use of a protecting group. The basic principles that are used to achieve these regioselective 1,2-additions have been proposed by Liotta and coworkers[85]. If the carbanion is made sufficiently bulky by varying its counterion, its degree of aggregation and/or its degree of solvation (i.e. steric factors) should dominate the transition state, resulting in regioselective addition to the less hindered carbonyl carbon. By contrast, if the carbanion is relatively small and only weakly solvated, electronic factors should dominate the transition state, resulting in regioselective addition to the more electrophilic carbonyl carbon. The effectiveness of these principles is exemplified by the reaction of 1,6-dimethylbenzoquinone (**39**) with various organometallic reagents (Table 7) (equation 10).

TABLE 7. Addition of organometallic reagents to quinone 39[85]

Reagent	Solvent	Additive	Temperature (°C)	Reaction products (%) 40	41	42
MeLi	THF	TMEDA[a]	−107	9	87	—
MeMgBr	THF		−78	60	—	10
n-BuLi	THF	TMEDA[a]	−107	12	66	—
n-BuLi	Et_2O		−78	60	15	—

[a]6 equivalents.



(39) (40) (41) (42) (10)

In comparison to the relatively large and heavily solvated carbanion of methyl magnesium bromide, which reacts in accordance with the above steric model, the methyl carbanion from methyl lithium in THF–TMEDA is in a non-aggregated, weakly solvated state and reacts in accordance with the electronic model discussed above. With the same organolithiated reagent, changing solvent and cosolvent alters the solvation and aggregation state and reverses the regioselectivity.

Stereoelectronic control has been used to perform regioselective organoalkali additions to enediones[86].

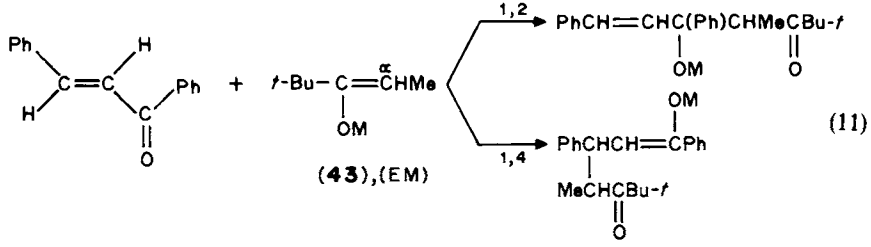
B. Metal Enolates and Related Compounds

Metal enolates are O-metalled species which react with α-enals, α-enones or quinones by their carbon atom. The metal is not bound directly to the nucleophilic centre. Evidently, the mode of reaction (1,2- or 1,4-attack) is highly dependent upon the different factors discussed above for C-metalled organoalkali reagents. However, in our opinion, the most relevant feature of these reagents is the influence of their associative states on the regioselectivity. House and coworkers[87] have shown by spectroscopy the existence of different kinds of ionic association between enolate and cation, depending on the nature of the partners and medium. The ion pairs can be of a loose type (e.g. in polar or strongly solvating solvents, and also, for some structural reason, such as *Z* or *E* configuration) or of a tight type. In the case of a contact ion pair, the reagent can exist in solution as molecular aggregates, especially with non-polar solvents[87–94]. In solvents such as ether or THF, metal enolates react in associated forms and the regioselectivity of additions is very sensitive to changes in nucleophilicity entailed by changes in associative states. This is exemplified by the results obtained by Maroni and coworkers[60] for additions of metal enolates EM **43** of 2,2-dimethyl-3-pentanone to *trans*-chalcone, under kinetic conditions (Table 8) (equation 11).

TABLE 8. Addition of metal enolates of 2, 2-dimethyl-3-pentanone (EM) to *trans*-chalcone in Et_2O at $-78\,°C$[60].

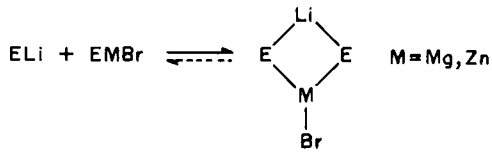
Entry	Enolate formation	Composition of **43**	$\delta^{13}C_{(a)}$[a]	1,2-Adduct	1,4-Adduct	Overall yield (%)
a	*t*-BuCOEt + *i*-Pr_2NLi	ELi	83.1	30	70	55
b	*t*-BuCOEt + *i*-PrMgBr or *t*-BuCOCHBrMe + Mg	EMgBr	95.4	95	5	40
c	*t*-BuCOCHBrMe + Zn	EZnBr	98.7	> 98	< 2	20
d	2 EMgBr + $MgBr_2$	E_2Mg	83.4–95.4	25	75	90
e	ELi + EMgBr	$E_2LiMgBr$	88.2	65	35	40
f	ELi + $ZnBr_2$	$E_2LiZnBr$	90.2	60	40	35
g	E_2Mg + 2ELi	E_4Li_2Mg	88.0	65	35	45
h	$2E_2Mg$ + 2ELi	$E_6Li_2Mg_2$	87.9	70	30	30

[a]Chemical shift (ppm/TMS) of the carbanionic centre of enolates.



(11)

When we compare the regioselectivities of ELi, EMgBr and $E_2LiMgBr$ (entries a, b and e in Table 8) or of ELi, EZnBr and $E_2LiZnBr$ (entries a, c and f), we can see that the 1,2/1,4 ratio from e or f is intermediate between those of a and b or a and c owing to the formation of mixed enolates $E_2LiMgBr$ or $E_2LiZnBr$ (equation 12).



(12)

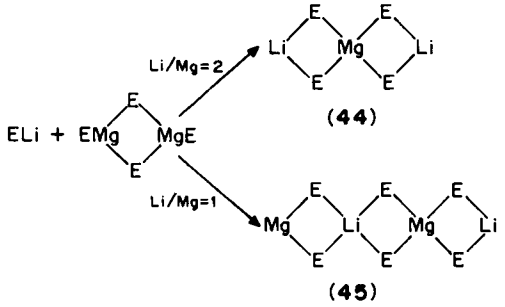
Most surprising are the cases of entries a and d compared to g and h. Metal enolates ELi and E_2Mg lead to a similar 1,2/1,4 ratio (30:70) and should give the same regioselectivity from a mixture of the two metal enolates (entries g and h). In fact, the regioselectivity is reversed (70:30) as the result of participation by associated forms **44** and **45**[91].

Examination of Table 8 also shows that the ratio of 1,2/1,4 attacks increases when the ^{13}C chemical shift of the carbanionic centre of metal enolates increases, i.e. when the charge on this carbon decreases[95]. So, the 1,2-addition is not charge controlled and the 1,2 and 1,4-attacks are probably under orbital control at $-78\,°C$. The less nucleophilic enolates (the most associated or most covalent) lead to the greatest per cent of 1,2-additions (M = MgBr, ZnBr, entries b and c).

Associative states are also influenced by other factors (such as solvent or temperature). This has to be kept in mind for the following discussion.

TABLE 9. Substituent effect of enolates **46–49** on the regioselectivity of addition to *trans*-chalcone

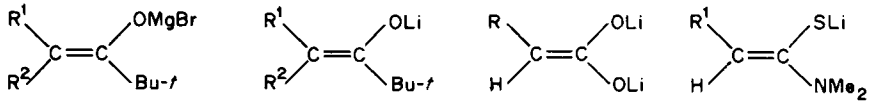
enolate	R^1	R^2	Temperature (°C)	Solvent	Time (min)	1,2-Attack	1,4-Attack	Overall yield (%)	Ref.
46	H	H	20	THF	1	100	0	55	96
46	Me	H	−78	Et_2O	1	>95	<5	40	96
46	Me	Me	−78	Et_2O	1	0	100	<30	96
47	H	H	−78	THF	1–60	80	20	40	96
47	Me	H	−78	Et_2O	1	30	70	55	96
47	Me	Me	−78	Et_2O	1	0	100	80	96
48	H		−50	THF	60	71	29	67	97
48	Me		−50	THF	60	68	32	85	97
48	Et		−50	THF	60	62	38	65	97
48	*i*-Pr		−50	THF	60	50	50	77	97
48	*t*-Bu		−50	THF	60	0	100	88	97
49	H		−45	THF	4	77	23	87	98
49	Me		−45	THF	2	70	30	68	98
49	Et		−45	THF	2	72	28	76	98
49	*i*-Pr		−80	THF	1	<5	>95	40	98
49	Ph		−45	THF	3	<5	>95	60	98



(44)

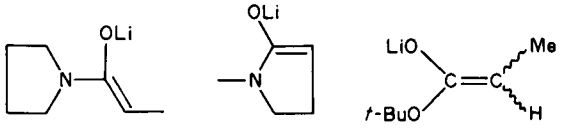
(45)

The results obtained from reactions of various metal 'enolates' with *trans*-chalcone under kinetic control (Table 9) show that the formation of 1,4-adduct is favoured as the substitution degree of the enolate is increased.



(46) (47) (48) (49)

As expected, metal enolates add preferentially to the 1,2-position of α-enals compared to α-enones under kinetic conditions[99–103]. When the steric hindrance around the carbonyl group of the α-enones increases, the 1,4-additions are favoured as exemplified in Table 10 with enolate **48** (R = H), **48** (R = Et), **50** and **51**.



(50) (51) (52) *E* or *Z*

TABLE 10. Effect of substituents at the carbonyl group on the regioselectivity of metal enolate additions to $R^2CH{=}CHCOR^1$ in THF

Enone								
R^1	R^2	Reagent	Temperature (°C)	Time (min)	1,2-Attack	1,4-Attack	Overall yield (%)	Ref.
Me	Ph	**48** (R = H)	−50	60	100	0	72	97
Et	Ph		−50	60	100	0	80	97
i-Pr	Ph		−50	60	100	0	73	97
Ph	Ph		−50	60	71	29	67	97
t-Bu	Ph		−50	60	69	31	45	97
Et	Ph	**48** (R = Et)	−50	60	100	0	85	97
Ph	Ph		−50	60	62	38	65	97
t-Bu	Ph		−50	60	0	100	83	97
Et	Me	**50**	−78	20–60	>97	<3	78	104
i-Pr	Me		−78	45	29	71	84	104
Ph	Me		−78	60	12	88	92	104
t-Bu	Me		−78	60	<3	>97	90	104
Et	Me	**51**	−78	60	>97	<3	50	104
i-Pr	Me		−78	60	80	20	64	104
Ph	Me		−78	60	63	37	67	104
t-Bu	Me		−78	60	14	86	67	104

For the four reagents, the isopropyl alkenyl ketones lead to a substantial preference for 1,2-addition in comparison with the corresponding phenyl alkenyl ketones. In both cases, the steric interactions for the 1,2-addition pathway are alike. The difference of behaviour between the two series is explained by the greater repulsive interactions between occupied orbitals of the nucleophiles and electrophiles in the phenyl ketones than in the isopropyl ketones. The resonance effect of the phenyl group which deactivates the carbonyl group towards nucleophilic attack can be also taken into account[97].

The 1,2/1,4 ratio depends also on the steric demand of the group at the β-position of the enones, as shown in Table 11[104,105]. The results show that when the two configurations of

TABLE 11. Effect of substituents at the β-position of enones on the regioselectivity of metal enolate additions to RCH=CHCOBu-*t* in THF at −78 °C[104,105]

Enone R	Reagent	Time (min)	1,2-Attack	1,4-Attack	Overall yield (%)
Me	**50**	60	<3	>97	90
Et		15	<3	>97	95
Ph		15	<3	>97	69
t-Bu		15	54	46	70
Me	**51**	60	14	86	72
Et		15	31	69	58
Ph		15	55	45	55
t-Bu		15	>97	<3	60
Me	**52** *Z*	15	<3	>97	78
	52 *E*	15	<3	>97	85
Et	*Z*	15	<3	>97	49
	E	15	<3	>97	86
Ph	*Z*	15	14	86	88
	E	15	40	60	95
t-Bu	*Z*	15	—	—	0
	E	15	>97	<3	65

TABLE 12. Product distribution as a function of lithiated enolate types for the addition to 2-cyclohexenone in THF

Entry	Reagent	Temperature (°C)	Time (min)	1,2-Attack	1,4-Attack	Overall yield (%)	Ref.
a	t-BuC(OLi)CH_2[a]	−47 to −50	10	100	0	93	106
b	t-BuC(OLi)CHMe	−78	1	40	60	—	107
c	t-BuC(SLi)CH_2	−78	15	0	100[b]	50	108
d	MeOC(OLi)CMe_2	−78	30	95	5	93	109
e	MeOC(OLi)C(OPh)Me	−78	30	92	8	96	109
f	MeOC(OLi)C(OMe)Me	−78	30	86	14	87	109
g	MeOC(OLi)C(SMe)Me	−78	30	90	10	70	109
h	MeOC(OLi)C(SPh)Me	−78	30	0	100	75	109
i	MeOC(SLi)CH_2	−78	15	70	30	43	108
j	$(CH_2)_4$NC(OLi)CHMe[c]	−78	20	97	3	78	104
k	Me_2NC(SLi)CH_2	−78	20	100	0	65	108
l	MeSC(OLi)CH_2	−78	10	100	0	73	108
m	MeSC(SLi)CH_2	−45	15	0	100	86	110
n	MeSC(SLi)CMe_2	−55	15	0	100[d]	66	111
o	HC(Me_2NNLi)CHMe	0	1	72	28	—	112
p	HC(Me_2NNLi)CMe_2	−78	1	>90	<10	—	112

[a] Reaction performed in Et_2O.
[b] 100% 1,4-S-addition.
[c] The substrate is 4-hexen-3-one.
[d] 1,4-S-addition/1,4-C-addition = 86/14.

enolates exist, *E* enolates exhibit a greater preference for 1,2-addition than *Z* enolates.

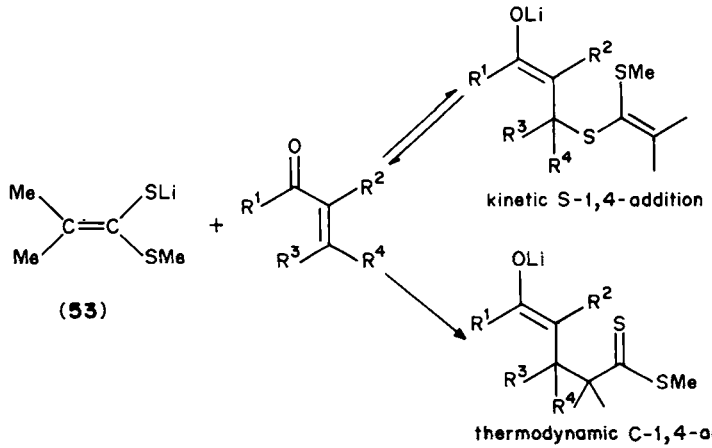
In a homogeneous set of metallated enolates, such as lithiated enolates, it is possible to apply the HSAB concept to predict the preferential orientation of additions according to the nature of the enolates (ketones, thione, amide, thioamide, ester enolates) and of hetero substituent bonded on the carbanionic centre: the most delocalized (soft) enolates should lead to the greatest proportion of 1,4-addition. Some results obtained with 2-cyclohexenone and various lithiated enolates at low temperature are summarized in Table 12.

Except for the surprising cases of 2,2-dimethyl-3-pentanone lithiated enolate (entry b), all O-lithiated derivatives react preferentially on the carbonyl group under kinetic conditions. For the α-thiophenyl derivatives of the methyl propionates series (entry h), it seems that equilibration due to the 1,2-addition reversibility occurs even at −78 °C[109].

TABLE 13. Addition of **53** to α-enones in THF[111]

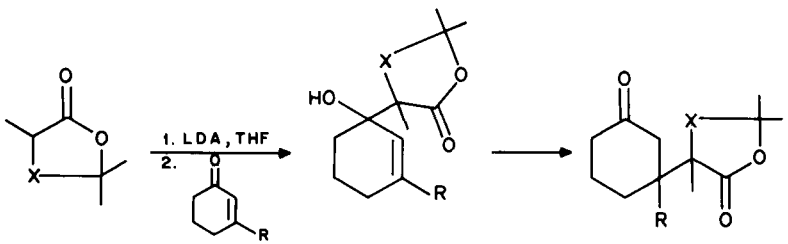
Enone	Temperature (°C)	Time (min)	S-1,4	C-1,4	Overall yield (%)
2-Cyclohexenone	−55	15	86	14	66
2-Cyclohexenone	−55 and then −20	15 15	4	96	82
2-Cyclohexenone	−20	10	1	99	72
3-Penten-2-one	−78	20	85	15	39
3-Penten-2-one	−30	20	5	95	70
2-Cyclopentenone	−126	—	0	100	—
2-Cyclopentenone	−78	10	0	100	45
2-Cyclopentenone	−20	10	0	100	70

The lithiated enolates derived from hydrazones (entries o and p) also favour the 1,2-addition. The situation is complex with S-lithiated reagents. Sulphur-lithiated enolates may be considered as softer nucleophiles than the corresponding oxygen-lithiated derivatives. The 1,2-orientation is unfavoured, but the softness is modulated by the nature of the enolates (thioketones, thioesters, dithioesters or thioamides). Thus, the effects of alkoxy or amino groups (entries i and k) counteract the sulphur effect, in contrast to thio and dithioenolates (entries c, m and n). Thioketones give regioselective sulphur 1,4-addition, whereas dithioesters can afford carbon 1,4-additions or sulphur 1,4-additions depending on the substitution of dithioesters, on the nature of enones and on the reaction conditions[111,113,114]. For instance, the reaction of lithium thioenolate of methyl 2-methyldithiopropanoate (**53**) gives kinetic sulphur 1,4-addition and thermodynamic carbon 1,4-addition when temperature and reaction time increase. An exception is that 2-cyclopentenone gives kinetic carbon 1,4-addition (Table 13) (equation 13)[111].



(13)

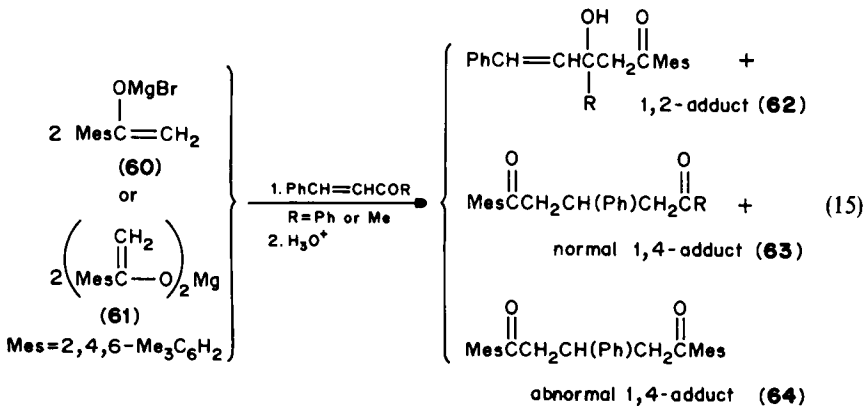
The effects of temperature, time and solvent on the reversibility from 1,2- to 1,4-addition have been largely documented. The reversibility of 1,2-addition is commonly observed for various metal enolates derived from ketones[96,107,115–118], esters[105,111,119], amides[104,120], thioamides[98], imines and hydrazones[112]. It has been exploited extensively to synthesize δ-functionalized ketones. Evidently, the reversibility of 1,2-addition is very sensitive to structural effects of the 1,2-adducts, as exemplified by the reactivity observed with the lithiated derivative of acetonide **54** (equation 14).



(14)

Reaction of **54** with 2-cyclohexenone at either −78 or 25 °C over prolonged reaction times gives only the product of 1,2-addition **56** (82% isolated yield). Substitution of 3-methyl-2-cyclohexenone for 2-cyclohexenone gives only **57**, isolated in 80% yield. When reaction of the ester enolate of **55** with 2-cyclohexenone is followed by addition of one equivalent of 3-methyl-2-cyclohexenone with stirring for 1 hour at 25 °C, only **56** and unreacted 3-methyl-2-cyclohexenone are recovered. Clearly, with the enolate of **54** and 2-cyclohexenone, 1,2-addition is irreversible under these reaction conditions. With thiaacetonide **55**, however, 1,2-addition is reversible and **58** gives the product of conjugate addition **59** at 25 °C[109].

If the 1,2-reversibility is established, reversibility of 1,4-addition is less expected and it leads to problems of redistribution and of stereochemistry. The first problem is illustrated by the reactions of magnesium derivatives **60** and **61** of mesityl methyl ketone with *trans*-chalcone and *trans*-benzalacetone in Et_2O at 20 °C (equation 15) (Table 14).

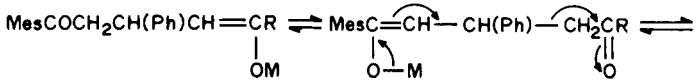


(15)

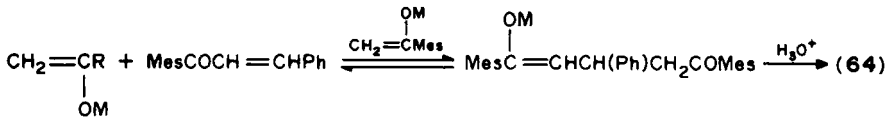
With the reagent **61**, a new 1,4-adduct (**64**) appears that can be explained by the reversibility of the normal 1,4-addition (equation 16) as demonstrated by isolation of acetophenone and 1,3,5-triphenyl-1,5-pentanedione after hydrolysis.

TABLE 14. Product distribution as a function of reaction times for additions of enolates **60** and **61** to chalcone and benzalacetone (20 °C, Et_2O, enolate/enone = 2)[118]

Enone	Reagent	Time (min)	Product distribution (%)			Overall yield (%)
			62	**63**	**64**	
Chalcone	**60**	5	100	0	0	70
		360	87	13	0	100
		1440	70	30	0	100
	61	5	0	100	0	> 90
		1440	0	50	50	> 90
Benzalacetone	**60**	5	100	0	0	100
		1440	> 95	< 5	0	100
	61	5	15	85	0	> 90
		1440	15	59	26	> 90

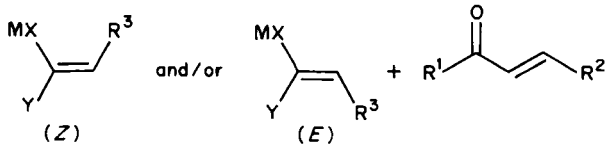


R=Ph or Me, Mes=2,4,6-$Me_3C_6H_2$ M=—MgO— (16)



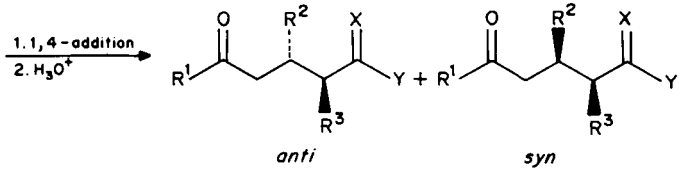
Redistribution reactions arise with **61** and the lithiated derivative of mesityl methyl ketone, but not with **60**. Thus, the phenomenon is joined to the associative states and nucleophilicity of metal enolates[118] and has some importance in the study of the stereochemistry of 1,4-additions.

The geometry of enolates is very important for the stereochemistry of the kinetic Michael-type additions of enolates to enones. Indeed, when the reaction involves a prochiral enolate and a prochiral enone, two diastereomers can be formed (equation 17).



X=O,S

Y=NR_2,OR,SR (17)



In the cases of some lithium enolates of ketones[96,121], esters[105] and dithioesters[122], a correlation has been observed between the enolate *Z* or *E* geometry and the Michael adduct stereostructure, under presumed kinetic conditions. It seems that *E* enolates tend towards *syn* selectivity and *Z* enolates towards *anti* selectivity (Table 15).

With the dithioester enethiolates, Metzner and coworkers[122] explained the stereospecificity of additions with acyclic enones by the intervention of the classical closed transition state[123–127], in which the metal ion is chelated in an eight-membered ring between the oxygen of the enone and the sulphur of enethiolate.

With ester and ketone enolates, Heathcock and Oare[105,121] proposed an open transition state in which the MX and Y groups (equation 17) competitively interact with the substituent R^2 of the enones. Although the chelation between the metal ion and the oxygen of the enone seems difficult, this open transition-state hypothesis explains why stereospecificity is not observed with large Y groups[104].

In our opinion, the attractive suggestion that *Z* enolates tend towards *anti* diastereosel-

TABLE 15. Stereochemistry of the addition of lithium enolates to *E*-s-*cis* enones $R^1COCH{=}CHR^2$ in THF

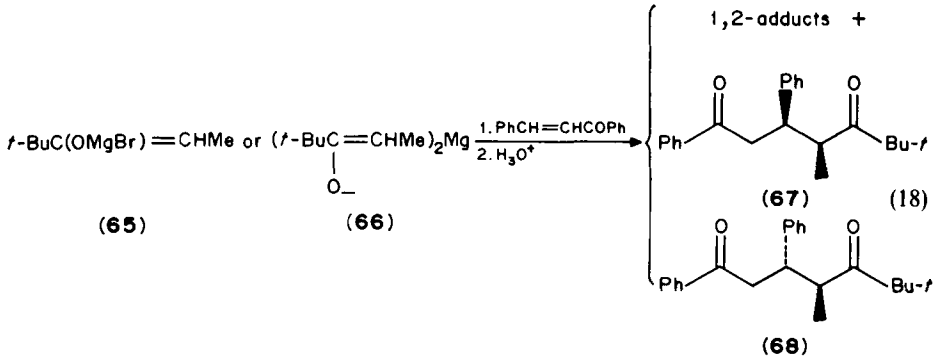
Enones				Temperature	Time	*syn*	*anti*	
R^1	R^2	Enolate	(*E*/*Z* ratio)	(°C)	(min)	(1,4-adduct)		Ref.
t-Bu	Me	*t*-BuOC(OLi)CHMe	(0/100)	−78	15	13	87	105
t-Bu	Ph		(11/89)	−78	15	7	93	105
t-Bu	Ph		(95/5)	−78	15	94	6	105
t-Bu	Ph	PhC(OLi)CHMe	(2/98)	−78	1440[a]	4	96	121
t-Bu	Ph		(87/13)	−20	1440	83	17	121
Me	Me		(2/98)	−78	1440	3	97	121
Me	Me	MeSC(SLi)CHMe	(4/96)	−50	10	8	92	122
Me	Me		(42/58)	−50	10	43	57	122
Ph	Ph		(24/76)	−70	10	28	72	122

[a]Reaction in THF/HMPA.

TABLE 16. Stereochemistry of addition of metal enolates **65** and **66** to *trans*-chalcone in Et_2O[116]

Reagent	Temperature (°C)	Time (min)	1,2-Attack	1,4-Attack	Overall yield (%)	*syn* **67**	*anti* **68**
65	20	1	48	52	85	0	100
66	20	1	0	100	100	15	85
65	20	5	40	60	100	0	100
66	−20	5	0	100	80	0	100
65	20	60	5	95	100	0	100
66	20	60	0	100	100	76	24
66	−20	60	0	100	80	0	100
65	20	1140	0	100	100	0	100
66	20	4320	0	100	100	84	16
66	−20	4320	0	100	80	15	85

ectivity whereas *E* enolates tend towards *syn* selectivity, should be regarded with caution and should not be generalized. First, the stereoselective hypothesis is based on reactions of particular lithiated enolates and enones; second, it is very difficult to confirm that the reactions are under kinetic control when only 1,4-additions are observed. The stereochemistry of 1,4-additions is highly dependent upon the enolate types and their degree of association[96], temperature and reaction times[120], as exemplified by the reactions of metal enolates derived from 2,2-dimethyl-3-pentanone, **65** or **66** and *trans*-chalcone (equation 18)[116] (Table 16).



In addition to the redistribution phenomenon discussed above, these results clearly show the possibility of reversibility of the 1,4-addition with accompanying changes of stereochemistry[120]. Therefore, even if a diastereoselectivity or diastereospecificity can be interpreted *a posteriori*, in some cases, the prediction of the stereochemistry of a 1,4-addition between metal enolates and enones seems illusive.

In agreement with the results on ambident organoalkali reagents (see Section II.A), ambident metal enolates usually give complex mixtures of α-1,2, γ-1,2, α-1,4 and γ-1,4 adducts. The product distribution is largely dependent upon all the reaction parameters (nature of reagent and substrate, reaction conditions)[128–131] with additional possibility of oxy-Cope rearrangement of the reversibly formed 1,2-adducts[132].

C. Other Organometallic Compounds

1. Organocopper reagents

Organocopper reagents are softer nucleophiles than Grignard and organolithium compounds[133]. They are relatively inactive towards saturated ketones and add almost exclusively to enones in a conjugate manner. This is now a well-reviewed part of synthetic methodology[134–143].

In most cases, organocopper reagents are prepared by adding an organomagnesium or an organolithium reagent to a copper(I) species (equations 19–22).

$$RM + CuX \longrightarrow RCu + MX \tag{19}$$

$$2RM + CuX \longrightarrow R_2CuM + MX \tag{20}$$

$$RM + CuR' \longrightarrow RR'CuM \tag{21}$$

$$RM + CuZ \longrightarrow R(Z)CuM \tag{22}$$

$$M = Li, MgX; \quad Z = OR', SR', CN$$

Although lithium diorganocuprates (R_2CuLi) have been the most frequently used, various copper-containing systems have been developed and successfully used with the α-enonic framework (Table 17).

The reactivity profile, which depends on the nature of reagents and substrates, may be altered by several parameters, such as the source of copper(I) species, the CuX/RM ratios[144–146] or reagent/enone ratios[146–150], the gegenion involved (M = Li or MgX)[151–155], the choice of solvent, and the presence of additives (Lewis acids, lithium salts[156–158], solubilizing or stabilizing ligands such as sulphides[154,157,159–161] or phosphines[157,161–167]).

The great number of possible combinations and the different influences of the above parameters on the chemical behaviour of the various organocopper reagents contribute to the complexity of choosing the best suitable reagent and optimum experimental conditions for a given enone. Nevertheless, it is now well established that a regio- and

TABLE 17. Examples of current useful copper-containing systems employed successfully for addition to the α-enonic framework

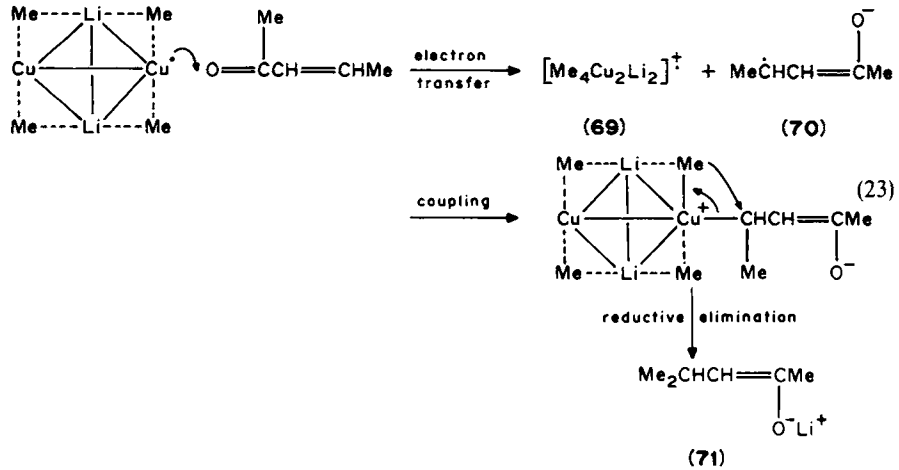
General name	General formula[a]
Copper-catalyzed Grignard reagents	$RMgX/Cu^+$
Organocopper reagent	RCu·MX
	RCu·MX·Ligand
Organocopper·Lewis acid complex	$RCu \cdot BF_3$
	$RCu \cdot AlCl_3$
	$RCu \cdot Me_3SiCl$
Homocuprates	R_2CuM
	$R_2CuM \cdot Ligand$
Mixed homocuprates	RR'CuM (R' = alkyl, phenyl, alkynyl, 2-thienyl)
Organo (hetero) cuprates	R(Z)CuM (Z = OR', SR', CN, NR'_2, PR'_2)
Higher-order cuprates	R_3CuM_2
	$R_2Cu(CN)Li_2$, $RR'Cu(CN)M_2$
Highly aggregated cuprates	R_3Cu_2Li
	$R_5Cu_3Li_2$
	$R_4R'Cu_3(MgX)_2$

[a] M = Li, MgX; X = halide; Ligand = Me_2S, PR_3.

stereoselective conjugate addition is often achieved more effectively by stoichiometric copper than by copper-catalyzed Grignard reagents[134,135]. Whereas alkyl, vinyl or phenyl groups can be transferred into the β-position of an enone, the alkynyl unit does not, the ethynyl ligand being tightly bound to copper[164,168], and allylation being a very versatile process (see Section IV).

Despite the increasing use of these reagents in synthesis, the mechanism by which the copper ion encourages the addition of the anionic moiety to the β-carbon of the unsaturated ketone still remains in question and many controversies exist. Almost all mechanistic studies have used lithium dimethyl cuprate (Me_2CuLi), which is assumed to be a dimeric cluster in Et_2O[169–172]. However, there is widespread agreement that: (i) coordination of the lithium ion to the oxygen of the enone seems a necessary first step[173,174] (addition of an excess of 12-crown-polyether inhibits the addition[175]); (ii) the reaction produces an enolate anion; (iii) a six-centre transition state is not a requirement[176]; and (iv) free alkyl radicals are excluded as intermediates[177–179].

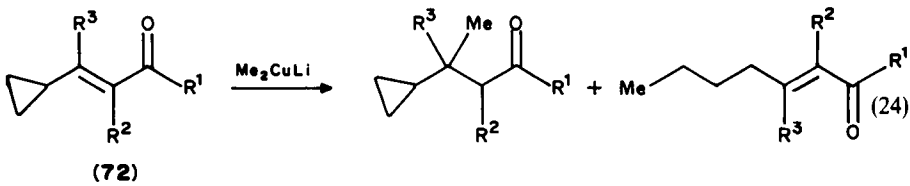
House and coworkers[162,171,180] suggested that the conjugate addition of lithium dimethyl cuprate proceeds by an initial single-electron transfer from the cuprate to the enone to form an electron-deficient metal cluster **69** and an anion radical **70** (equation 23). Rebonding these two species at the sites of high spin density, followed by intramolecular transfer of a methyl group from the metal cluster to the β-position of the enone, leads to the observed enolate **71**.



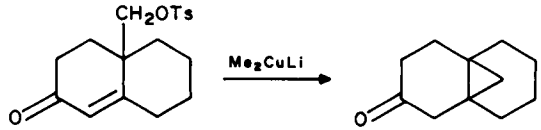
Several reactions which occur concurrently with the conjugate addition of lithium dimethyl cuprate have been cited as evidence for the formation of an intermediate radical anion:

(i) *cis–trans* isomerization[181],

(ii) alkylative ring opening of β-cyclopropyl-α,β-unsaturated ketones **72** (equation 24)[106,182,183],



(iii) cyclopropane ring formation by internal displacement of a good leaving group in the δ-position of the enone (equations 25 and 26)[184–186],



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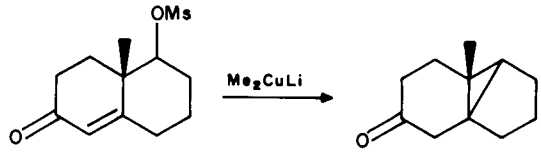
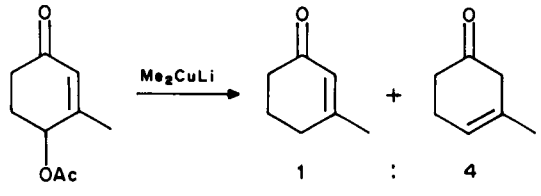


(26)

(iv) reductive cleavage of γ-O-acetoxy-α,β-unsaturated ketones **73** (equation 27)[186–189].

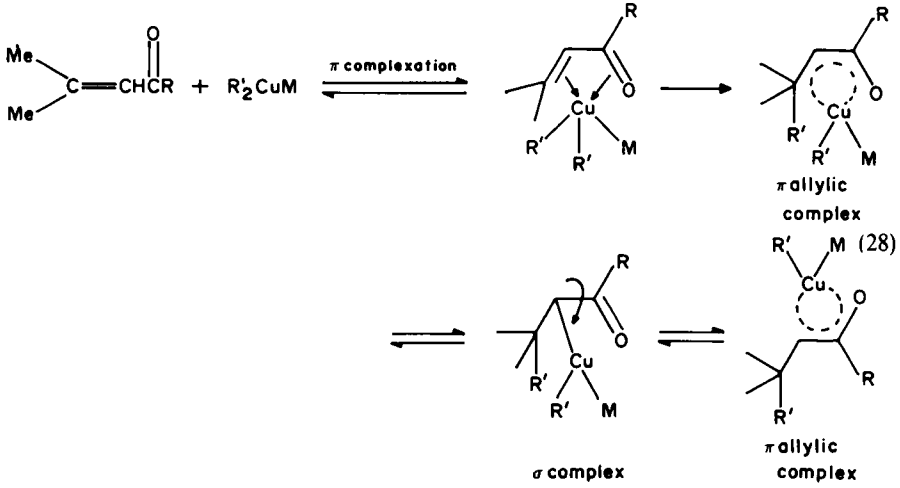


(27)

(73) **(74)** **(75)**

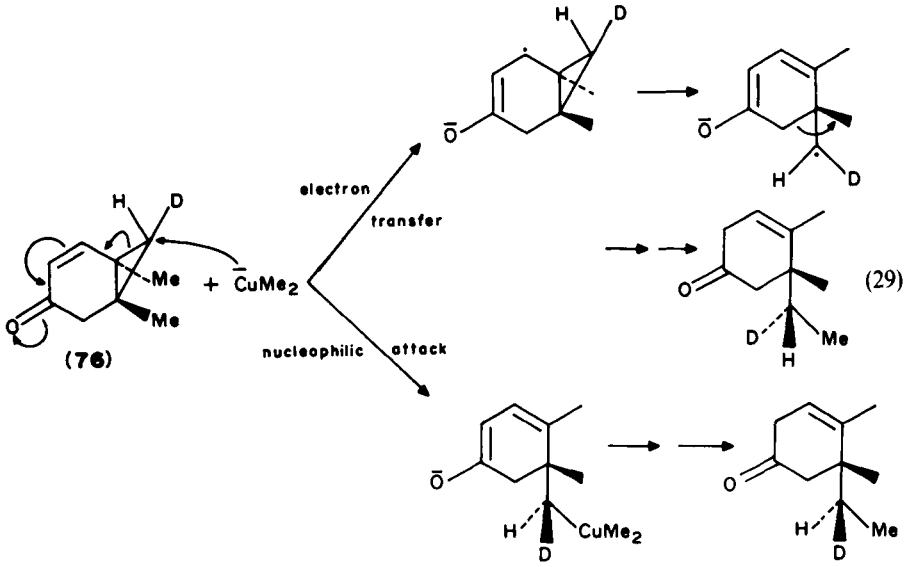
However, no ESR or CINDP signal attributable to an unpaired electron was observed[168,190] and, in the last-named case, when the γ-acetoxy group is replaced by a poorer leaving group, such as alkoxy, the normal addition takes place[191–193].

Other working hypotheses have been formulated which involve either a R^- transfer and formation of an α-cuproketone via π allylic and σ complexes (equation 28)[151,194,195] or via 1,2-addition of the cuprate to the enone double bond[196,197], or formation of a Cu(III) β-adduct via a dianion formed by a bielectronic transfer[190,198].



(28)

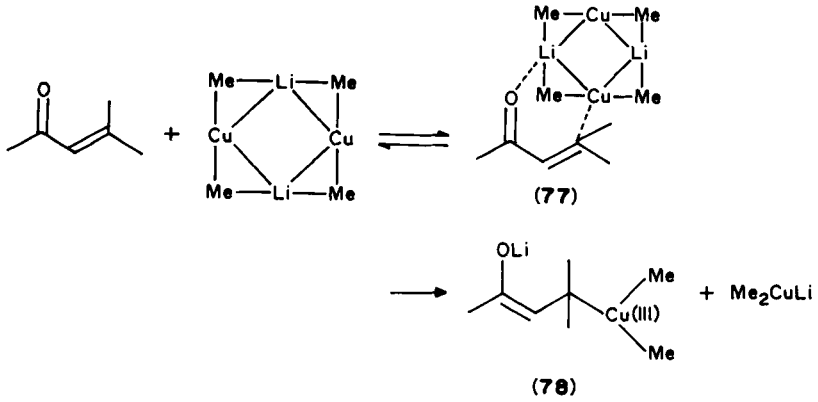
Casey and Cesa showed that the ring opening of the cyclopropyl-α,β-unsaturated ketone **76** is highly stereospecific, providing evidence against an anion radical intermediate and in favour of a direct nucleophilic attack of the cuprate on the cyclopropane ring (equation 29)[199].



(29)

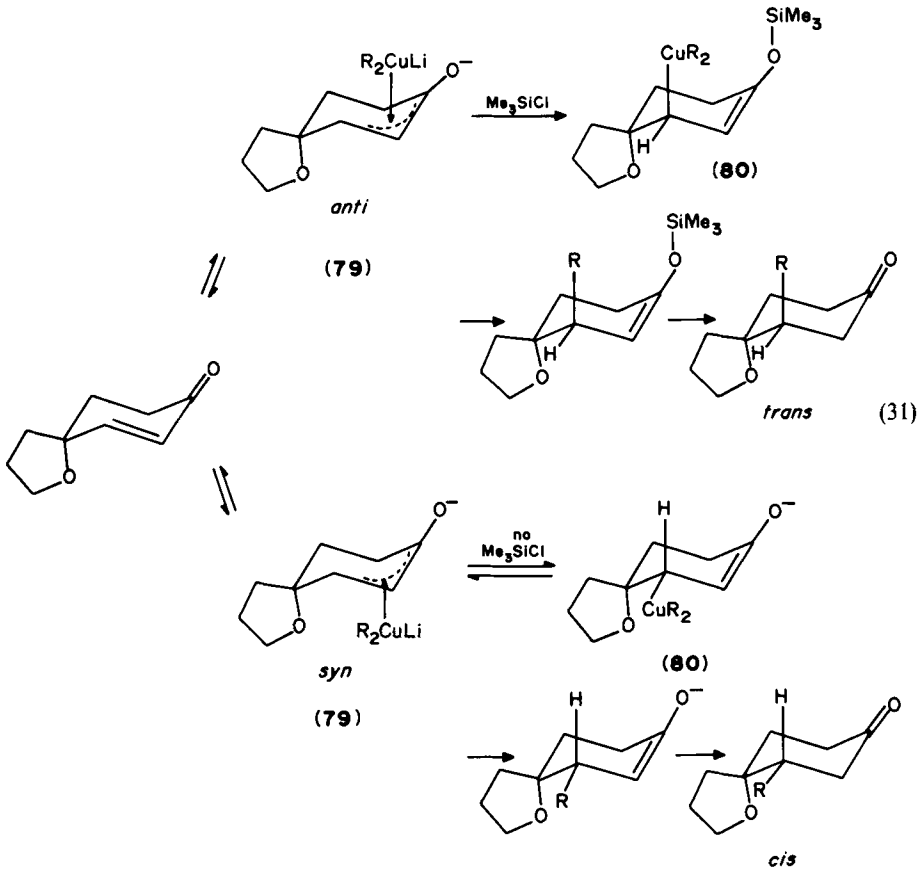
Moreover, on the same type of substrate, Jullien and coworkers[200,201] found no evidence for a correlation between the radical anion half-lives and the formation of ring-opened products. In many cases, the broken bond is different from the bond involved in the reduction by solvated electron in liquid ammonia[202].

In addition Krauss and Smith[156], by kinetic studies using stopped-flow spectroscopy, have implicated an equilibrium of the reactants with the intermediate complex **77**, which may unimolecularly rearrange to form a trialkylcopper(III) species **78** with copper bound to the β-carbon of the lithium enolate (equation 30).



(30)

More recently Corey and Boaz, by trapping intermediates by chlorotrimethylsilane (TMSCl) and studying the stereochemical course of the reaction, provide evidence for a pathway involving a reversible d–π^* cuprate–enone complex **79** and a β-cuprio-adduct **80** (equation 31)[193,203].



(31)

Finally, we think that different mechanisms might be operating depending on the reaction conditions.

For given organocopper reagents or substrates, the success of 1,4-addition is very much dependent on the solvent. As shown in Table 18, the conjugate addition is usually very fast in solvents such as Et_2O, hexane, toluene or dichloromethane. In more polar and coordinating solvents such as THF, pyridine or DME, the conjugate addition is substantially slower or inhibited. It has been proposed[171] that in such donor solvents the activating effect of Li^+ coordination to the C=O oxygen of the substrate could be hampered by complexation between Li^+ and solvent molecules and therefore could alter the whole reaction. More recent NMR studies[204] indicate that the electronic surroundings of the methyl group in Me_2CuLi are relatively similar in Et_2O and dichloromethane, while in pyridine the ionic character of the C–metal bond and the nucleophilicity of Cu are

TABLE 18. Influence of the solvent on the conjugate addition of organocopper reagents to α-enones

Enone	Reagent	Solvent	Time (min)	Yield (%)	Ref.
Benzalacetone	Me_2CuLi	Et_2O	1	>98	204
		CH_2Cl_2	1	>98	204
		PhMe	1	>98	204
		Hexane	1	>98	204
		THF	1	85	204
		THF	10	82	204
		Pyridine	1	17	204
		Pyridine	10	28	204
		MeCN	1	28	204
		MeCN	10	50	204
Mesityl oxide	Me_2CuLi	Et_2O	10	82	148
	Me_2CuLi	THF	180	51	148
	$Ph_2Cu(CN)Li_2$	Et_2O	60	98	205
	$Ph_2Cu(CN)Li_2$	DME	60	8	205
	$Ph_2Cu(CN)Li_2$	THF	60	1	205
Isophorone	Me_2CuLi	Et_2O	10	100	148
	Me_2CuLi	THF	300	0	148
	$(CH_2{=}CH)_2Cu(CN)Li_2$	Et_2O	210	98	205
		DME	210	11	205
		THF	210	34	205

changed. Thus, the reduced reactivity of lithium diorganocuprates towards enones in polar solvents is due, at least in part, to structural changes in the cuprate clusters caused by coordination of solvent. Exchange between clusters of different composition could also be anticipated[204].

In reaction of organocopper reagents with α,β-unsaturated aldehydes, a low-polar solvent such as pentane favours conjugate addition versus the 1,2-addition[155,206,207] (Table 19). However, the solvent effect is less marked using organocuprates stabilized by Me_2S[154].

TABLE 19. Influence of the solvent on the mode of addition of cuprates to enals $R^2R^3C{=}CR^1CHO$

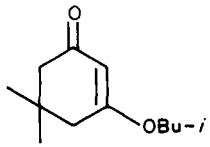
Enal								
R^1	R^2	R^3	Reagent	Solvent	$C_{(1)}$ Attack	$C_{(3)}$ Attack	Overall yield (%)	Ref.
Me	H	Et	Me_2CuLi	Et_2O	18	82	85	206
Me	H	Et	Me_2CuLi	Et_2O/pentane	5	95	75	206
Me	H	Et	Me_2CuLi	Et_2O/THF	60	40	55	206
Me	H	Et	Me_2CuLi, Me_2S	THF	10	90	53	154
Me	H	Et	$Bu_2CuMgCl$	THF	91	9	22	154
Me	H	Et	$Bu_2CuMgCl$	THF/Et_2O	27	73	78	154
Me	H	Et	$Bu_2CuMgCl$, Me_2S	THF	4	96	83	154
Me	H	Et	$Bu_2CuMgCl$, Me_2S	Et_2O/pentane	6.5	93.5	87	154
Me	Et	Et	Me_2CuLi	Et_2O	45	55	75	206
Me	Et	Et	Me_2CuLi	Et_2O/pentane	18	82	86	206
Me	—$(CH_2)_4$—		$Me_5Cu_3Li_2$	Et_2O	22.5	77.5	85.5	155
			$Me_5Cu_3Li_2$	Et_2O/pentane	15	85	88	155

TABLE 20. Influence of substituents in the α and β position of enones on the yields of 1,4-addition in the reaction of R_2CuLi with $R^3R^2C{=}CR^1COMe$[171]

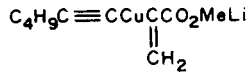
Enone				Reagent	1,4-Addition
R^1	R^2	R^3	E_{red} (V)	R	yield (%)
H	H	Me	−2.08	Me[a]	94
H	Me	Me	−2.21	Me[a]	93
Me	Me	Me	−2.35	Me[a]	21
H	H	Me	−2.08	*s*-Bu[b]	87
H	Me	Me	−2.21	*s*-Bu[b]	77
Me	Me	Me	−2.35	*s*-Bu[b]	17–43

[a]In Et_2O at 10–30 °C.
[b]In 1:1:2 Et_2O–Me_2S–cyclohexane, V/V/V, at −50 to −55 °C.

Electronic and steric factors and the degree of substitution of the substrate also play an important role. The nature of the substituent governs the charge distribution of the LUMO orbital. House[208,209] demonstrated a qualitative correlation between the success of copper-mediated conjugate addition reactions and the ease of the enone to insert an electron into the LUMO orbital as quantified by the first electrochemical reduction potential (E_{red}) of the enone. Substrates with reduction potentials more negative than −2.4 V (versus SCE) failed to react with lithium dimethyl cuprate, while those with potentials less negative than −2.4 V react successfully[180]. This is exemplified by the inefficiency of Me_2CuLi to transfer its methyl group to enone **81** (E_{red} = −2.43 V) and by decreasing yields observed in reactions of Me_2CuLi and *s*-Bu_2CuLi with 3-penten-2-one, 4-methyl-3-penten-2-one and 3,4-dimethyl-3-penten-2-one whose reduction potentials are −2.08, −2.21 and −2.35 V, respectively (Table 20). Such a correlation between the reduction potentials and the enone reactivity suffers from the failure to obtain an electrochemical wave of the cuprate reagent[173]. The presence of an electron-withdrawing group in reagent **82** significantly influences its reactivity and leads predominantly to the 1,2-addition products[210].



(81)



(82)

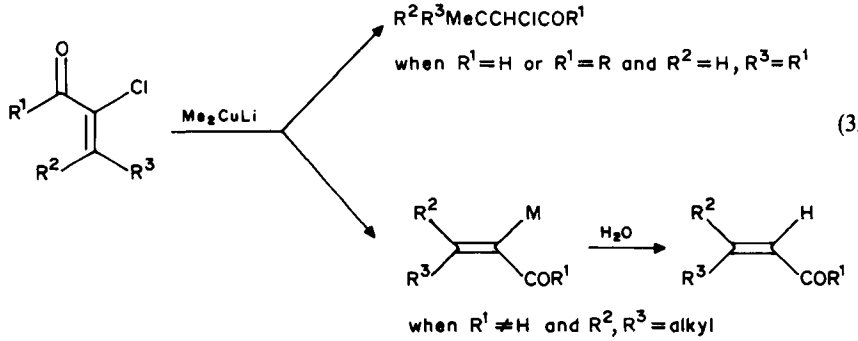
The kind of substituent present on the substrate also affects the course of the reaction. For instance, α-fluoro- and α-chloro-α,β-unsaturated carbonyl compounds whose reduction potentials are greater than −2.4 V react in different ways with lithium dimethyl cuprate[211]. With α-fluoro derivatives, both 1,2- and 1,4-additions are observed, and their ratios depend on the steric hindrance at the β-position (Table 21).

1,4-Addition products are obtained from α-chloroenals and β-monosubstituted-α-chloroenones while β,β-disubstituted-α-chloroenones give only elimination of the halogen via halogen–metal exchange (equation 32).

Successful conjugate additions to 2-bromo-2-cyclohexenones and 2-bromo-2-cyclopentenones have been achieved with a variety of organocopper reagents[212]. Reaction of the α-bromo enone **83** with Me_2CuLi affords a mixture of compounds arising from 1,4-addition and halogen exchange[213].

TABLE 21. Reaction of Me_2CuLi with α-fluoro-α,β-unsaturated carbonyl compounds: $R^3R^2C{=}CFCOR^1$ in Et_2O[211]

Substrate			Temperature	Time			Overall yield
R^1	R^2	R^3	(°C)	(min)	$C_{(1)}$ attack	$C_{(3)}$ attack	(%)
Bu	H	Pr	−30	90	0	100	80
Me	$-(CH_2)_5-$		−30	60	20	80	64
Et	H	Ph	−45	60	30	70	70
Et	Me	Me	−40	60	23	77	65
Me	Me	*t*-Bu	−10	120	100	0	50
H	H	Pr	−40	30	5	95	33
H	$-(CH_2)_5-$		−40	60	40	60	85



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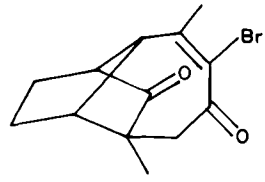
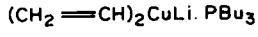


(83)

In a general manner, the reactivity of acyclic enones is affected by α, β, β′-substitutions (Tables 20 and 22), while for cyclic enones it is also often affected by substituents which are not directly connected to the reactive site of the molecule (Table 23).



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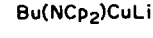

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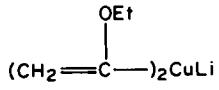

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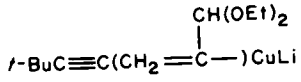

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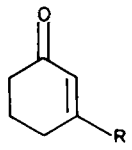
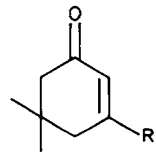
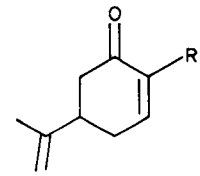




(88) (89) (90)

An increase in the number and/or the bulk of substituents at the β position affords decreasing yields for the same experimental conditions (Table 20, Table 22, entries c, d and f, g and Table 23 entries e, f), or requires change in the experimental conditions, such as time or temperature (Table 22, entries a–e, g, h and Table 23, entries a and b). With α,β-unsaturated aldehydes, steric hindrance at the α,β and β' positions leads to a relatively important proportion of 1,2-addition products (Table 24).

In the case of aldehydes, it is noteworthy that the method for workup of reactions is an important factor in determining the yield and the purity of the products. The aldehydes released after conjugate alkylation and protonation are unstable in the reaction medium,

TABLE 22. Influence of substituents in the β position of enones on the yield of 1,4-addition in the reaction of $R_2CuLi \cdot PBu_3$ with acyclic enones $R^1R^2C{=}CHCOMe$

Entry	Enone		Reagent	Temperature	Time	Addition	Ref.
	R^1	R^2	R	(°C)	(h)	yield (%)	
a	H	H	$CH_2{=}CH$	−78	0.75	70	163
b	Me	Me	$CH_2{=}CH$	−78	2	72	163
c	H	*i*-Pr	Bu	−78 to −40	1.5	94	167
d	Me	Me	Bu	−78 to −40	2	48	167
e	Me	Me	Bu	0	0.1	88	167
f	H	*i*-Pr	*i*-Pr	−78 to −40	1.5	95	167
g	Me	Me	*i*-Pr	−78 to −40	2	68	167
h	Me	Me	*i*-Pr	0	0.2	99	167

TABLE 23. Reactions of organocopper reagents **84–87** with substituted 2-cyclohexenones **88–90**

Entry	Enone	Reagent	Temperature (°C)	Time (h)	1,4-Addition yield (%)	Ref.
a	**88** (R = H)	**84**	−78	0.5	65	163
b	**88** (R = Me)	**84**	−78	1	72	163
c	**88** (R = H)	**85**	−50 to 25	3	92	214
d	**89** (R = Me)	**85**	−50 to 25	3	29	214
e	**88** (R = H)	**86**	−78 to 0	—	84	215
f	**88** (R = Me)	**86**	−78 to 0	—	0	215
g	**88** (R = H)	**86**			67	216
h	**90** (R = H)	**86**			50	216
i	**90** (R = Me)	**86**	−70	2–3	65	159
j	**88** (R = H)	**87**	−40	2–3	96	159
k	**90** (R = Me)	**87**	−40	2–3	0	159

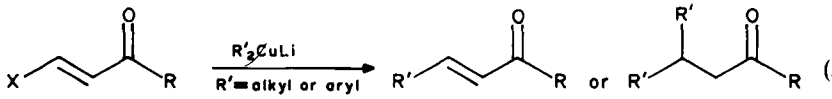
TABLE 24. Influence of substituents on the substrate in the reaction of cuprates with enals $R^3R^2C{=}R^1CHO$

Enal							
R^1	R^2	R^3	Reagent	$C_{(1)}$ attack	$C_{(3)}$ attack	Overall yield (%)	Ref.
H	Pr	H	Me_2CuLi	2	98	84[a]	206
H	Et	Et	Me_2CuLi	18	82	73[a]	206
Me	Et	H	Me_2CuLi	18	82	85[a]	206
Me	Et	Et	Me_2CuLi	55	45	75[a]	206
Me	$-(CH_2)_4-$		Me_2CuLi	64	36	86[a]	206
Me	$-CH_2)_5-$		$Me_5Cu_3Li_2$	0.5	99.5	88	155
Me	$-(CH_2)_4CH(CH_3)-$		$Me_5Cu_3Li_2$	54	46	88	155

[a]Yield of trimethyl silyl enol ether.

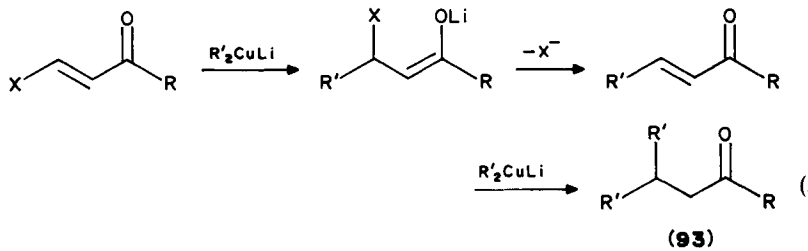
and the yields are improved by quenching the reaction with acetic acid[155] or with trimethylchlorosilane in the presence of triethylamine[153,206].

Depending on the kind of substituent and on the specific reaction conditions, including stoichiometry, the conjugate addition of dialkyl or diaryl organocuprates to enones possessing a heteroatom substituent, such as OAc[217], OEt[218], SBu[217,218] or halide[145,219,220], on the β-carbon, produces enones **91** or **92** (equation 33). Likewise, α-enones which possess a heteroatom substituent on the β' carbon lead to β,β'-dialkylated ketones[221].



X=OAc, OEt, SBu, halide **(91)** **(92)**

The overall reaction sequence might involve an initial 1,4-conjugate addition to generate an enolate which, under the reaction conditions, expels the β heteroatom substituent. Then, the 1,4-conjugate addition of a second equivalent of cuprate affords the dialkylated product **93** (equation 34)[217,218,221].



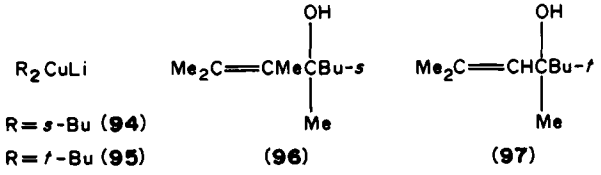
(93)

The regioselectivity and the yield of the reaction of organocopper reagents with α,β-unsaturated carbonyl compounds is also affected by the nature and the steric bulk of the organic moiety transferred. While lithium cuprates with primary alkyl, phenyl or vinyl group usually add in conjugate manner to α-enones[171] or unhindered aldehydes[206], the cuprate **94** reacts with crotonaldehyde to afford a mixture of 1,2- and 1,4-adducts in 55/45 ratio[153]. The reaction of **94** with 3,4-dimethyl-3-penten-2-one and of **95** with mesityl oxide are both complicated by the formation of alcohols **96** and **97**[171]. The amount of these by-

TABLE 25. Conversion of 2-cyclohexenone into 3-*t*-butylcyclohexanone using mixed cuprates R(*t*-Bu)CuLi in THF

R(*t*-Bu)CuLi R	Temperature (°C)	Time (min)	Overall yield (%)	Ref.
PhS	0	120	86	223
PhO	−30	120	66	223
t-BuO	−50	240	62	223
PrC≡C	−78	15	95	164
$Me_2(MeO)CC{\equiv}C$	−78 to −20	—	95	224

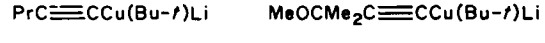
products appears to be related to the amount of thermal decomposition of the cuprate reagent, and therefore the presence of organolithium compounds in the medium[171].



Ashby and Watkins showed that the higher-order species Me_3CuLi_2 exists to an appreciable degree of equilibrium with Me_2CuLi and free MeLi[170]. This complex, which rapidly reacts with ketones[222], delivers the methyl group in a 1, 2 sense upon reaction with the sterically hindered ketone, isophorone, at room temperature[148], whereas only the β-adduct is obtained in good yield at −69 °C[222].

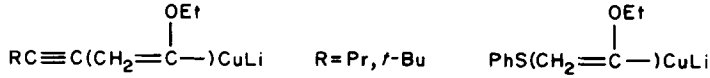
Thus, the efficiency of the conjugate addition of organocopper reagents to α-enones appears to result from a complex balance between the stability and the reactivity of the reagent, the steric hindrance at the substrate and the steric demand of the organic moiety transferred.

As shown in Table 25, in the series of hetero(alkyl)copper reagents Het(R)CuLi, PhS-(*t*-Bu)CuLi is the most effective for the conversion of 2-cyclohexenone into 3-*t*-butyl cyclohexanone. This reagent is also the more stable. The stability of the reagents follows the order for Het: PhS > PhO > *t*-BuO > *t*-BuS ~ Et_2N. Moreover, mixed cuprates **98** and **99** using an ethynyl as a residual group afford the β-adduct in the highest yields.



(98) **(99)**

Mixed cuprates **100** are more effective than the heterocuprate analog **101** (Table 26, entries a–c), but **100** (R = *t*-Bu) is more sensitive to the steric hindrance of the substrate than the corresponding homocuprate **86** (entries b, d–f). The failure of cuprate **100** (R = *t*-Bu) to conjugately add to the more hindered carvone could only qualitatively be attributed to the increased stabilization by the alkyne ligand[159].

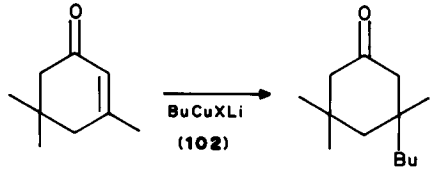


(100) **(101)**

TABLE 26. Reaction of cuprates **86**, **100** and **101** with 2-cyclohexenone and carvone

Entry	Enone	Reagent	Yield (%)	Ref.
a	Cyclohexenone	**100** (R = Pr)	65	225
b	Cyclohexenone	**100** (R = *t*-Bu)	92–95	159,225
c	Cyclohexenone	**101**	50	225
d	Cyclohexenone	**86**	80	159
e	Carvone	**100** (R = *t*-Bu)	0	159
f	Carvone	**86**	65	159

As exemplified by the reaction of the heterocuprates **102** with isophorone (equation 35), steric inhibition in the reagent makes cuprate **102** (X = NCp_2) less effective than the less stable but smaller heterocuprate **102** (X = NEt_2)[215].



X = PPh_2 75%
NCp_2 18%
NEt_2 60%

(35)

Lipshutz and coworkers[141,142,205,226–228] have recently introduced higher-order cyanocuprates **103** as reagents with improved stability.

$RR'Cu(CN)Li_2$

(103)

Comparative results summarized in Table 27 show the higher efficiency of these reagents in delivering a vinyl group in conjugate manner to isophorone, except for **103** R = vinyl, R′ = 2-Thienyl; entry g) for which the 1,2-addition by the thienyl group also takes place[227].

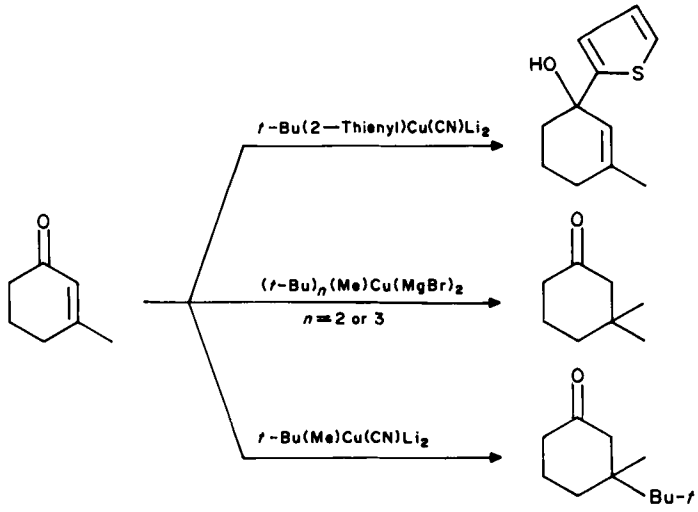
TABLE 27. Conjugate addition of a vinyl group to isophorone using various cuprates

Entry	Reagent	Yield (%)	Ref.
a	$(CH_2{=}CH)Cu(C{\equiv}C.Bu\text{-}t)Li$	52	168
b	$(CH_2{=}CH)_2CuLi.PBu_3$	60	163
c	$(CH_2{=}CH)Cu(PPh_2)Li$	64	214
d	$(CH_2{=}CH)Cu(NCp)_2Li$	18	214
e	$(CH_2{=}CH)_2Cu(CN)Li_2$	88	226
f	$(CH_2{=}CH)(Me)Cu(CN)Li_2$	> 97	228
g	$(CH_2{=}CH)(Th)^a$ $Cu(CN)Li_2$	49[b]	227

[a] Th = 2-Thienyl.
[b] 1,2-addition of the thienyl group also takes place.

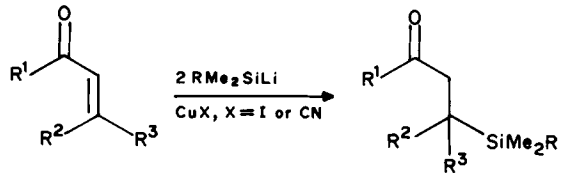
An analogous 1,2-addition of the 2-thienyl group occurs in the reactions of lithium bis(2-thienyl)cuprate with 2-cyclohexenone and benzalacetone[150].

In some cases, the auxiliary group becomes the transferred group, depending upon the nature of the organic moieties in the copper reagent (equation 36).



(36)

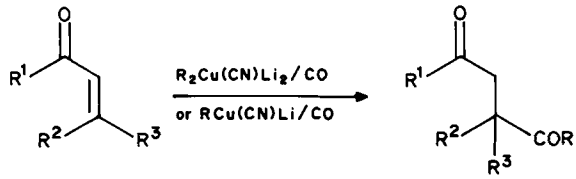
Organocopper reagents proved to be useful in the formation of β-silyl carbonyl compounds **104** (equation 37)[142,229–231].



(37)

(104)

Seyfert and Hui[232,233] described a method for direct nucleophilic acylation of enones and enals, using acylcuprates obtained by carbonylation of lower- or higher-order mixed organocuprates (equation 38).



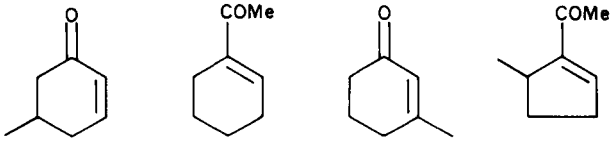
(38)

Yamamoto and coworkers described the reaction of the RCu–BF_3 complex with α,β-unsaturated compounds[234–236]. These organocopper–Lewis acid reagents have proved to be useful in the key steps of total synthesis of many natural products[237]. Comparative

TABLE 28. Reaction of Bu_2CuLi and $BuCu-BF_3$ with α-enones

Entry	Enone	Reagent	Yield (%) 1,2-adduct	Yield (%) 1,4-adduct	Ref.
a	$Me_2C{=}CHCOMe$	Bu_2CuLi	—	83	171
b	$Me_2C{=}CHCOMe$	$BuCu-BF_3$	55	45	236
c	$Me_2C{=}C(Me)COMe$	Bu_2CuLi	77	19	236
d	$Me_2C{=}C(Me)COMe$	$BuCu-BF_3$	7	14	236
e	**105**	Bu_2CuLi	—	72	236
f	**105**	$BuCu-BF_3$	—	20	236
g	**106**	Bu_2CuLi	—	74	236
h	**106**	$BuCu-BF_3$	—	90	236

results obtained from the reaction of the $RCu-BF_3$ complex and R_2CuLi with various α-enones are summarized in Table 28.



(105) **(106)** **(107)** **(108)**

Although the mechanism by which the complex $RCu-BF_3$ reacts still remains unclear[237] (a cyclic transition state had been proposed[234–236]), it is noteworthy that this reagent is more sensitive to β,β-disubstitution than R_2CuLi (entries a and b), whereas an α substituent prevents the 1,2-addition (entries c and d). Moreover, the conjugate addition to the transoid enone **105** (entries e and f) is more effective with Bu_2CuLi than with $BuCu-BF_3$, while that to the cisoid enone **106** proceeds smoothly with the latter (entries g and h).

As shown in Table 29, the 1,4-addition of higher-order mixed organocuprates **109–111** is also largely improved by addition of BF_3-Et_2O. Other Lewis acids tested were ineffective[238].

$Ph_2Cu(CN)Li_2$ **(109)** $(CH_2{=}CH)(2\text{-Thienyl})Cu(CN)Li_2$ **(110)** $Me(2\text{-Thienyl})Cu(CN)LiMgBr$ **(111)**

TABLE 29. Effect of BF_3-Et_2O on conjugate addition of higher-order cuprates **109–111** to α-enones

Enone	Reagent	Additive	Yield (%)	Ref.
Isophorone	**109**	—	0[a]	142
Isophorone	**109**	BF_3-Et_2O	95	142
Isophorone	**110**	—	49[a]	227
Isophorone	**110**	BF_3-Et_2O	98	238
108	**111**	—	29	228
	111	BF_3-Et_2O	85	228
107	**111**	—	34	228
	111	BF_3-Et_2O	73	228

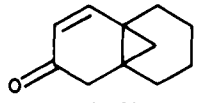
[a] 1,2-adduct is obtained in various amounts depending on the reaction temperature.

TABLE 30. Reaction of MeCu–$AlCl_3$ and Me_2CuLi with enones **76** and **112**

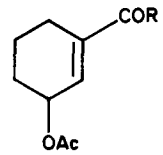
Enone	Reagent	1,4-addition	Ring opening	Overall yield (%)	Ref.
76	MeCu–$AlCl_3$	100	0	72	239
76	Me_2CuLi	48	52	—	199
112	MeCu–$AlCl_3$	100	0	75	239
112	Me_2CuLi	55	39[a]	90	182

[a]Reduction compound is also obtained (6%).

Ibuka and coworkers[239,240] have already demonstrated that organocopper(I)–Aluminium trichloride (RCu–$AlCl_3$) is a useful reagent for regio- and stereoselective 1,4-additions to the β'-cyclopropyl-α-enone **72**. Using homocuprate (Me_2CuLi), the 1,4-addition competes significantly with cyclopropane ring opening (see equation 24). Comparative results obtained in the reaction of these two reagents with enones **76** and **112** are summarized in Table 30.



(112)



R=Me **(113)**
R=Ph **(114)**

The conjugate addition of a methyl or a phenyl group has been performed by RCu–$AlCl_3$ on γ-acetoxy or γ-trialkylsilyloxy α,β-unsaturated ketones[241,242], while these ketones are reduced by lithium dimethylcuprate to give α,β- and/or β,γ-unsaturated ketones[186,188,191,241,242] **74** and **75** (see equation 27). An illustration is given in Table 31 with γ-acetoxy enones **73**, **113** and **114**.

Chlorotrimethylsilane (TMSCl) can be used in combination with organocopper reagents, and added before the α,β-unsaturated carbonyl compound. It acts not only as a simple enolate trap[143], but it accelerates and improves the 1,4-addition reactions[149,193,243–246].

As exemplified in Table 32, the addition of chlorosilanes greatly enhances the rate of conjugate addition of homocuprates. Chlorosilanes used together with an activator such as HMPA or 4-dimethylaminopyridine (DMAP) strongly promote the conjugate addition of the unreactive BuCu[245].

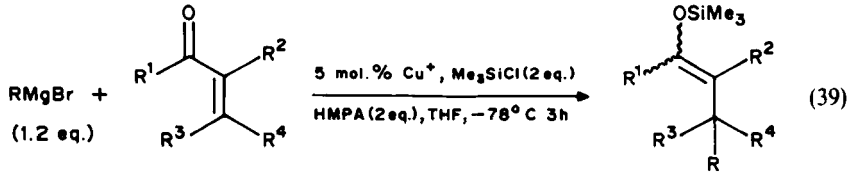
TABLE 31. Reaction of MeCu–$AlCl_3$ and Me_2CuLi with γ-acetoxy-α,β-enones **73**, **113** and **114**

		Yield (%)		
Enone	Reagent	1,4-addition	Reduction products	Ref.
73	MeCu–$AlCl_3$	82	—	241
	Me_2CuLi	—	67	186
113	MeCu–$AlCl_3$	71	—	241
	Me_2CuLi	—	39	241
114	MeCu–$AlCl_3$	81	—	241
	Me_2CuLi	—	91	241

TABLE 32. Chlorosilane-assisted addition of organocopper reagents to α,β-unsaturated carbonyl compounds

Enone or enal	Reagent	Additive	Yield (%)	Ref.
Acrolein	Bu_2CuLi	—	25	206
Acrolein	Bu_2CuLi	Me_3SiCl	60	206
2-Cyclohexenone	$(EtCH{=}CH)_2CuLi$	—	65	149
2-Cyclohexenone	$(EtCH{=}CH)_2CuLi$	Me_3SiCl	86	244
3-Me-2-cyclohexenone	Bu_2CuLi	—	28	245
3-Me-2-cyclohexenone	Bu_2CuLi	Me_3SiCl	99	245
3-Me-2-cyclohexenone	Bu_2CuLi	t-$BuMe_2SiCl$	31	245
3-Me-2-cyclohexenone	Bu_2CuLi	t-$BuMe_2SiCl$/HMPA	95	245
3-Me-2-cyclohexenone	BuCu	Me_3SiCl	24	245
3-Me-2-cyclohexenone	BuCu	Me_3SiCl/HMPA	89	245

The TMSCl/HMPA mixture also promotes the conjugate addition of copper-catalyzed Grignard reagents[247] (equation 39) or zinc homoenolate[248] (equation 40) to enals and enones.



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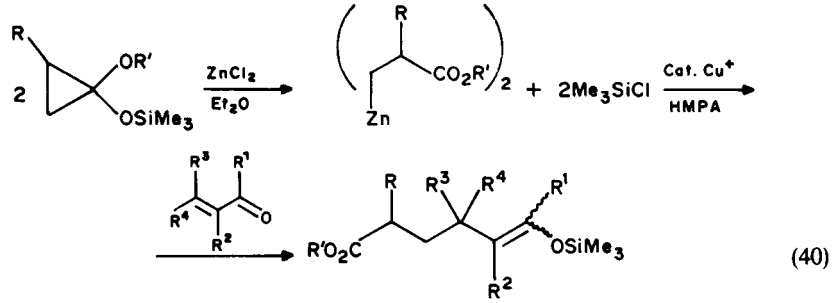
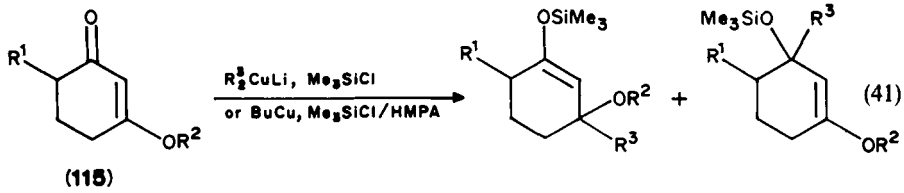


(40)

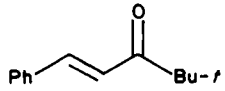
3-alkoxy-2-cyclohexenones **115**, reported to be unreactive towards organocopper species, due to their very low reduction potential ($E_{red} < -2.40$ V), react with R_2CuLi in the presence of TMSCl[244,245] or with BuCu in the presence of TMSCl/HMPA[245], although a mixture of 1,2- and 1,4-adducts is obtained (equation 41).



(115)

(41)

An attractive hypothesis to account for the observed rate acceleration involves coordination of TMSCl with the carbonyl oxygen which raises the reduction potential. However, several lines of evidence argue against this hypothesis: (i) ^{1}H NMR studies of a mixture of enone and TMSCl reveal no sign of such coordination[243,245], (ii) there is only a minor increase in relative reaction rate with increasing concentration of TMSCl[243], and (iii) enone **116** reacts faster with Me_2CuLi than acrylate **117** although the carbonyl of **117** would appear more basic than that of **116**[243]. Corey and Boaz[193,243] suggest that TMSCl accelerates cuprate–enone conjugate addition by trapping an initial d–π^* complex **79** and forcing conversion to β-carbon adduct **80** (see equation 31).



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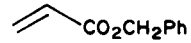
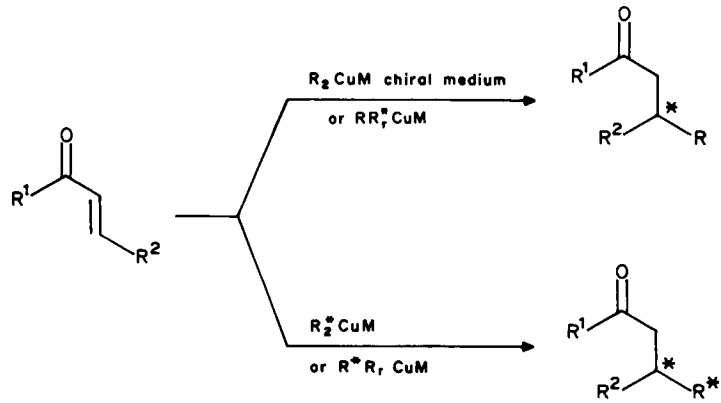


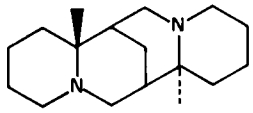
(117)

Regioselective conjugate addition of organocopper reagents to prochiral α-enones provides possibilities for asymmetric synthesis with the introduction of a new chiral centre in the β-position of the substrate. Studies have focused on two points: (i) the selective formation of one enantiomer using a chiral medium (usually in the form of a chiral coordinating ligand) or cuprates ($R_tR_r^*CuM$) containing a chiral non-transferable group, and (ii) the formation of diastereomeric products using cuprates with a chiral transferable ligand (R_2^*CuM or $R_t^*R_rCuM$) or chiral substrates (equation 42).



(42)

Asymmetric 1,4-addition of achiral magnesium or lithium dialkyl cuprates to prochiral α,β-unsaturated ketones in a chiral medium such as (−)sparteine (**118**)[249] or (+)-*S*,*S*-1,4-dimethylamino-2,3-dimethoxybutane (**119**)[250,251] results in low optical yields (3–6% and 6.5–15%, respectively).



(118)

$Me_2NCH_2CH(OMe)CH(OMe)CH_2NMe_2$

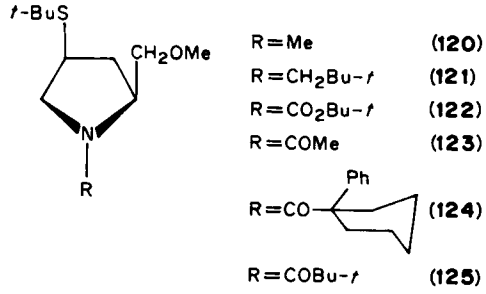
(119) (+)(*S*,*S*)

The use of 4(alkylthio)hydroxyproline derivatives **120**–**125** as bidentate ligands yields

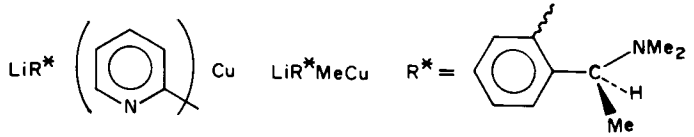
TABLE 33. Asymmetric methylation of chalcone using Me_2CuLi in Et_2O at $-50\,^{\circ}C$ in the presence of chiral ligands **120–125**[252]

Ligand	Yield (%)	e.e. (%)	Configuration
120	98	2	*R*
121	97	7	*R*
122	95	33	*R*
123	71	33	*R*
124	93	68	*R*
125	95	75	*R*
125 + TMEDA	95	50	*R*

up to 75% of enantiomeric excess (e.e.) in the β-methylation of chalcone with lithium dimethyl cuprate[252]. As shown in Table 33, in all cases the R enantiomer is formed predominantly and the N-alkylated ligands **120** and **121** induce very low enantioselectivity, whereas the N-carboalkoxylated and N-acylated ligands **122–125** lead to much higher optical yields. The effectiveness of amide ligands in comparison with amine ligands indicates the importance of chiral ligand–lithium complexation, which is confirmed by the decrease in the enantiomeric excess upon addition of TMEDA.



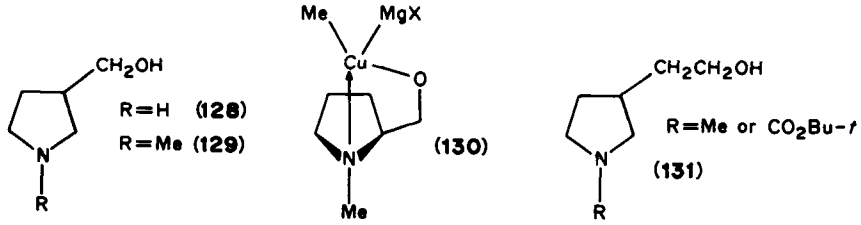
The degree of the asymmetric induction obtained in the reaction of benzalacetone with the mixed cuprate **126** is considerably higher (e.g. 84%)[253] than when a methyl group is transferred (e.e. 5%)[254,255] by cuprate **127** using the same chiral ligand. It seems probable that the pyridine nitrogen atom interacts with the metal atom in a stereodifferentiating step.



(126) (127)

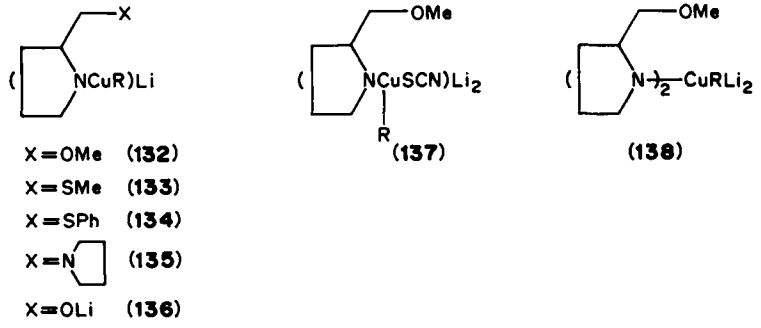
Although the heterocuprates LiR(Het)Cu (Het = R'O, R'S, R'_2N) are valuable reagents for conjugate addition, the methylation of chalcone using reagents generated from various aminoalcohols affords optical yields of 0–31%[256]. Similarly, the alkylation of 2-cyclohexenone with heterocuprates derived from chiral alcohols[257,258], thiols[258] and amines[257] and from N-methyl ephedrine[259] affords equally low optical yields. The higher

enantiomeric excess (e.e. 15%) is obtained with organocopper reagents derived from the (*S*)-prolinol **128**[257] or N-methyl prolinol **129**[258].



Imamoto and Mukaiyama have achieved β-methylation of chalcone in high optical yield (68%) using a large excess of chiral magnesium heterocuprate derived from (*S*)-prolinol[260]. This work was extended by Leyendecker and coworkers[261] (Table 34). Except for chalcone, the highest asymmetric induction is realized with (*S*)-prolinol. The optical yields increase on going from toluene (or benzene) to THF for the (*S*)-N-methyl prolinol derived cuprate and decrease for the (*S*)-prolinol bound cuprate. Asymmetric induction is viewed as arising from different chelation mechanisms: magnesium-arene π-coordination in the N-methyl system and hydrogen-carbonyl chelation in the prolinol system[261]. Higher optical yields (80%)[262] are achieved upon dilution, suggesting the importance of an internally chelated species **130** assumed to possess higher enantiodifferentiating ability. Higher homologues such as **131** proved less effective (0–2% e.e.)[262].

Very recently Dieter and Tokles undertook an extensive investigation of the conjugate addition of chiral organoheterocuprates **132**–**138** derived from (*S*)-prolinol[263]. The more characteristic results are summarized in Table 35.



The magnitude of the optical yields is sensitive to all the reaction parameters. The highest enantiomeric excesses are obtained at lower temperature in solvents such as Et_2O or toluene for cyclohexenone and acyclic enones using lower-order cuprates **132** or **133** and higher-order cuprate **138**. The (−)-*S*-prolinol-derived chiral cuprates induce predominant formation of either the *R*- or *S*-enantiomer depending upon the solvent, the cuprate composition and the substrate structure. The lower order cuprates **132** and **133** selectively afford the *S*-enantiomer in Et_2O and the *R*-enantiomer in THF or toluene, while higher-order cuprates **137** and **138** selectively afford the *R*-enantiomer in Et_2O or toluene, except for cyclopentenone.

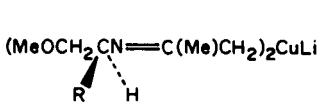
The influence of the substrate structure, the cuprate composition and the solvent upon the induced absolute stereochemistry is more difficult to understand owing to the lack of a thorough knowledge of the structure and aggregation of the cuprate reagent, and the

TABLE 34. Asymmetric induction in methylation of α-enones with $CH_3(R^*O)CuLi$ derived from **128** or **129**[261]

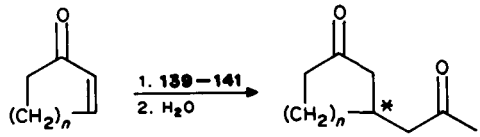
Enone	Alcohol inductor	Solvent	Yield (%)	e.e. (%)	Configuration
2-Cyclohexenone	**129**	PhH	64	1	*R*
2-Cyclohexenone	**129**	THF	70	5	*R*
2-Cyclohexenone	**128**	PhH	36	37	*S*
2-Cyclohexenone	**128**	THF	61	29	*S*
Benzalacetone	**129**	PhMe	80	3	*R*
Benzalacetone	**129**	THF	82	10	*S*
Benzalacetone	**128**	PhMe	36	37	*S*
Benzalacetone	**128**	THF	61	29	*S*
Chalcone	**129**	PhMe	82	2	*S*
Chalcone	**129**	THF	81	41	*S*
Chalcone	**128**	PhMe	42	20	*S*
Chalcone	**128**	THF	70	15	*S*

reaction mechanism. However, a simple model has been proposed to rationalize a body of data[263].

Methodologies based upon diastereoselective C—C bond formation by conjugate addition of a chiral transferable group are, in general, more successful. Interesting diastereoselectivities are observed by Yamamoto and coworkers[264,265] in the addition of chiral lithium bis(azoenolato)cuprates **139–141** to prochiral cyclic enones. The primary products, hydrolyzed during the workup, yield optically active 3-acetonylcycloalkanones **142** in enantiomeric excess ranging from 17 to 75% (equation 43) (Table 36).



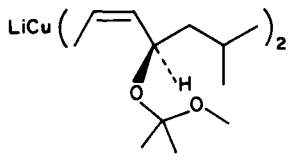
R = CH_2Ph (**139**)
R = *i*-Pr (**140**)
R = *t*-Bu (**141**)



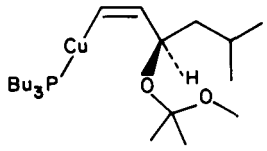
(43)

(142)

The conjugate addition of chiral organocopper reagents **143–145** to 2-methyl-2-cyclopentenone proceed with a high degree of stereoselectivity (Table 37)[266,267].



(143)



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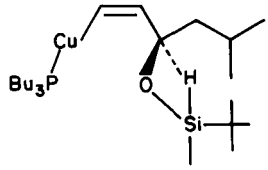


(145)

TABLE 35. Asymmetric induction from conjugate addition of chiral organo (hetero) cuprates **132–138** to α-enones at −78 °C[263]

Enone	Reagent	Solvent	Yield (%)	Optical yield (%)	Configuration
2-Cyclohexenone	**132** (R = Me)	Et_2O	73	75	*S*
	132 (R = Me)	PhMe	62.5	70	*R*
	132 (R = Me)	THF	60	53	*R*
	132 (R = Bu)	Et_2O	38	56	*S*
	132 (R = t-Bu)	Et_2O	25	67	*S*
	133 (R = Me)	Et_2O	68	80	*S*
	133 (R = Bu)	Et_2O	46	58	*S*
	133 (R = *t*-Bu)	Et_2O	51	69	*S*
	134 (R = Me)	Et_2O	77.5	71	*S*
	134 (R = Me)	PhMe	71	80	*R*
	134 (R = Me)	THF	70	52	*R*
	135 (R = Me)	Et_2O	39	8	*S*
	136 (R = Me)	Et_2O	54	69	*R*
	137 (R = Me)	Et_2O	57	75	*R*
	137 (R = Me)	PhMe	68	83	*R*
	138 (R = Me)	Et_2O	24	20	*R*
2-Cyclopentenone	**132** (R = Me)	Et_2O	36	23	*S*
	132 (R = Me)	PhMe	70	37	*R*
	132 (R = *t*-Bu)	Et_2O	56	35	*S*
	133 (R = Me)	Et_2O	60	33	*S*
	134 (R = *t*-Bu)	Et_2O	50.4	50	*S*
3-Penten-2-one	**132** (R = Bu)	Et_2O	36	64	*S*
	133 (R = Bu)	Et_2O	52	64	*S*
	134 (R = Bu)	Et_2O	51	61	*S*
	137 (R = Bu)	Et_2O	37	68	*R*
3-Octen-2-one	**132** (R = Me)	Et_2O	46	58	*R*
	133 (R = Me)	Et_2O	78	83	*R*
	134 (R = Me)	Et_2O	42	74	*R*
	137 (R = Me)	Et_2O	56	75	*R*

TABLE 36. Asymmetric conjugate addition of chiral reagents **139–141** to 2-cyclohexenone and 2-cyclopentenone (equation 43)[264]

Enone	Reagent	Yield (%)	Optical yield (%)	Configuration
2-Cyclohexenone	(*S*) **139**	21	28.6	*R*
	(*S*) **140**	46	22.5	*R*
	(*S*) **141**	30	44.2	*S*
	(*R*) **141**	31	43.6	*R*
2-Cyclopentenone	(*S*) **139**	54	16.5	*R*
	(*S*) **140**	75	26.9	*S*
	(*S*) **141**	89	75.4	*R*

TABLE 37. Relative yields of diastereomers **146** and **147** from the conjugate addition of reagents **143–145** to 2-methyl-2-cyclopentenone[266]

Reagent	146	147	Overall yield (%)
143	14	86	67
144	10	90	70
145	18	82	54

Owing to the interaction between the isobutyl group and the cyclopentenone ring, the addition reaction mainly proceeds through path B rather than A, giving rise preferentially to the diastereomer **147** (equation 44).

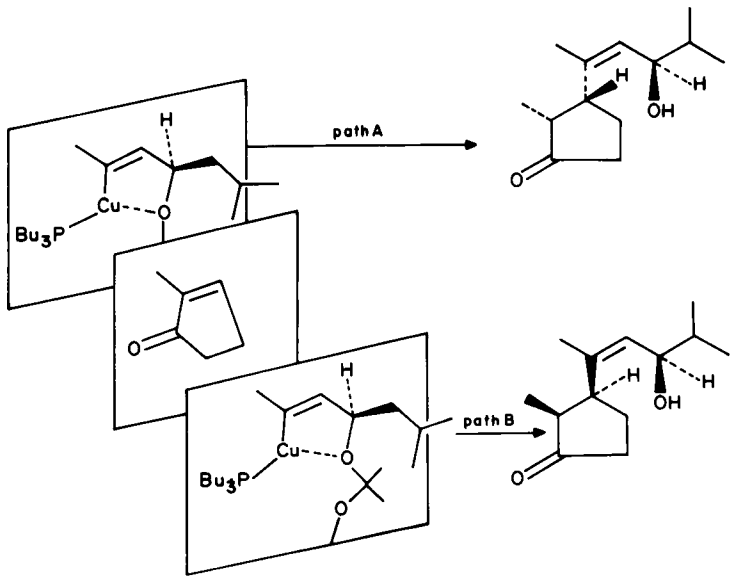
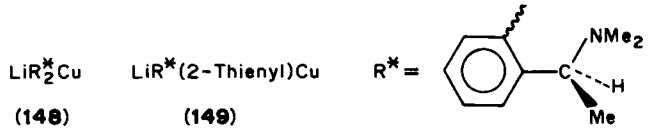


TABLE 38. Diastereomeric excess (d.e.) from conjugate addition of cuprates **148** and **149** to various enones in Et_2O at 0 °C[268]

Enone	Reagent	d.e. (%)	Overall yield (%)
2-Cyclohexenone	**148**	> 98	87
2-Cyclohexenone	**149**	> 98	57
2-Cyclopentenone	**149**	84	—
MeCH=CHCOMe (*E*)	**148**	80	30
MeCH=CHCOMe (*E*)	**149**	82	70
PhCH=CHCOMe (*E*)	**148**	> 98	50
PhCH=CHCOMe (*E*)	**149**	> 98	44
PhCH=CHCOBu-*t*	**148**	76	67
PhCH=CHCOBu-*t*	**149**	> 98	42

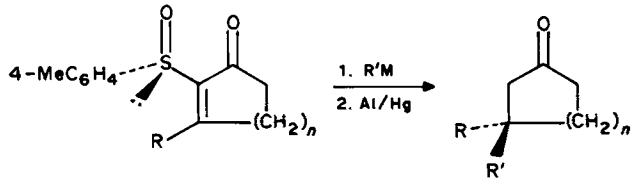
One diastereomer is also formed in large excess (76–98%) on addition of the chiral (*S*)-2-(1-dimethylaminoethyl)phenyl group to various enones (Table 38) using the homocuprate **148** or the mixed 2-thienyl cuprate **149**[268–270].



(148) (149)

The steric outcome leading preferentially to the (*S*,*S*)-diastereomer is the same for all the enones, and the diastereoselectivities are of the same order of magnitude, indicating that the chelation by the dimethylaminoethyl group in the entering group is more important than the steric difference between the substrates[270].

Similarly, Posner and coworkers have introduced an elegant synthetic methodology for the enantio-controlled formation of a β C—C bond via asymmetric conjugate addition of various achiral organometallic reagents to the enantiomerically pure 2-(arylsulphinyl)cycloalkanones **150** (equation 45)[271–277].



(45)

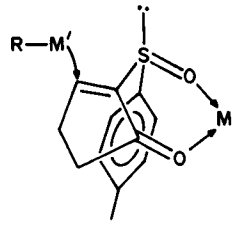
(150) $n = 1, 2$ (151)

The data from Table 39 on asymmetric synthesis of 3,3-disubstituted cyclopentanones **151** show that no one type of organocopper reagent is superior over the others. Although lithium dimethyl cuprate and lithium ditolylcuprate work well (entries a and f), lithium di-*n*-butyl cuprate does not (entry d).

The configuration of the opposite enantiomers resulting from the reversed sequences, i.e. the addition of a methyl group to 3-tolylcyclopentenone sulphoxide or of a tolyl group to 3-methylcyclopentenone sulphoxide, may be predicted using the chelate model **152** proposed for asymmetric conjugate addition of Grignard reagents in the presence of a complexing metal[276].

TABLE 39. Asymmetric synthesis of 3,3-disubstituted cyclopentanones **151** ($n = 1$) via equation 45 in THF[275]

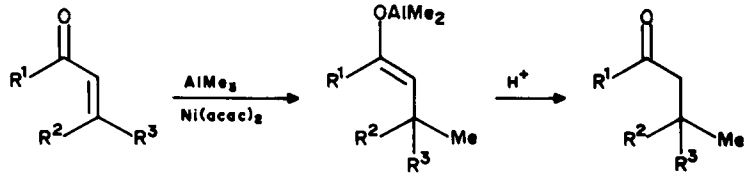
Entry	R in enone **150**	Reagent	e.e. (%)	Yield (%)	Configuration
a	4-MeC_6H_4	Me_2CuLi	78	58	*S*
b	4-MeC_6H_4	Me(PhS)CuMgBr	73	77	*S*
c	4-MeC_6H_4	$Me_5Cu_3Li_2$	65	44	*S*
d	4-MeC_6H_4	Bu_2CuLi	—	0	—
e	4-MeC_6H_4	Bu(PhS)CuMgCl	81	69	—
f	Me	$(4\text{-}MeC_6H_4)_2CuLi$	90–93	53	*R*
g	Me	Bu(PhS)CuMgCl	53	79	—
h	Me	Bu(*t*-BuO)CuMgCl	88	61	—



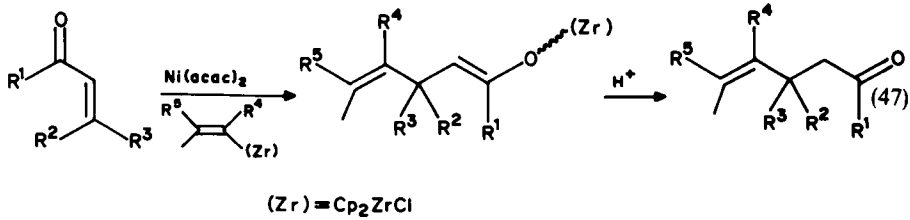
(152)

2. Aluminium, zirconium, zinc, palladium, lanthanides

$Ni(acac)_2$-catalyzes the conjugate methylation of several unsaturated ketones by trimethylalanes with varying degrees of success (equation 46)[277,278] and the addition of terminal alkenyl units to α-enones using alkenylzirconium(IV) complexes (equation 47)[279–282].



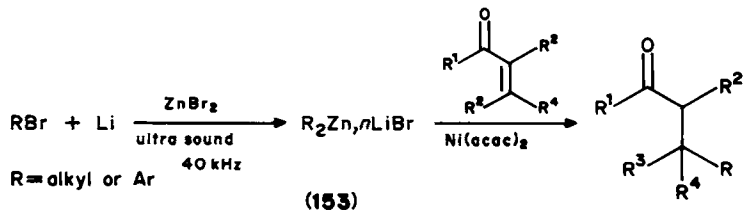
(46)



(47)

$(Zr) = Cp_2ZrCl$

Luche and coworkers used $Ni(acac)_2$ for the conjugate addition of diorganozinc reagents **153**, prepared by sonication (equation 48)[283–286].



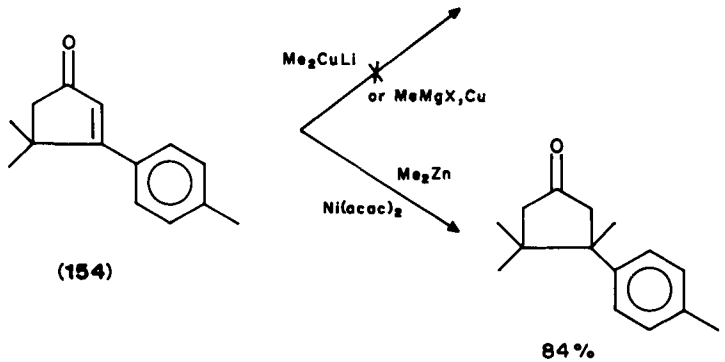
(48)

The thermal stability of these reagents allows the reaction to proceed at room temperature in many instances. Arylation or alkylation of α,β-unsaturated ketones usually proceeds well even with β,β-disubstituted-α-enones (Table 40) or with the enone **154**[287],

TABLE 40. Conjugate addition of R_2Zn reagents to α-enones[283–285]

Enone	R in R_2Zn	Yield (%)
2-Cyclohexenone	n-C_7H_{15}	88
	$Me_2C{=}CH$	83
	4-PhC_6H_4	92
	$PhCH{=}CH$	84
	$PhCH_2$	64
2-Cyclopentenone	$Me_2C{=}CH$	21
	4-MeC_6H_4	76
3-Me-2-cyclopentenone	2-MeC_6H_4	72
	4-MeC_6H_4	87
Isophorone	Me	90
	4-MeC_6H_4	94
Mesityl oxide	Ph	98

which fails to react with lithium dimethyl cuprate or in a copper-catalyzed Grignard reaction[288] (equation 49).



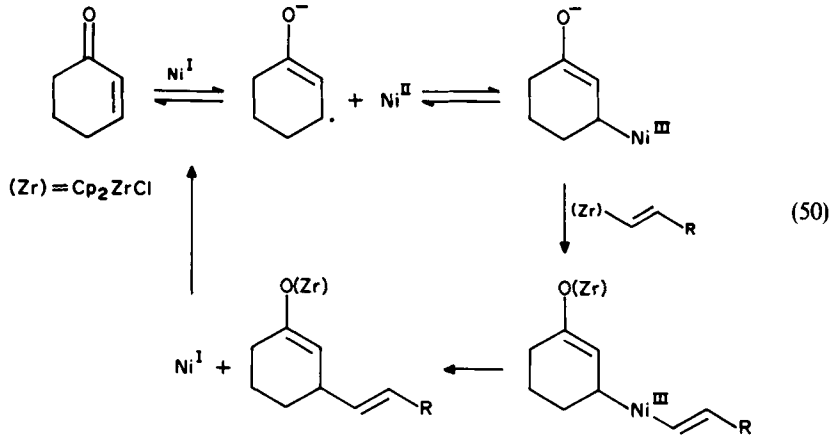
(49)

Although aryl groups are selectively transferred to the β-position of α,β-unsaturated aldehydes, the delivery of an alkyl group is not satisfactory[286].

The role of $Ni(acac)_2$ is quite important, since in its absence the reaction of (4-$MeC_6H_4)_2Zn$ with 2-cyclohexenone proceeds in a much reduced rate and the methylation of enone **154** does not occur[285]. The reaction mechanism is assumed to have some analogy to the one proposed by Schwartz and coworkers for the nickel-catalyzed organozirconium addition reactions[279–282] which involve one-electron reduction of the substrate by catalytically active reduced valent Ni(I) species (equation 50).

Triorganozincates **155** and **156** are another type of reagent that can be used to add alkyl groups in a 1,4-fashion to α,β-unsaturated ketones. They have not, however, been as extensively studied as cuprates, and the scope of their reactions remains to be established.

Isobe and coworkers demonstrated that R_3ZnLi, prepared in THF by mixing zinc halide (or its TMEDA complex) and alkyl lithium in a 1:3 molar ratio (equation 51), reacts with the enone **157** (equation 52) to give excellent yield of the 1,4-addition product[289].

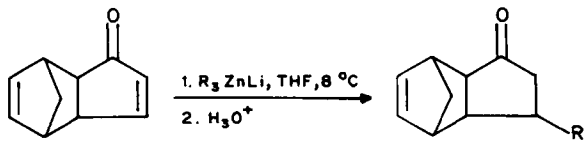


(50)

R_3ZnM $R'R_2ZnM$ M=Li or MgX

(155) (156)

$$3\,RLi \xrightarrow[ZnCl_2/TMEDA]{ZnCl_2\ or} R_3ZnLi + 2\,LiCl \qquad (51)$$



(52)

(157)

The yields are dependent of the counter halide anion, the highest yields being obtained with zinc chloride. The steric effect of R in the complex has been examined using primary, secondary and tertiary butyllithium. Steric bulk does not affect the mode of addition but reduces the reaction velocity, since bulkier reagents give a lower amount of 1,4-adducts for a limited reaction period.

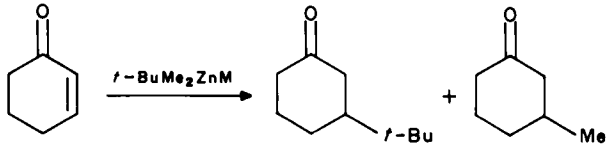
Langer and Seebach have shown that, like cuprates, the 1,4-addition reactions of zincates are enantioselective when carried out in a chiral medium[250]. More recently, Watson and Kjonaas showed that mixed triorganozincates **156** (M = Li, R = Me) selectively transfer the R′ group (R′ = *n*-Bu or *s*-Bu) rather than the methyl group[290].

Solvent effect and additive studies have been carried out by Oshima and coworkers with symmetrical and unsymmetrical triorganozincates. THF or Et_2O is the best solvent[291]. Hydrocarbon solvents are usually employed. Methylene chloride gives lower yields and unsymmetrical decreased selectivity with unsymmetrical zincates. DME and DMF suppress the reaction. Among the various additives studied it appears that the methylation of 2-cyclohexenone with Me_3ZnLi is catalyzed by cobalt complexes.

Grignard reagents have been also used in place of alkyllithium. Depending upon the halide, the 1,4-addition of R_3ZnMgX is contaminated by 1,2-addition products when

R = Ph and Me, but is essentially free of these compounds when R = *n*-Bu or *i*-Pr. Evidently, the yields are highest when X = Cl[292].

With unsymmetrical zincates, the selectivity of the transfer of the different groups is very dependent on the metal counter ion, as exemplified by the reactions of 2-cyclohexenone with 1.2 molar equivalents of *t*-BuMe$_2$ZnM in THF at − 78 °C for one hour (equation 53).

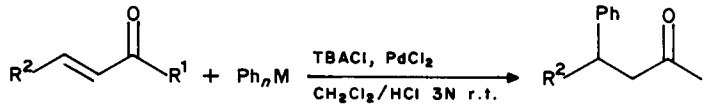


(53)

M=MgCl 5% 68%

M=Li 20% 10% (+38% recovered enone)

Phenyl palladium compounds, generated *in situ* from phenylmercury or phenyltin compounds and palladium(II) salts, react with α,β-unsaturated ketones in a two-phase acidic system in the presence of a catalytic amount of tetrabutyl ammonium chloride (TBACl) to give the conjugate addition product (equation 54)[293–297].

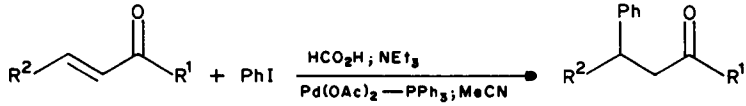


(54)

M=Sn; $n=4$

M=HgCl; $n=1$

Iodobenzene, in the presence of a catalytic amount of palladium, an excess of formic acid and triethylamine, provides a useful alternative to phenylmercury compounds (equation 55)[297,298].



(55)

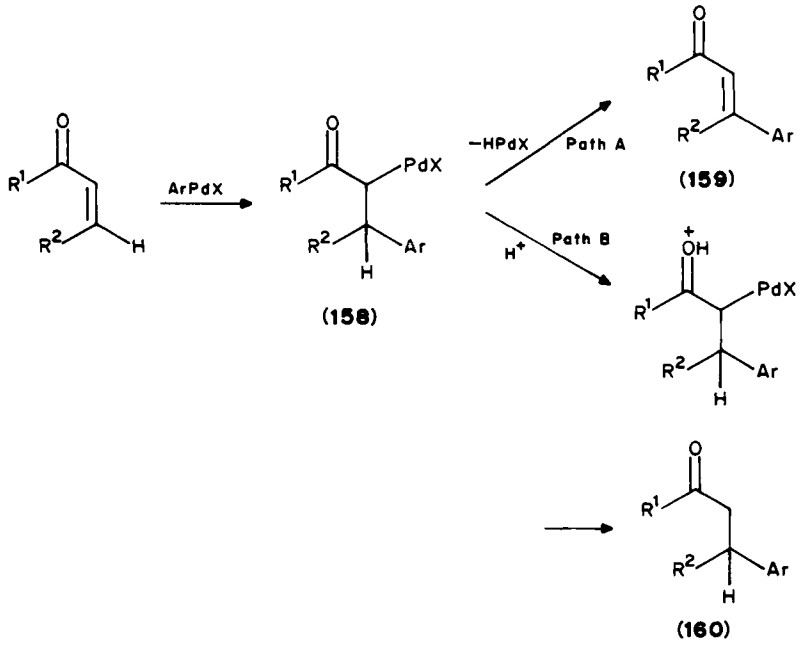
Unhindered α-enones react with these reagents, giving rise to the conjugate addition-type products. The main limitation seems to arise from the steric hindrance in the substrate. Thus, isophorone, cholest-4-ene-3-one and carvone fail to react with phenylmercury or phenyltin compounds under palladium catalysis[293].

By contrast, a wide variety of aryl units containing electron-donating and electron-withdrawing substituents, such as Me, Cl, CHO, COOMe, COOH, OH, OMe, NHCOMe and NO_2, are successfully transferred to the β-carbon of benzalacetophenone[294,298]. However, the substituent in the aryl moiety of the reagent can affect the reaction rate.

The reaction proceeds through an initial addition of the arylpalladium reagent to form the intermediate **158**, which undergoes *cis* elimination of HPdX (path A) or heterolytic fission of the palladium carbon bond (path B) giving rise to either the product of vinylic substitution **159** or the conjugate adduct **160** (equation 56).

Competition between $C_{(\alpha)}$Pd bond cleavage, coupled with the formation of $C_{(\alpha)}$H bond and *syn* elimination of HPdX, appears to be dependent upon a complex combination of steric, electronic and medium factors. An acidic medium is critical: in its absence, the

percentage of the vinylic-substituted product is related to the amount of the added palladium. The formation of the aryl palladium intermediate **158** seems to be the rate-limiting step and the acid-catalyzed elimination of the Pd(II) species is faster than any other reaction pathway. The ammonium salt or triethylamine is also important.



(56)

α-enals[299] and α,β,γ,δ-dienones[300] give exclusively the 1,4-addition products. β,β-diaryl ketones or aldehydes **162** are obtained from aryl iodide in the presence of a palladium catalyst and β-unsubstituted α,β-carbonyl compounds (equation 57)[301].

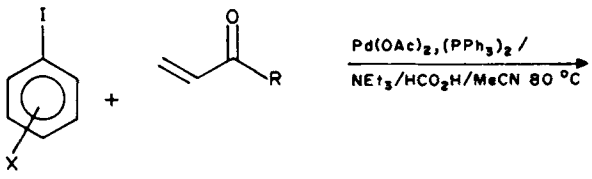
The reaction proceeds through a vinylic substitution followed by an *in situ* conjugate addition to the β-substituted α,β-unsaturated carbonyl compounds **161**. Compounds **163**, derived from a double vinylic-substitution reaction, are also obtained in variable amounts[301].

By contrast, benzene addition to α-substituted chalcones **164** using palladium-catalyzed reaction of benzene/acetic acid in reflux leads to the vinylic substitution. The conjugate adduct is obtained only when the α substituents are bulky and powerfully electron-withdrawing (equation 58)[302].

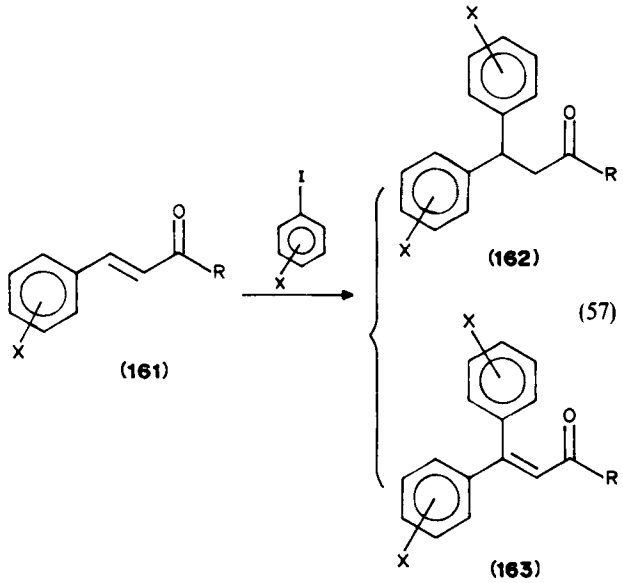
Organometallic compounds involving lanthanides are harder nucleophiles than Grignard reagents[303,304]. Divalent organolanthanide σ-complexes (RLnI with Ln = Ce, Sm, Eu and Yb)[304–306] or organocerium(III) reagents ($RCeCl_2$)[307–310] react with α-enones to afford the 1,2-addition products in higher regioselectivity as compared to organolithium and Grignard reagents (Table 41).

The reactions of various organocerium reagents $RCeCl_2$ (R = Me, Bu, Ph) with (*E*)- and (*Z*)-1-(4-methoxyphenyl)-3-phenyl-2-propenone leads to the allylic alcohols in excellent yields without isomerization of the double bond[310]. This selective 1,2-addition proceeds through a direct nucleophilic addition like the selective 1,2-reduction of α-enones with $NaBH_4/CeCl_3$ reagent system[311].

Results obtained in reactions of reagents **165**[303] and **166**[312] with α-enones (Table 42)



R=H or alkyl



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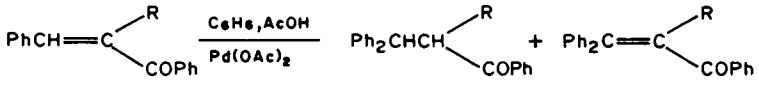


(58)

(164)

R=H	0%	74.8%
R=Br	0%	42.6%
$R=NO_2$	20.2%	5.1 %
$R=CO_2Et$	12.2 %	56.5%
R=COPh	52.5%	8.0%

show that the 1,2-addition is favoured over the 1,4-addition by the presence of β-substituents on the substrate (entries a and b) the lower bulk of the organic moiety delivered (entries b and c) and by low temperatures (entries d, f and g).

$[Li(TMEDA)_2][Lu(Bu\text{-}t)_4]$ (165) $[Li(TMEDA)]_3[LnMe_6]$ (166) Ln = Pr or Sm

TABLE 41. Product distribution in the reactions of organolithium, organomagnesium and organolanthanides with α-enones in THF

Enone	Reagent	Temperature (°C)	Time (min)	Yield (%) 1,2-adduct	Yield (%) 1,4-adduct	Ref.
Chalcone	PhLi	−30	40	75	15	306
	PhMgI	20	180	—	90	306
	PhYbI	−40	40	75	—	306
	PhCeI	−40	40	60	—	306
	PhEuI	−40	40	55	—	306
	PhSmI	−40	40	65	—	306
	PhMgBr	0	60	5	81	309
	PhMgBr, $CeCl_3$	0	60	58	33	309
Benzalacetone	BuMgBr	0	60	21	69	309
	BuMgBr, $CeCl_3$	0	60	78	6	309
Cyclohexenone	*i*-PrMgCl	0	60	12	53	309
	i-PrMgCl, $CeCl_3$	0	60	91	5	309

TABLE 42. Product distribution in reactions of **165** and **166** with α-enones[303,312]

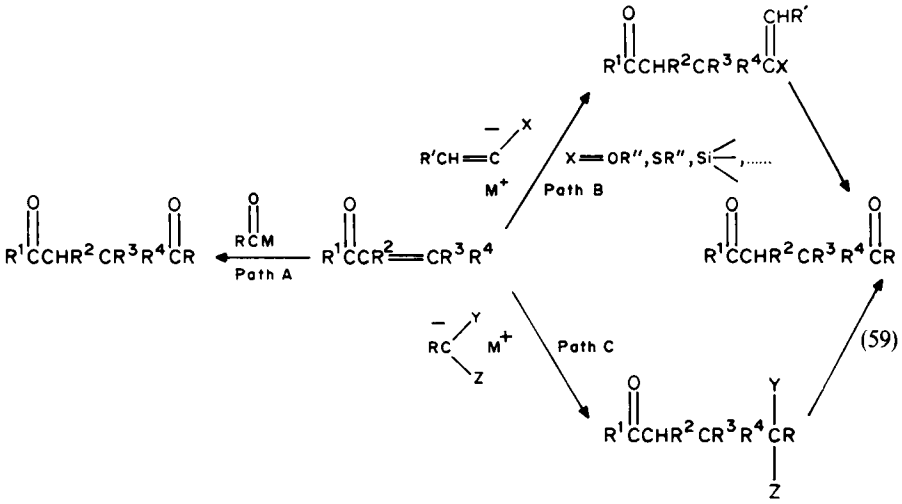
Entry	Enone	Reagent	Solvent	Temperature (°C)	Yield (%) 1,2-adduct	Yield (%) 1,4-adduct
a	CH_2=CHCOMe	**165**	Et_2O	−78	50	50
b	Me_2C=CHCOMe	**165**	Et_2O	−78	> 80	< 20
c	Me_2C=CHCOMe	**166**	THF	−78	> 95	< 5
d	Cyclohexenone	**165**	Et_2O	−78	70	30
e	Cyclohexenone	**166**	THF	−78	> 80	< 20
f	Cyclohexenone	**165**	Et_2O	20	> 75	< 25
g	Cyclohexenone	**165**	Et_2O	34	> 66	< 33

III. NUCLEOPHILIC 1,4-ACYLATION OF ENALS AND ENONES

Among the numerous reagents which lead to a conjugate nucleophilic addition to α,β-unsaturated aldehydes or ketones, those that correspond to an acyl anion addition present a great potential interest to organic chemists. The resulting 1,4-diketones or 1,4-keto aldehydes are useful intermediates for further elaboration of natural products and related compounds involving furan and cyclopentenone ring systems[313,314].

The general area of acylation was reviewed by Seebach in 1969[315] and by Seebach and Kolb in 1974[316], and more recently by Lever[317] and Hase and Koskimies[318]. The use of acyl anion equivalents derived from cyanohydrins, protected cyanohydrins and α-dialkylaminonitriles was very well explored by Albright in 1983[12]. The more recent and valuable methods are discussed below in the peculiar case of nucleophilic 1,4-addition of acyl anion to α,β-unsaturated aldehydes and ketones. Although some methods are laboratory curiosities and/or mechanistic challenges related to the 1,2 and 1,4 competitive additions discussed above, other methods are taking their place beside classical carbonyl chemistry as important synthetic procedures.

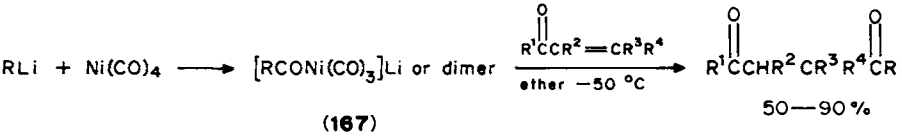
The two pathways to the formation of 1,4-dicarbonyl derivatives from nucleophilic addition to enones and enals use (i) direct nucleophilic 1,4-acylation with acylmetallic compounds (path A in equation 59) and (ii) reagents containing masked functionality to invert carbonyl reactivity of the electrophilic acyl group (equation 59, path B and C, e.g. metallated derivatives of enols and other latent carbonyl functions).



(59)

A. Acylmetallic Reagents

Acylmetallic intermediates in which the metal ion is not of the transition series have little preparative value[317]. Those of the transition series lead to compounds and reaction intermediates with higher stability and greater synthetic appeal. Corey and Hegedus[319] reported a general process in which lithium acyl tricarbonylnickelate **167**, prepared by addition of an organolithium reagent to nickel tetracarbonyl, forms Michael adducts with enones and other unsaturated carbonyl compounds, including β,β-disubstituted substrates (equation 60). The insensitivity of this reaction to steric effects is an advantage that is not shared by all nucleophilic acylating reagents which undergo conjugate additions. The high toxicity of nickel tetracarbonyl limits the usefulness of the procedure and leads to the development of other acylmetallic reagents. For example, acyllithium reagents, generated by the alkyllithium–carbon monoxide reaction, give only 1,2-addition products with 2-cyclohexenone and 2-cyclopentenone and mixtures of 1,2- and 1,4-products with other



(167)

(60)

enones[320]. Conversely, $R(CN)CuLi_2$/CO or R(CN)CuLi/CO reagents give with α,β-unsaturated aldehydes and ketones the expected 1,4-dicarbonyl compounds in 50–90% and 70–95% yields, respectively[232,233].

B. Masked Acyl Anion Equivalents

The term *umpolung*[316] describes the inversion of reactivity which occurs when a normally electrophilic CO group is transformed into a nucleophile through the use of masked reagents. Masked acyl anion equivalent for 1,4-acylation of enals and enones must satisfy three requirements: (i) the reagent must be easy to prepare, (ii) the resulting carbanion must be highly delocalized so as to afford preferentially the 1,4-adduct either directly or from the reversibility of 1,2-addition and (iii) the masking group must be removable under gentle specific conditions. Most masked acyl anions fall into the two general classes of metallated derivatives of enols and metallated derivatives of carbon acids. Other methods use masked functionality of a different nature, e.g. the sp-hybridized cyanide and acetylide ions.

1. Cyanide ions

Conjugate addition of cyanide to α,β-unsaturated ketones produces β-cyano ketones, which can be considered as hemi-protected 1,4-dicarbonyl systems. Nagata and coworkers[321] found that side-reactions sometimes encountered in traditional procedures (e.g. KCN in aqueous alcohol) are minimized when cyanide is used in the presence of NH_4Cl[322]. They also developed organoaluminium reagents (alkylaluminium cyanide R_2AlCN or a combination of an alkylaluminium compound and HCN) for hydrocyanation of enones[323]. Conjugate addition to enones is also observed with cyanotrimethylsilane[324,325] using Lewis acid catalysts.

2. Acetylide ion

The β-acetylenic ketones are valuable synthetic precursors for 1,4-diketone formation[326], indicating that any reagent able to add an acetylenic unit on $C_{(3)}$ of enone can be considered as a masked acyl anion equivalent. Lithiated derivatives of primary acetylenes add in conjugate fashion only when the carbonyl group of α-enones is highly hindered[327,328]. The use of alkynyl copper reagents is precluded by the tenacity with which copper binds alkynyl ligands[164,168]. The regiospecific 1,2-addition of cuprate **168** to enals[153] or cyclic enones[329] can be performed in the presence of HMPA as cosolvent; without this additive, reagents of this nature are rather inactive towards either 1,2- or 1,4-additions.

Corey and Wollenberg[330] have developed an indirect method, which involves the temporary transformation of the acetylene to a vinyl-stannane derivative. The addition of the mixed cuprate **169**, and subsequent oxidative elimination of the stannyl group, results in the conjugate addition of the acetylide to the enone. Extensions of this synthesis to higher acetylenes have not been reported.

$(RC{\equiv}C)_3CuLi_2$ (**168**) $\qquad$ n-$Bu_3SnCH{=}CHCuC{\equiv}CPrLi$ (**169**)

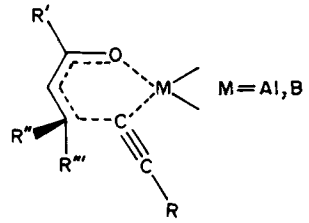
Diethylalkynyl alane **170** undergoes 1,4-addition reactions with α,β-unsaturated ketones to give γ,δ-alkynyl ketones[331,332]. The reaction may be complicated by the concurrent formation of large amounts of 1,2-addition products[332]. It is highly sensitive to the solvent and to β,β-disubstitution of the substrate. It is restricted to ketones that can achieve *s-cis*-conformation. Cyclic ketones such as 2-cyclohexenone or isophorone, in

which the enone system is rigidly constrained to a transoid geometry, react with alane reagents to provide the tertiary carbinol (80–85%) derived from the 1,2- rather than 1,4-addition of the alkynyl unit[331].

(170) (171)

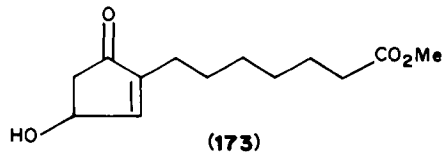
Trialkynyl boron derivatives have been successfully added to methyl vinyl ketone[333]. The use of B-1-alkynyl-9-borobicyclo[3.3.1]nonanes (**171**)[334] avoids the waste of the two residual alkynyl units. A variety of structural modifications on the acetylenic unit, including the presence of a heteroatom, can be accommodated. As for alkynylalanes, the cisoid ketones react satisfactorily to give the 1,4-addition product. The transoid ketones do not react in the desired manner, and do not lead to the 1,2-addition products.

In the cases of alanes and boron derivatives, the pathway involves the intramolecular delivery of the alkynyl group through a six-membered transition state **172** with a necessary *syn* geometry[331,334].



(172)

1,4-addition of trialkynylalane reagents was achieved in the particular case of the fixed *S-trans*-enone **173**. The *cis* stereochemistry of the hydroxyl functional group and the acetylide unit in the adduct indicates the participation of the hydroxy group in the 1,4-addition process. In addition, when the hydroxyl function is blocked by a tetrahydropyranyl group, the reaction with the aluminium reagent is prevented[335,336].



(173)

Conjugate addition of a terminal alkynyl unit has been successfully performed by Schwartz and coworkers[337,338] using diethylalkynyl alane and the complex formed by the reaction of $Ni(acac)_2$ and diisobutylaluminium hydride as catalyst. *S-cis*, *S-trans* and hindered α-enones are alkynylated in the β-position in good yields. Reactive transition-metal species are believed to be involved in the conjugate addition step[337,338].

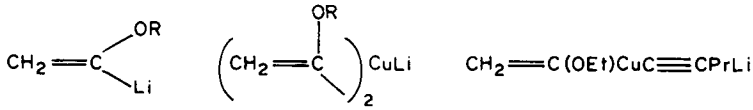
3. *Nitronate anion*

Michael addition of nitronate anions to enones has been an established reaction for many years[339,340]. Recently, improved methods have been elaborated using catalysts such as amines[341,342], tertiary phosphines[343–349], barium hydroxide[350] and fluoride ion[351–357] or the combined effects of catalysts and phase-transfer[358] or high-pressure con-

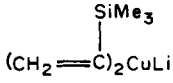
ditions[359,360]. They have been successfully used for conjugate additions of nitroalkanes to enals or enones. Moreover, a variety of mild methods are capable of efficiently converting γ-nitroketones into the corresponding 1,4-diketones[339,351,361-370] with none of the disadvantages that accompany other nitro transformation reactions[317,361] (e.g. the Nef reaction[371]).

4. Metallated enol derivatives

Lithiated enol ethers **174** give exclusively the product of carbonyl addition with unsaturated carbonyl compounds. The copper 'ate' complexes **175** of **174** and mixed cuprates (e.g. **176**) behave as true cuprates and lead to exclusive conjugate additions to α,β-unsaturated ketones. While the yield of 1,4-adduct is not markedly affected by substitutions at $C_{(2)}$, $C_{(5)}$ or $C_{(6)}$ in 2-cyclohexenone (50–91% yields), these reagents are acutely sensitive to additional substitutions in the β- or γ-position (e.g. starting material was recovered with 3-methyl and 4-*t*-butyl-2-cyclohexenones)[215,216]. A similar effect was found with acyclic enones. Cuprate **177** proves to be strongly reactive with a variety of α,β-unsaturated ketones, including β,β-disubstituted ones (56% and 25% yields were obtained with 3-methyl and 4-*t*-butyl-2-cyclohexenones, respectively[216]).



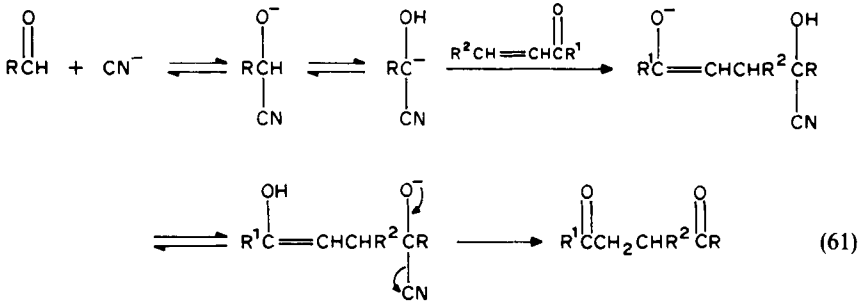
(174) R=Me,Et **(175)** **(176)**



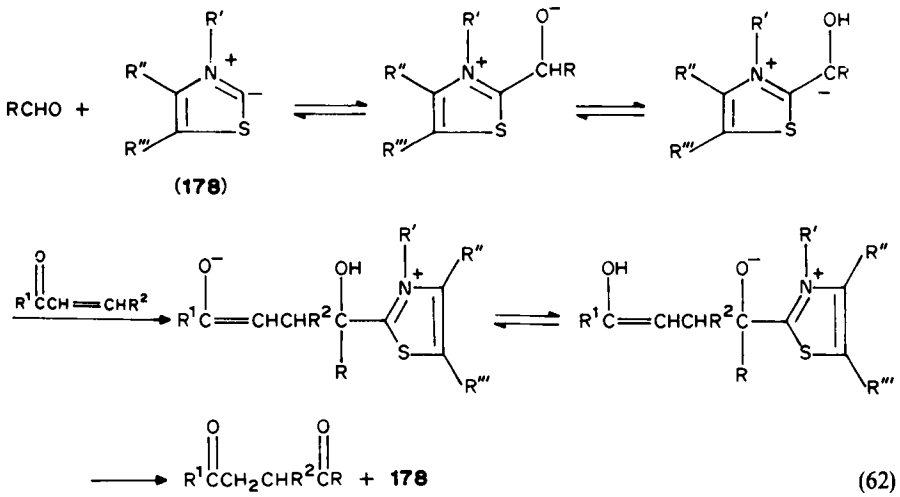
(177)

5. Cyanohydrin carbanion and related reagents

In formal analogy with the benzoin condensation, aromatic and heterocyclic aldehydes are added conjugatively as the corresponding acyl anion equivalents to α,β-unsaturated ketones and other activated olefines in the presence of catalytic amounts of cyanide ion (equation 61) or the conjugate base of the thiazolium salt **178** (equation 62)[372,373].



(61)



(178)

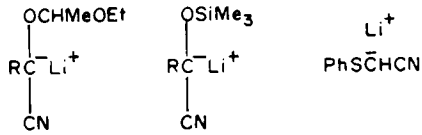
(62)

Stetter and coworkers[374–389] found that aliphatic aldehydes and various functionalized aldehydes can also be used with the latter catalyst, while the cyanide ion is too reactive to be employed with these substrates. α-keto acids are used instead of aldehydes in the thiazolium salt catalyzed addition to α-enones[390]. Polymer attached thiazolium salts have also been used[391].

6. *Acyl anion equivalents derived from carbon acids*

Most masked acyl reagents may be considered as metallated derivatives of carbon acids. The efficiency of the acylation method is dependent on different factors which promote the conjugate addition to enals and enones, such as the structure of nucleophiles and electrophiles, and reaction conditions. These factors have been discussed in the previous section. The masked acyl anion equivalents may be divided into two classes: (i) protected cyanohydrin anions and related reagents (e.g. α-disubstituted aminonitriles), and (ii) anions of 1,3-dithianes, dithioacetals, diselenoacetals and derivatives.

For protected cyanohydrins, the 2-ethoxyethyl[46,288,392,393] and the trimethylsilyl groups[36–38,394] are the most widely used. Lithiated derivatives of suitable protected cyanohydrins **179** and **180** of aliphatic, aromatic and α,β-unsaturated aldehydes undergo 1,4-additions to cyclic and acyclic enones under favourable reaction conditions. Usually, conjugate additions predominate with bulky anions or with an enone containing a hindered carbonyl function. Demasking is obtained by successive acid and base hydrolysis[395]. The lithium salt of phenylthioacetonitrile (**181**) can also be used for formylation[396].

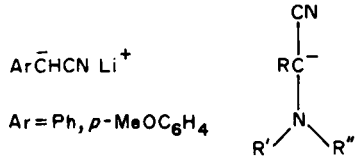


(179) **(180)** **(181)**

In the peculiar case of benzoyl equivalents, lithiated derivatives of arylacetonitrile (**182**) have been employed successfully using THF as solvent under thermodynamic control[23,42]

or THF–HMPA under kinetic control[14,41,397]. Demasking is obtained under phase transfer conditions with or without preliminary protection of the carbonyl group, from oxidative decyanation of the 1,4-adducts using 50% NaOH/DMSO in the presence of benzyltriethylammonium chloride[396,398].

α-disubstituted aminonitrile anions (**183**) allow easy demasking of the acyl group[12,57,399–404]. Apart from questions connected with 1,2 and 1,4 competitive additions to enones and enals, the usefulness of disubstituted amino acetonitriles is also dependent on the choice of the disubstituted amino component[12].

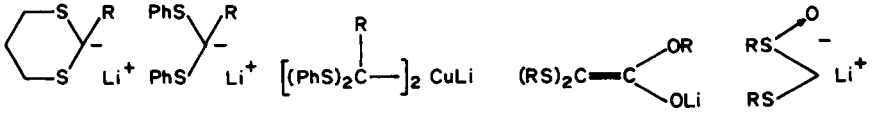


(**182**) (**183**)

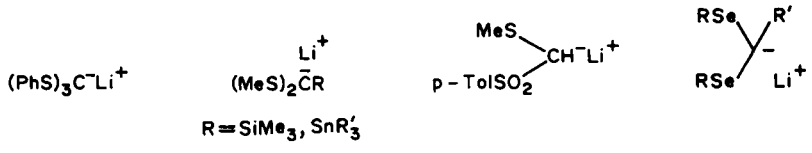
Zervos and Wartski[405] showed that the three lithiated derivatives **179** (R = Ph), **182** (Ar = Ph) and **183** (R = Ph, R′ = R″ = Me) exhibit similar reactivities towards $C_{(3)}$ unsubstituted α-cycloenones, but that **183** and other aminonitriles[12,57,405] do not react with β-disubstituted cyclohexenones.

Since the initial communication by Corey and Seebach[406], describing the use of 2-lithio-1,3-dithianes **184** as masked acyl anions, the chemistry of these reagents and other dithioacetals such as bis(phenylthio) alkyllithiums **185** has been widely explored[407–409].

The advance in the understanding of factors influencing the regioselectivity of nucleophilic attacks on enals and enones is joined to developments of acyl anion equivalents containing sulphur. Indeed, it appeared for a time that anions of 1,3-dithianes **184** or other thiocetals **185** normally add exclusively in a 1,2 manner to α,β-unsaturated carbonyl compounds in THF or give a mixture of the two adducts[317,410–413]. Some rather complicated methods have been proposed to overcome this problem, such as the use of lithium bis[tris(phenylthio) methyl] copper **186** (R = PhS) or lithium [α,α-bis(phenylthio)benzyl] copper **186** (R = Ph)[414], lithium enolates of bis(alkylthio)acetate **187**[415–419], lithiated derivatives of thioacetal monosulphoxide **188**[420,421], tris(phenylthio)methyl **189**[422–425], trimethylsilyl- and triorganylstannyl-substituted lithio bis(methylthio) methane **190**[426,427] or lithio derivatives of (methylthio) methyl *p*-tolyl sulphone **191**[428].



(**184**) (**185**) (**186**) (**187**) (**188**)



(**189**) (**190**) (**191**) (**192**)

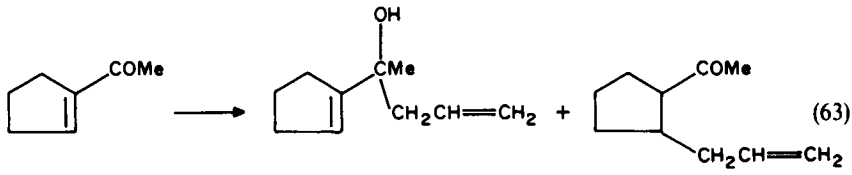
The discovery that polar solvents favour the 1,4-addition of some alkyllithiums has led to the successful reinvestigation of the reaction of the simplest acyl anion equivalents containing sulphur with enals[29,30,429,430] and enones[31,33,34,49,431]. Side by side with lithiothio derivatives, α-lithio seleno-acetals **192**[432–435] proved to be efficient acyl anion equivalents. Krief and coworkers[32] have performed an interesting comparative study of the conjugative addition of acyl anion equivalents **184**, **185** and **192** to α-enones. Among the different methods allowing the preparation of 1,4-dicarbonyl compounds from the thio- and seleno-acetal adducts, the $CuCl_2/CuO$ method was the most satisfactory[32,414,436,437].

IV. NUCLEOPHILIC ALLYLATION OF ENALS AND ENONES

Control of 1,4- versus 1,2-addition of allylic organometallic reagents to α,β-unsaturated carbonyl compounds is rather difficult compared with that of alkyl organometallic derivatives.

Conjugate addition of an allyl group is more effective with organocuprates than with Grignard reagents. The almost exclusive 1,2-addition of allyl magnesium bromide to α-enones has often been rationalized by the impossibility of achieving an eight-membered transition state[438,439]. Only one exception is reported in the case of the highly hindered mesityl vinyl ketone, where 1,4-addition is claimed but in unspecified yield[440].

The addition of lithium diallyl cuprate to an α,β-unsaturated ketone is highly substrate-dependent[441]; for example, 2-cyclohexenone reacts to give 3-allylcyclohexanone in 90% yield, whereas a more hindered substrate such as isophorone gives only the tertiary alcohol via 1,2-addition and $\Delta^{1,9}$ 2-octalone fails to undergo conjugate addition. Reaction of diallyl cuprate with acetylcyclopentene (**193**) affords a mixture of 1,2-adduct **194** (31%), 1,4-adduct **195** (29%) and recovered ketone (11–24%) while the allyl Grignard reagent gives the tertiary alcohol **194** in 83% yield (equation 63)[442].



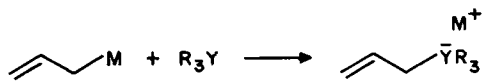
(63)

(193) **(194)** **(195)**

$(CH_2{=}CHCH_2)_2CuLi$ 31% 29%

$CH_2{=}CHCH_2MgX$ 83%

Allylic boron and aluminium 'ate' complexes **197**, prepared by addition of trialkylboranes or alanes to allylic organometallic reagents **196** (equation 64), react exclusively in a 1,2 manner with α-enals, while they react with α,β-unsaturated ketones in a competitive 1,2- and 1,4-addition[443,444]. Although the relative importance of the 1,4-addition increases with the formation of the 'ate' complex, the effect is not so noteworthy (Table 43).



(64)

(196) **(197)**

M = Li, MgX, Cu Y = Al, B

TABLE 43. Reaction of allylic 'ate' complexes **197** with α-enones[443]

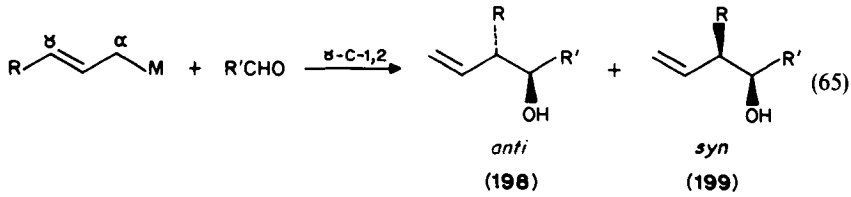
Enone	M in **196**	Additive	$C_{(1)}$ attack	$C_{(3)}$ attack	Overall yield (%)
PhCH=CHCOMe	MgCl	*n*-Bu-9-BBN	95	5	70
PhCH=CHCOMe	Li	*n*-Bu-9-BBN	83	17	72
PhCH=CHCOMe	Cu	*n*-Bu-9-BBN	75	25	62
PhCH=CHCOMe	MgCl	Et_3Al	90	10	85
CH_2=CHCOMe	Li	*n*-Bu-9-BBN	50	50	30

Allyl silanes (see Section V.B) and allyl stannanes are less reactive. Lewis acid mediated reactions of allylic stannanes with α,β-unsaturated aldehydes afford only the 1,2-adduct[445-447]. BF_3–Et_2O catalyzed allylation of quinones with allyltin reagents gives the corresponding allylhydroquinones[448].

Allylation of α-enals has also been performed with allyltin reagents under thermal[449] or hyperbaric[450] conditions. In both cases only the 1,2-adduct is obtained.

All other allylic organometallic reagents add exclusively in a 1,2 manner. These include allyl halides in the presence of manganese powder[451], cerium amalgam[307,308] or chromium(II) salts[452,453], B-allyl derivatives of 9-BBN[454-456] and dibutylallyltin chlorides[457-461].

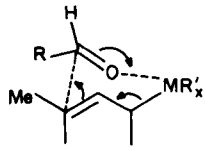
Allylic organometallic derivatives are ambident nucleophiles and, in the case of an unsymmetrical allyl group, both $C_{(\alpha)}$ and $C_{(\gamma)}$ adducts are obtained. Diastereo- and regioselectivities of $C_{(\alpha)}$ or $C_{(\gamma)}$ addition of organometallic reagents have mainly been studied with α,β-enals. In most cases, addition of an unsymmetrical allyl group to carbonyl compounds gives predominantly the product in which the allylic group is attached at the most substituted position (γ adduct) leading, in the case of 1,2-addition, to the formation of *anti* and/or *syn* homoallylic alcohols **198** and **199** (equation 65).



(65)

anti (**198**) *syn* (**199**)

Formation of these rearranged compounds has often been accounted for in terms of a six-membered transition state **200**, owing to the affinity of the metal atom for the carbonyl oxygen[446,449,453-455].



M=B,Cr,Sn

(**200**)

The stereochemistry of the reaction depends upon the geometry of the allylic unit; the *anti* isomer is formed predominantly from the *E* allylic metal compound, while the *Z* derivative gives preferentially the *syn* isomer[446,449,453,456,460].

By contrast, BF_3–Et_2O mediated reactions of crotyltrialkyl stannanes with α-enals produce preferentially the *syn* homoallylic alcohol, regardless of the geometry of the crotyl unit[446]. An acyclic transition state has been proposed, following activation of the carbonyl group by the Lewis acid which prevents the coordination of the Sn atom (equation 66)[446]. In such a transition state, steric interaction is minimized along the newly formed bond, and the reaction has a stereoselective course. As shown in Table 44, the nature of the Lewis acid used is important for the stereochemical convergence. In addition, in $TiCl_4$ promoted reactions, adjustment in stoichiometry can be made to favour *anti* or *syn* products. In this case, an allyltitanium reagent has been postulated as the reactive species[462]. In the presence of Bu_2SnCl_2, the *syn/anti* ratios of the recovered homoallylic alcohols are roughly related to the *Z/E* ratios of the allyltin reagents[460]. In this case, the stereochemical course of the reaction depends on the formation and redistribution *in situ* of allyltin metal compounds (equations 67–69).

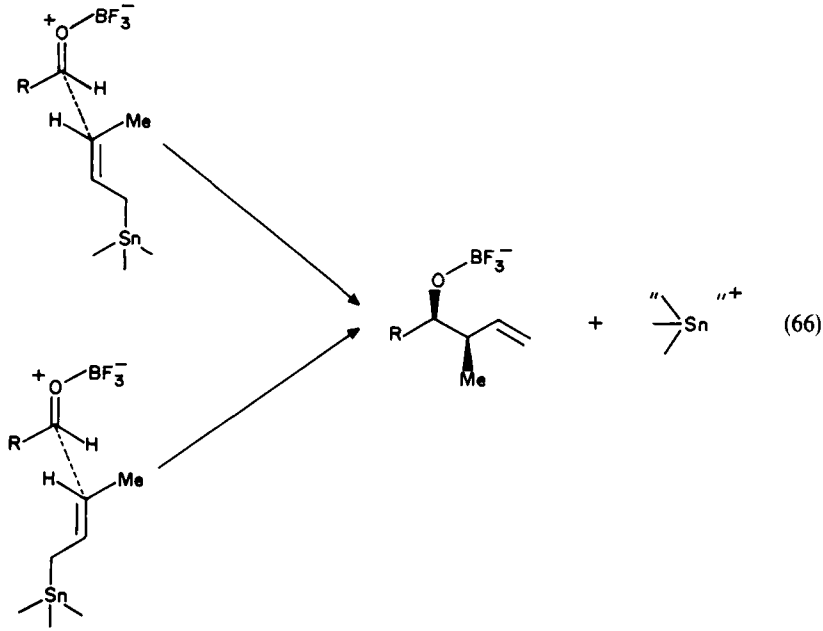


TABLE 44. Addition of allylstannanes RCH=CHCH$_2$SnBu$_3$ to crotonaldehyde in the presence of Lewis acids

R in allylstannane	Lewis acid	Overall yield (%)	*syn*	*anti*	Ref.
Me (*Z*)	$BF_3 \cdot Et_2O$	83	91	9	446
Me (*Z*/*E* = 55/45)	Bu_2SnCl_2	75	56	44	460
Me (*Z*/*E* = 40/60)	Bu_2SnCl_2	70	44	56	460
TBSO(CH$_2$)$_3$ (*Z* + *E*)[a]	$BF_3 \cdot Et_2O$	73	90	10	447
TBSO(CH$_2$)$_3$ (*Z* + *E*)[a]	$TiCl_4$	47	5	95	447

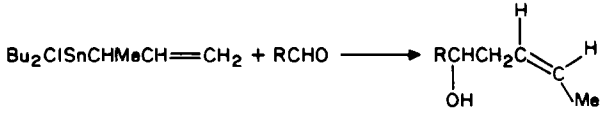
[a]TBS = *t*-Bu(Me)$_2$Si.

$$Z \text{ or } E \quad Bu_3SnCH_2CH{=}CHMe \xrightarrow{Bu_2SnCl_2} Bu_2ClSnCHMeCH{=}CH_2 + Bu_3SnCl \tag{67}$$

$$Bu_2ClSnCHMeCH{=}CH_2 \xrightarrow{Bu_2SnCl_2} (Z+E)Bu_2ClSnCH_2CH{=}CHMe \tag{68}$$

$$Z \quad Bu_2ClSnCH_2CH{=}CHMe \xrightarrow{Bu_2SnCl_2} E\ Bu_2ClSnCH_2CH{=}CHMe \tag{69}$$

The reaction of α-methylallyl substrate **201** is kinetically controlled and yields almost exclusively the linear homoallylic alcohol **202** wholly in the *Z* configuration (equation 70)[457].

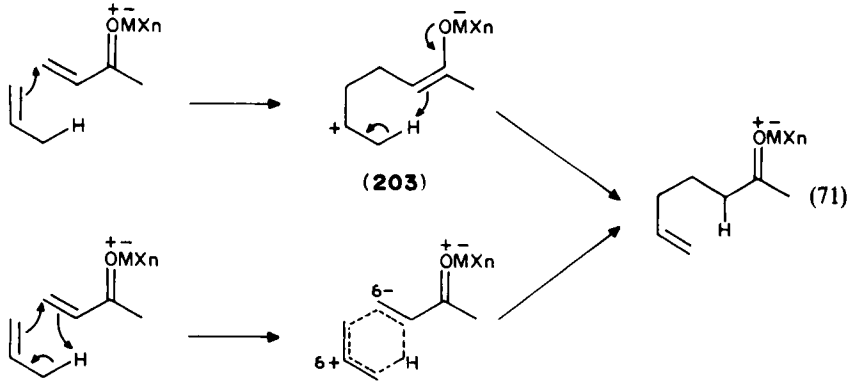


(70)

(201) **(202)**

Preferential allyl $C_{(\alpha)}$ 1,2-addition can be accomplished by crotyl magnesium bromide in the presence of $AlCl_3$, BF_3 or $EtAlCl_2$, while in the presence of $TiCl_4$, $SnCl_4$ or $SnCl_2$ the $C_{(\gamma)}$ 1,2-adduct is preferentially obtained[463].

Lewis acid catalyzed 'ene' reactions between α,β-unsaturated ketones or aldehydes and alkenes having an allylic hydrogen proceed either via a stepwise mechanism with a zwitterionic intermediate **203** or a concerted mechanism with a polar transition state **204** (equation 71)[464].



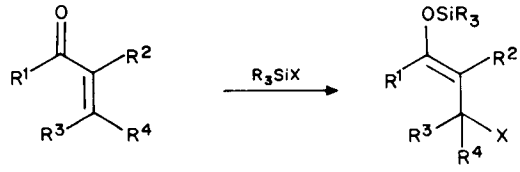
(71)

The energetics of the two mechanisms are similar and the lower energy process varies as a function of the ene, enophile and catalyst. For the 'ene' reactions of α-enals and α-enones, Me_2AlCl is a very useful catalyst[464]. This method of allylation is, however, limited to β-unsubstituted enones and enals such as acrolein, methyl vinyl ketone or isopropyl vinyl ketone. Other β-substituted enones and enals such as 3-penten-2-one or crotonaldehyde do not undergo Lewis acid catalyzed 'ene' reactions with alkenes and side-reactions are observed[465]. Even with β-unsubstituted enones or enals, depending on the structure of

the ene, δ-unsaturated carbonyl derivatives or bicyclic alcohols arising from annelation are obtained[466-468].

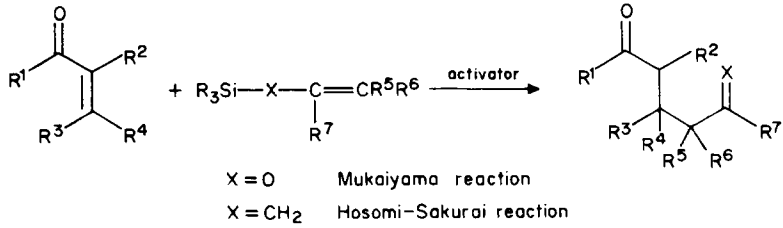
V. CARBON–CARBON BOND FORMATION FROM NUCLEOPHILIC ATTACKS OF ORGANOSILICONS

The use of organosilicons in organic synthesis has greatly increased in the last few years[469-474]. Conjugate additions of R_3SiX species to enones led to numerous silyl enol ethers and the corresponding β-substituted carbonyl compounds as synthetic intermediates[475-477] (equation 72).



(72)

Only the Mukaiyama reaction[478,479] and the Hosomi–Sakurai reaction[480,481], which exhibit similarities, will be considered here. They are shown schematically in equation 73.



(73)

A. Michael-type Reactions with Silyl Enol Ethers and Related Compounds

The Michael reactions with metal enolates are often complicated by side-reactions and concomitant 1,2-addition[482] (see Section II.B). For synthetic purposes, some of these problems are overcome by the use of silyl enol ethers as functional equivalents of enolates (equation 73). In the original procedure described by Mukaiyama and coworkers, the conjugate addition of silyl enol ethers or O-silylated ketene acetals to α-enones was promoted under mild conditions (−78 °C) by an equimolar amount of titanium tetrachloride in dichloromethane. When the enones are very sensitive to $TiCl_4$, the activation of enones is accomplished by the use of both $TiCl_4$ and $Ti(OPr\text{-}i)_4$ (Table 45).

In sharp contrast to these results, condensation of S-silylketene S,N-acetals with α-enones activated by $ClTi(OPr\text{-}i)_3$ affords exclusively 1,2-addition in good yields, while O-silylketene O,N-acetals afford a mixture of 1,2- and 1,4-additions under identical reaction conditions. 1,2-Condensation with S-silylketene S,N-acetals promoted by $ClTi(OPr\text{-}i)_3$ does not seem to involve titanium enethiolate as intermediate[486].

In the Mukaiyama reaction, the Lewis acid acts as an activator of the enone species and is used in equimolar quantities. Corriu and coworkers have elaborated two valuable methods to carry out the conjugate addition using fluoride ion activation (Lewis base activation) of the silicon atom by heterogeneous catalysis. In the former procedure, the silyl enol ether reacts with the enals or enones without solvent, between 25–80 °C in the presence of caesium fluoride which can be recovered[487] (Table 46). Cinnamaldehyde leads

TABLE 45. Michael reaction between $R^1COCR^2=CR^3R^4$ and $R_3SiOCR^7=CR^5R^6$ in the presence of Lewis acids at $-78\,^{\circ}C$ in CH_2Cl_2

Enone				Reagent				Lewis acid				
R^1	R^4	R^2	R^3	R_3Si	R^5	R^6	R^7	$TiCl_4$ (eq./reag.)[a]	$Ti(OPr\text{-}i)_4$ (eq./reag)[a]	Time (h)	Yield (%)	Ref.
Me	Me	H	Me	Me_3Si	H	H	Ph	1	—	0.03	76	483
Me	Me	H	Me	Me_3Si	H	$-(CH_2)_3-$		1	—	0.25	66	483
Me	Me	H	Me	Me_3Si	H	CH_2Ph	OMe	1.1	—	3	72	484
Me	Me	H	Me	Me_3Si	Me	Me	OMe	1.1	—	3	72	484
Ph	H	H	Ph	Me_3Si	H	H	Me	1.0	0.5	0.5	44	483
Ph	H	H	Ph	Me_3Si	H	H	Me	1.0	0.8	0.5	63	485
Ph	H	H	Ph	Me_3Si	H	$-(CH_2)_3-$		1.0	—	0.75	85	483
Ph	H	H	Ph	Me_3Si	H	$-(CH_2)_4-$		1.0	—	1	95	483
Ph	H	H	Ph	Me_3Si	H	CH_2Ph	OMe	1.1	—	3	90	484
Ph	H	H	Ph	Me_3Si	Me	Me	OMe	1.1	—	5	>99	484
Ph	H	H	Ph	t-$BuMe_2Si$	H	H	OEt	1.1	—	3	98	484
$-(CH_2)_3-$		H	H	Me_3Si	H	Ph	Me	1.0	—	1	55	483
$-(CH_2)_3-$		H	H	Me_3Si	H	H	Ph	1.0	0.4	0.5	70	485
$-(CH_2)_3-$		H	H	Me_3Si	H	CH_2Ph	OMe	1.1	0.55	3	81	484
$-(CH_2)_3-$		H	H	Me_3Si	Me	Me	OMe	1.1	0.55	3	74	484
$-(CH_2)_3-$		H	H	Me_3Si	H	$-CH_2CH_2O-$		1.1	0.55	3	82	484
Me	H	H	H	Me_3Si	H	CH_2Ph	OMe	1.1	—	3	0	484
Me	H	H	H	Me_3Si	H	CH_2Ph	OMe	1.1	0.55	3	38	484
Me	Me	H	H	Me_3Si	H	H	Ph	1.0	0.8	0.5	56	485

[a]eq./reag. = equivalent/reagent.

TABLE 46. Reaction between $R^1COCR^2{=}CR^3R^4$ and silyl enol ethers $R_3SiOCR^7{=}CR^5R^6$ in the presence of CsF (1g/1g of silyl enol ether)[487]

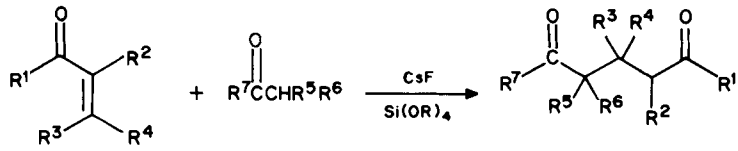
Substrate					Reagent				Time	Temperature			Overall
R^1	R^4	R^2	R^3	(eq)[a]	R_3Si	R^5	R^6	R^7	(h)	(°C)	1,2-attack	1,4-attack	yield (%)
Ph	Ph	H	H	(1)	Me_3Si	H	$-(CH_2)_4-$		0.5	25	0	100	80
Ph	Ph	H	H	(1)	Me_3Si	H	H	Ph	3	25	14	86	84
$-(CH_2)_3-$		H	H	(2)	Me_3Si	H	$-(CH_2)_4-$		1	80	0	100	40
$-(CH_2)_3-$		H	H	(2)	$Me(OEt)_2Si$	H	$-(CH_2)_4-$		1	80	0	100	40
$-(CH_2)_3-$		H	H	(1)	Me_3Si	H	H	Ph	4	25	0	100	55
H	Ph	H	H	(1)	Me_3Si	H	H	Ph	3	25	100	0	70
H	Ph	H	H	(1)	Me_3Si	H	H	*t*-Bu	5	80	100	0	60

[a]equivalent = mmol/mmol of silyl enol ether.

TABLE 47. Michael additions of $R^7COCHR^5R^6$ to $R^1COCR^2{=}CR^3R^4$ in the presence of $Si(OEt)_4$/CsF (Method A) or $Si(OMe)_4$/CsF (Method B)

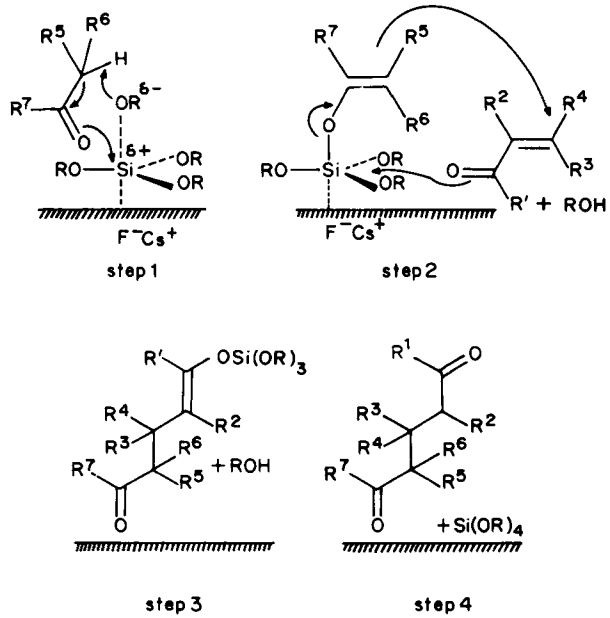
Substrate				Michael donor				Time	Temperature	Yield	
R^1	R^4	R^2	R^3	R^5	R^6	R^7	Method	(h)	(°C)	(%)	Ref.
Ph	Ph	H	H	Me	$-(CH_2)_4-$		A	2	60	65	388
Ph	Ph	H	H	Me	$-(CH_2)_3-$		B	1	20	82	355
$-(CH_2)_3-$		H	H	Me	$-(CH_2)_4-$		A	6	25	65	488
Carvone				Me	$-(CH_2)_4-$		B	4	25	70	489
Carvone				H	$-(CH_2)_3-$		B	3	80	60	489
Carvone				H	H	Ph	B	4	70	60	355
Carvone				Me	Me	Me	B	2	80	60	355
Pulegone				H	H	Ph	B	6	80	65	489

to 1,2-additions, and the corresponding 1,3-dienes are isolated. In the latter procedure, the heterogeneous reactions are carried out without solvent and in the presence of stoichiometric amounts of caesium fluoride, tetraalkoxysilane, ketone precursor of silyl enol ether and enone[355,488–490] (equation 74). Selected results are indicated in Table 47.



(74)

The great value of this method is that it avoids preparation of the silyl enol ether. The following mechanism has been proposed (equation 75)[489]. The first step is nucleophilic activation of $Si(OR)_4$ by the fluoride ion to give a basic species able to promote enolate formation. The enolate is silylated very quickly, giving the corresponding silyl enol ether. In a second step, the salt-activated silyl enol ether promotes formation of the 1,4-adduct from the enone. The adduct reacts *in situ* with the alcohol obtained during the formation of the silyl enol ether (step 3) to give the 1,5-diketone (step 4). Hydrolysis is not necessary to give the final product[489].



(75)

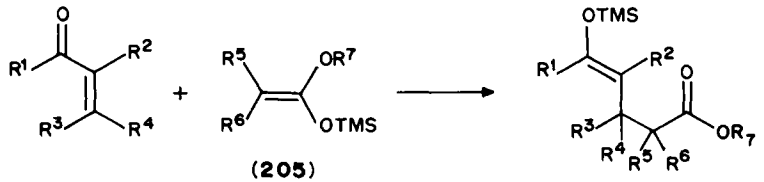
The original Mukaiyama procedure has been used for the preparation of numerous key intermediates in the synthesis of natural products, particularly *via* Robinson-type annelation[491–499]. However, the synthetically valuable silyl enol ethers are not isolated in both $TiCl_4$-promoted Michael reaction and Corriu methods. The first case reported in which the silyl enol ether intermediate has been isolated is the reaction between the trimethylsilyl enol ether of cyclohexanone and α,β-unsaturated aldehydes, such as cinnamaldehyde or 2-hexenal, promoted by tetra-*n*-butylammonium fluoride (TBAF)[500]. Unfortunately, these enals give only 1,2-addition products (50–60%)[501]. Yet, Gerlach and

TABLE 48. Conjugate additions of trimethylsilyl ketene acetals **205** to α-enones

Enone	Reagent R^5	R^6	R^7	Method[a]	Time (h)	Temperature (°C)	Yield (%)	Ref.
Cyclopentenone	Me	H	Me	A	0.5	−78	91	503
	Me	H	Me	B	18	r.t.[b]	82	503
	Me	H	Me	C	4	55	98	504
	Me	Me	Me	A	0.5	−78	61	503
	Me	Me	Me	B	18	r.t.[b]	< 5	503
Cyclohexenone	Me	H	Me	A	0.5	−78	94	503
	Me	H	Me	B	18	r.t.[b]	58	503
	Me	H	Me	C	4	55	96	504
	Me	H	Et	D	144	r.t.[b]	80	508
	Me	Me	Me	A	0.5	−78	65	503
	Me	Me	Et	D	144	50	80	508

[a]Method A: 4 mmol% TASF suspended in anhydrous THF; Method B: nitromethane only; Method C: acetonitrile only; Method D: in dichloromethane at 10 Kbar.
[b]r.t. denotes room temperature.

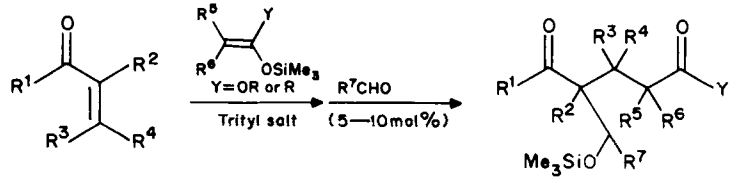
Künzler showed, using a catalytic amount (10 mol%) of TBAF, that the trimethylsilyl enol ether of S-*t*-butyl thioacetate reacts smoothly with an equimolar amount of 2-cyclopentenone in THF at low temperatures, giving the silyl enol ether of the 1,4-addition product in 72% yield[502]. Other appropriate Lewis base catalysts can be used to generate potent carbon nucleophiles from silyl enol ethers. Thus, the fluoride-catalyzed 1,4-addition of ketene trimethyl acetals to enones can be performed at low temperature using tris(dimethylamino)sulphonium difluorotrimethyl siliconate (TASF)[503] (Table 48). In fact, it has been demonstrated that direct Michael addition of silyl enol ethers can be carried out without additives using a more polar solvent such as nitromethane[504] or acetonitrile[504,505] at 20–60 °C. In these cases, it is assumed that the silyl enol ethers behave much like a Lewis acid and activate the enone for nucleophilic addition[503]. However, these thermal reactions are useful for relatively unhindered cases, and the high-pressure technique provides an alternative means of inducing silyl enol ether additions to sensitive enones having steric and conformational constraints[506–508]. Representative results of TASF-catalyzed reactions, thermal and high-pressure reactions of O-silylated ketene acetals **205** and enones (equation 76) are summarized in Table 48.



(76)

Michael reactions between enones and silyl enol ethers of ketones[509], esters[510] and thioesters[510] or siloxydienes[511] have been more recently shown to proceed smoothly at −78 °C in dichloromethane under non-basic conditions and using catalytic amounts (5–10 mol%) of trityl salts such as trityl perchlorate. The synthetically useful silyl enol ether intermediate can be isolated by quenching the reaction mixture with pyridine or 2-(hydroxymethyl)pyridine. Nevertheless, if appropriate electrophiles are added to the

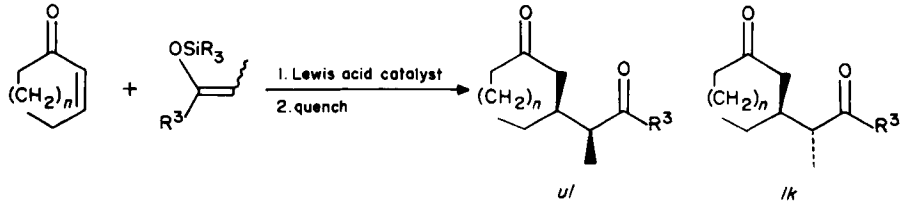
reaction before the quenching, it is possible to obtain the products from further reactions of the intermediate silyl enol ethers with the electrophiles, such as aldol condensation[510,512,513] (equation 77).



(77)

Several papers have been devoted to the interpretation of stereoselective trends of the Lewis and promoted Mukaiyama reactions[492,510,514–516]. However, coherent transition-state hypotheses that could explain the stereoselectivity observed in particular cases of well homogeneous series are often invalidated with another series. In order to illustrate this point, we discuss below representative results among the important works of Heathcock and coworkers[514,515] and Mukaiyama and coworkers[510,516].

Table 49 shows that silyl enol ethers derived from acyclic ketones have a general tendency for *ul* selectivity, regardless of the stereostructure of the silyl ether, even if the silicon substituents play a significant role in the diastereoselectivity (equations 78 and 79). For the trityl salt promoted reactions, Mukaiyama and coworkers[516] explain the *ul* selectivity from the *Z* enolates by assuming the open transition state as shown in Scheme 1.

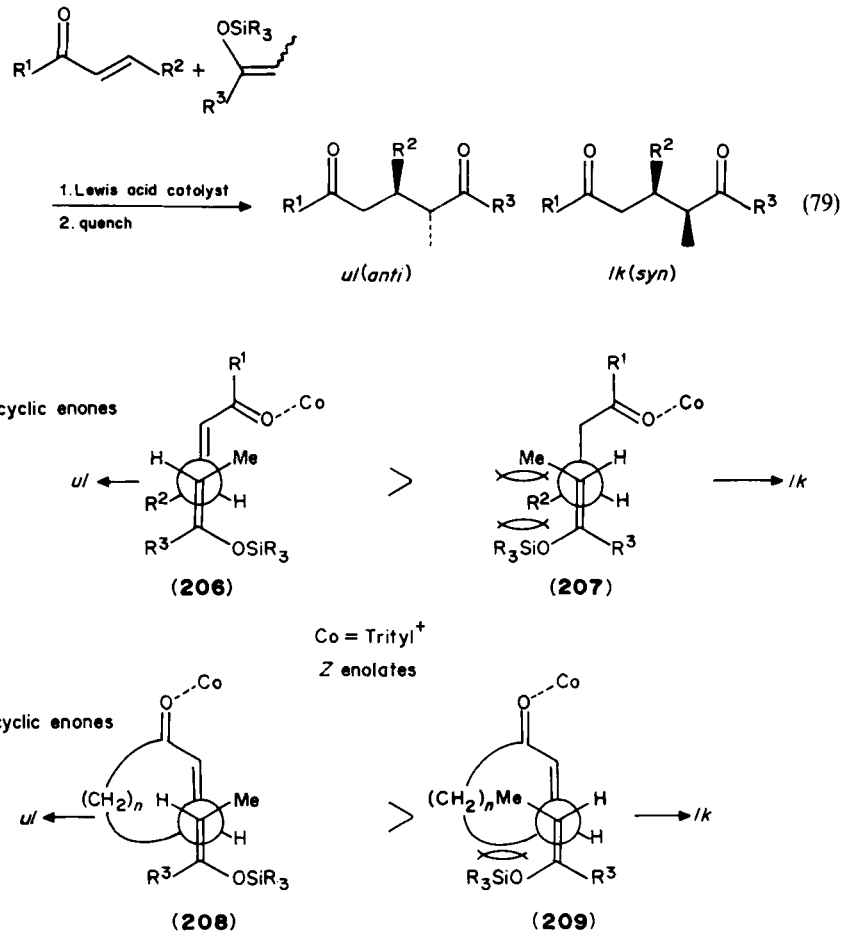


(78)

TABLE 49. Stereochemistry of additions of silyl enol ethers $R^3C(OSiR_3)=CHMe$ to enones $R^1COCH=CHR^2$ at low temperature ($-45\,^{\circ}C$ to $-78\,^{\circ}C$) in dichloromethane

Enone		Silyl enol ether						
R^1	R^2	R_3	R^3	Configuration	Lewis acid[a]	*ul*	*lk*	Ref.
—$(CH_2)_3$—		*t*-BuMe_2	Ph	*Z*	$TrClO_4$	77	23	516
—$(CH_2)_3$—		*t*-BuMe_2	Ph	*Z*	$TrPF_6$	78	22	516
—$(CH_2)_3$—		*t*-BuMe_2	Ph	*Z*	$TrSnCl_5$	79	21	516
—$(CH_2)_3$—		*t*-BuMe_2	Et	*Z*	$TrClO_4$	54	46	516
Ph	Me	*t*-BuMe_2	Et	*Z*	$TrClO_4$	85	15	516
Ph	Me	*t*-BuMe_2	Et	*E*	$TrClO_4$	77	23	516
Ph	Me	Et_3	Et	*E*	$TrClO_4$	71	29	516
Ph	Me	Me_3	Et	*E*	$TrClO_4$	59	41	516
t-Bu	Me	Me_3	Et	*E*	$SnCl_4$	87	13	514
t-Bu	Me	Me_3	Et	*Z*	$SnCl_4$	89	11	514
t-Bu	Me	Me_3	Et	*Z*	$TiCl_4$	88	12	514

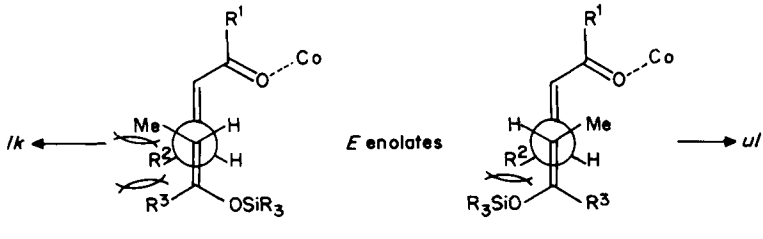
[a]Tr = Trityl.



SCHEME 1

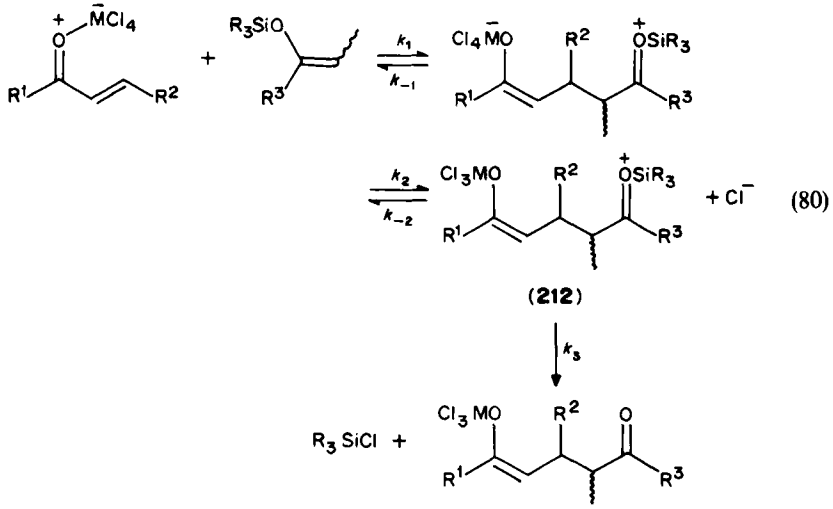
The sterically large trityl cation initially interacts with the enone, and the activated enone is attacked by the silyl enol ether with its bulky siloxy group in such a way that the steric hindrance between trityl cation and the trialkylsiloxy group can be minimized. Transition state **206** is favoured over transition state **207** for an acyclic enone and transition state **208** is preferred to transition state **209** for a cyclic enone, because of both the gauche interaction between R^2 and Me and the steric hindrance between R^2 and the siloxy group[516]. Transposition of this hypothesis to the *E* enolates leads to the transition states shown in Scheme 2. Since an *ul* selectivity is also observed, the transition state **211** must be favoured. Questions that remain are: (i) why are the gauche interactions between Me, R^2 and R^3 in **210** greater than those between R^2 and the siloxy group in **211**? and (ii) why is the *ul* diastereomer favoured when the size of the siloxy group increases (Table 49)?

In contrast to the Mukaiyama results[516], Heathcock and coworkers presume that the reactions of the silyl enol ether in the presence of $TiCl_4$ or $SnCl_4$ are under some degree of thermodynamic control, due to Michael reversion before loss of the silyl group from the



SCHEME 2

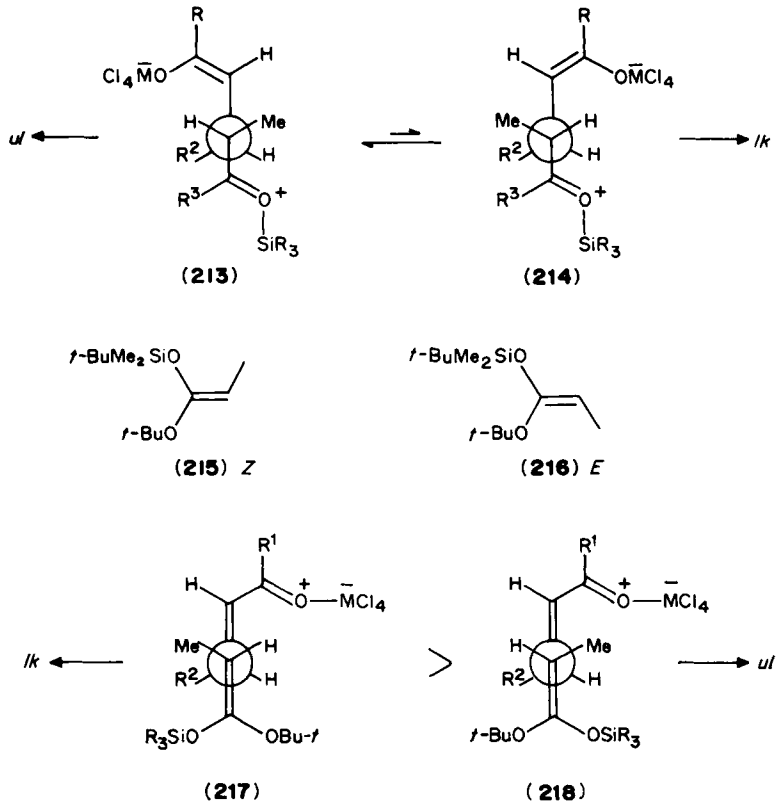
oxygen atom of the new carbonyl group[514] (equation 80). It seems that the initial equilibrium is not very favorable, and the retro-Michael reaction competes with desilylation of **212**. It is possible that *anti* stereochemistry predominates because gauche interactions are minimized in conformation **213**, relative to **214** (Scheme 3). This hypothesis explains the fact that stereoselectivity is largely independent of the silyl enol ether stereostructure. The mechanism shown in equation 80 also provides an explanation for the *lk* selectivity observed with the silyl ketene acetals **215** and **216** (Table 50). With the ketene acetals, Heathcock and coworkers[514] proposed that the initial equilibrium in equation 80 lies far to the right because the oxonium ion is delocalized. Desilylation of the (trialkylsilyl) oxonium ion is fast, relative to the retro-Michael reaction. Therefore, the stereochemistry observed with **215** and **216** seems to be the result of interactions in the isomeric transition states leading to *lk* and *ul* diastereomers. The *lk* selectivity will be the result of a preference for transition-state conformation **217** relative to **218**. We note that similar transition states (such as **206** and **218** or **207** and **217**) have been used to explain the generation of opposed stereoselectivities.



(80)

In addition, results obtained from silyl enol ethers of methyl esters and thioesters in the presence of trityl salts show that *E* silyl enol ethers tend towards a *lk* selectivity whereas *Z* silyl enol ethers tend towards *ul* selectivity[510] (Table 51).

Finally, the stereochemistry observed for additions of silyl enol ethers derived from ketones and esters to chiral enones is hardly reconcilable with the mechanistic



SCHEME 3

interpretation proposed by Heathcock and Uehling[515]. In fact, the stereochemistry of Lewis acid mediated Michael additions of silyl enol ethers to enones is very dependent on several reaction parameters, such as the solvent, the reaction temperature, the nature of silyl enol ether and the siloxy group, the geometry of the enolate and the nature and

TABLE 50. Stereochemistry of reactions of silyl ketene acetals **215** and **216** with $R^2CH{=}CHCOR^1$ at $-78\,^{\circ}C$ in dichloromethane in the presence of $TiCl_4$[514]

Enone				
R^1	R^2	Reagent	*ul*	*lk*
$-(CH_2)_3-$	—	**215**	25	75
$-(CH_2)_3-$	—	**216**	38	62
t-Bu	*i*-Pr	**215**	4	96
t-Bu	*i*-Pr	**216**	2	98

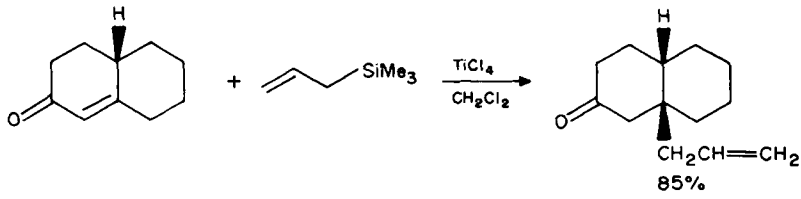
TABLE 51. Stereochemistry of reactions of silyl enol ethers $XC(OSiR_3)=CHMe$ with enones $R^2CH=CHCOR^1$ at $-78\,^{\circ}C$ in dichloromethane in the presence of Trityl perchlorate[510]

Enone		Silyl enol ether				
R^1	R^2	X	R_3	Configuration	*ul*	*lk*
Ph	Me	OMe	*t*-BuMe$_2$	*Z*	62	38
Ph	Me	SBu-*t*	Me_3	*Z*	71	29
Ph	Me	SBu-*t*	*t*-BuMe$_2$	*Z*	95	5
Ph	Me	SBu-*t*	*t*-BuMe$_2$	*E*	31	69
Me	Me	SBu-*t*	*t*-BuMe$_2$	*Z*	>95	<5
$-(CH_2)_2-$		SBu-*t*	*t*-BuMe$_2$	*Z*	66	34
$-(CH_2)_2-$		SBu-*t*	Me_3	*E*	23	77

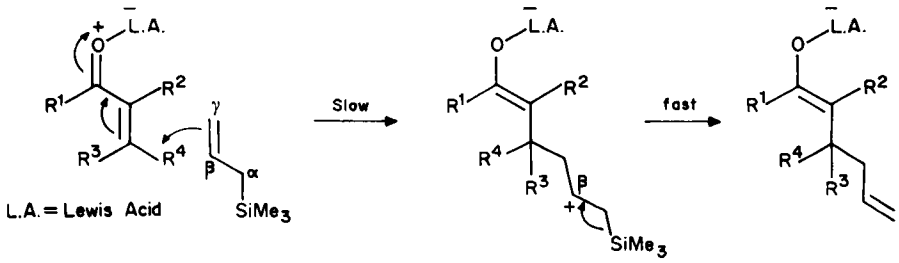
amount of the catalyst. To date, the rationalization of these effects has not yet been realized.

B. Michael-type Reactions with Allylsilanes

Allylsilanes are versatile reagents for the allylation of a variety of electrophiles with regiospecific transposition of the allylic part[473,474]. There is a striking parallel in the evolution of the methodologies of Mukaiyama and Hosomi–Sakurai reactions[480,481]. Calas and coworkers[517,518] were the first to demonstrate that allylsilanes add to activated carbonyl compounds such as chloroacetone in the presence of Lewis acids. Soon afterwards, Hosomi and Sakurai reported that many carbonyl compounds react with allylsilanes, provided that the carbonyl function is activated with titanium tetrachloride[519]; then, they showed that allylsilanes undergo regiospecific conjugate addition to an α-enone when activated by strong Lewis acid catalysts[520], and they also reported the first stereoselective introduction of an angular allyl group into a fused α-enone by using this procedure (equation 81). House and coworkers[442] showed the superior conjugate allylation capabilities of the allyltrimethylsilane–titanium tetrachloride procedure, as compared with allylmagnesium bromide–copper(I) salts and lithium diallylcuprate[441]. The Hosomi–Sakurai procedure was reviewed in 1982. Although the detailed mechanism is not yet clear, it seems that the Lewis acid first interacts with the carbonyl oxygen and activates the carbonyl compound to a regiocontrolled nucleophilic attack of the allylsilane. The γ-carbon of the allylsilane nucleophilically attacks the enone and induces positive-charge development at the β-carbon; the β-silyl carbenium ion undergoes rapid loss of the silyl group. The rate-limiting step is assumed to be the nucleophilic attack of the allylsilane double bond on the Lewis acid coordinated enone[521] (equation 82).



(81)



(82)

Among the usual Lewis acids, $TiCl_4$ is generally the most efficient as shown in Table 52.

The initial Hosomi–Sakurai addition procedure has been widely exploited in annelation, particularly for natural product synthesis[480,495,499,523–531]. Usually, a stoichiometric amount of Lewis acid is required for the completion of the allylation. From their previous results on trityl salt mediated Michael addition of silyl enol ethers, Hayashi and Mukaiyama showed that catalytic amounts of trityl perchlorate promote the conjugate allylation of α-enones with allyltrimethylsilane to afford the corresponding adducts in good yields[532].

α-Enals fail to give conjugate addition with Lewis acid–allylsilane procedure. There is no reaction when $TiCl_4$ is used with cinanamaldehyde or α-methylcinnamaldehyde. 1,2-addition products are observed with BF_3–Et_2O. In the case of $TiCl_4$, it seems that the highly reactive enal functionality is rapidly consumed by a Lewis acid-catalyzed 1,2-addition of chloride ion, leading to a hemichloroacetal, which is hydrolyzed back to the aldehyde upon aqueous workup[533,534].

The $TiCl_4$-mediated Hosomi–Sakurai reaction has been used for allylation of quinones. Usually, *p*-quinones react to produce allyl-substituted hydroquinones; 2,6-disubstituted *p*-quinones produce *p*-allylquinols regioselectively in 50–90% yield[480,535].

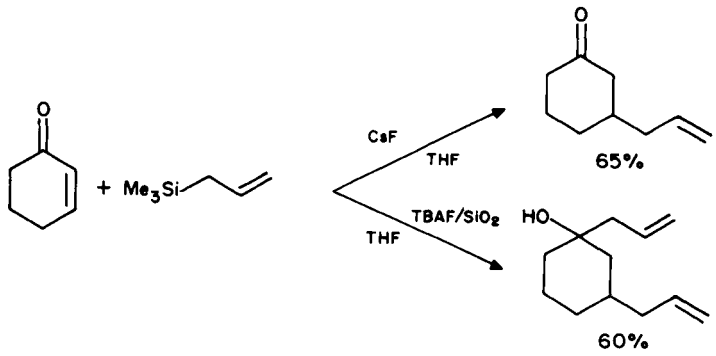
Fluoride ion catalysis can be used as an alternative to the Lewis acid-mediated allylation[536]. Although its mechanism is not clearly established, it seems that addition of a fluoride salt to an allylsilane probably occurs via the rapid formation of a non-basic pentacoordinate organosilicon nucleophile[537].

The regioselectivity of the reaction of the allylsilane with an α-enone appears to depend on the catalyst. For instance, when a silica-supported tetrabutylammonium fluoride ($TBAF/SiO_2$) is used with cyclohexenone, conjugate addition takes place along with 1,2-addition, affording the product of double allylation. With CsF, only the expected product of conjugate addition is formed[538] (equation 83).

TABLE 52. Allyltrimethylsilane addition to 5-phenyl-3-hexen-2-one in dichloromethane[522]

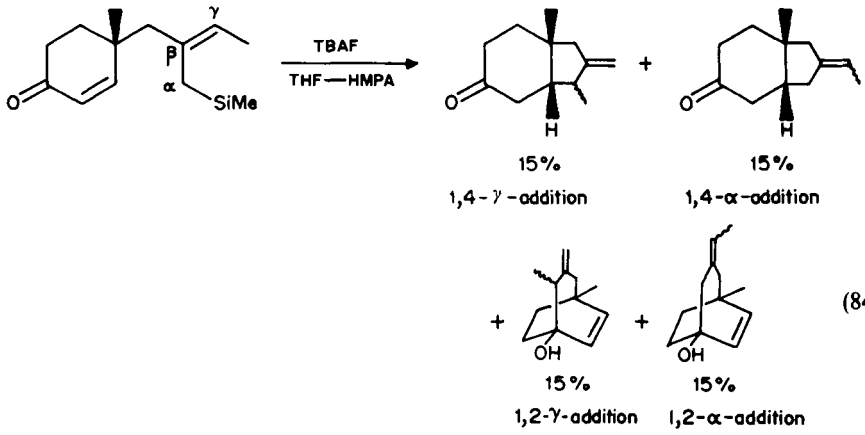
Lewis acid	Temperature (°C)	Time (h)	Yield (%)
$TiCl_4$	−78	1	74
BF_3–Et_2O	−78 to 25	24	< 50
BF_3	−78 to 25	24	no reaction
BCl_3	−78	32	< 20
$ZnCl_2$[a]	−78	72	no reaction

[a]A 1:1 mixture of ether and dichloromethane was used as solvent.



(83)

Majetich and coworkers compared the relative efficiency of fluoride ion and Lewis acids for annelation reactions[539-543]. They showed that the stereochemical outcome for intramolecular Hosomi–Sakurai reactions was dependent on the choice of catalyst, and that the fluoride ion-catalyzed allylation is highly substrate-dependent. Complex mixtures of 1,2- and 1,4-addition products are obtained with carbon–carbon bond formation with both the α and γ atoms of the allyl moiety (equation 84)[537]. It is noteworthy that the easy fluoride ion-catalyzed desilylation of organosilicon compounds containing a carbon–silicon bond has been developed into a general method for the transfer of carbanions other than allyl to the β-position of α-enones[538] (equation 85).



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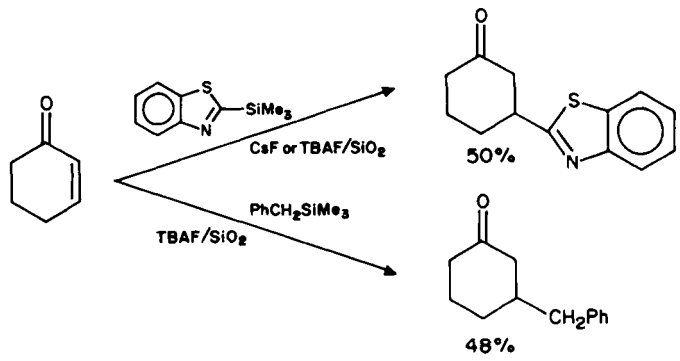


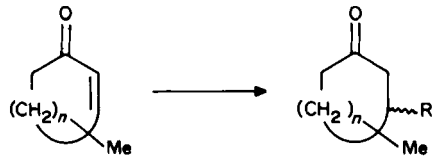
(85)

TABLE 53. Conjugate additions of allyltrimethylsilane and *n*-propylmagnesium bromide to methyl-substituted cyclic enones[521]

Enone	CH_2=$CHCH_2SiMe_3$, $TiCl_4$ CH_2Cl_2, −78 °C			*n*-PrMgBr, CuI THF, −20 °C		
	yield (%)	*trans*[b]	*cis*[b]	yield (%)	*trans*[b]	*cis*[b]
4-Methyl-2-cyclohexen-1-one	76	32	68	78	80	20
5-Methyl-2-cyclohexen-1-one	83	>98	<2	81	93	7
4-Methyl-2-cycloheptenone-1-one	71	35	65	65[a]	83[a]	17[a]
5-Methyl-2-cycloheptenone-1-one	76	98	2	74	82	18
6-Methyl-2-cycloheptenone-1-one	71	11	89	71	37	63

[a]Data given for conjugate addition of the di-*n*-propylcopper boron trifluoride complex.
[b]In the product.

In a comparative stereochemical study of allylation and alkylation reactions of methylated cyclohexenones and cycloheptenones from the $TiCl_4$-mediated additions and the CuI-promoted addition of Grignard reagents (Table 53) (equation 86), Blumenkopf and Heathcock have shown that the stereoselectivity for both reactions can be fully explained by stereoelectronic and steric hindrance considerations. Nevertheless, it appears that the allylsilane addition product is the stereoelectronically preferred one. In the cuprate additions there is a significant steric hindrance effect, which reduces the amount of the stereoelectronically favoured isomer[521].



(86)

VI. CARBON–CARBON DOUBLE BOND FORMATION FROM WITTIG-TYPE REACTIONS

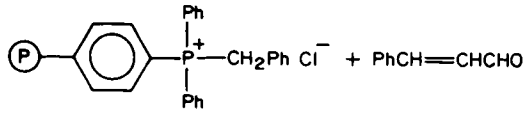
Among the usual approaches to the synthesis of olefins from a carbonyl compound, such as Knoevenagel condensations[544,545] or Peterson olefinations[474,546–548], Wittig-type reactions seem to be the most general and the most easily applicable to α,β-unsaturated aldehydes and ketones. In fact, the papers that have recently been published on olefination reactions and their synthetic use were not specifically devoted to enals and enones but rather to aldehydes and ketones[549–555]. Some of the reagents and processes that have recently been developed can be successfully applied to α-enals and α-enones and will be discussed with particular attention to the stereoselectivity. As expected, enals are more reactive than enones.

A. Olefination with Phosphoranes (Wittig reactions)

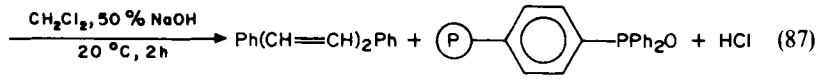
Usually, double or triple bonds conjugated with the carbonyl do not interfer in the Wittig reactions, the attack being at the carbonyl double bond.

As an example of new methodologies, polymer-supported Wittig reactions have been successfully applied to α-enals and α-enones such as cinnamaldehyde and cholest-4-en-3-

one[556]. They may be associated to phase-transfer-catalyzed reactions. Phase-transfer-catalyzed polymer-supported Wittig reactions have been performed with cinnamaldehyde, while ketones failed to react[557] (equation 87).

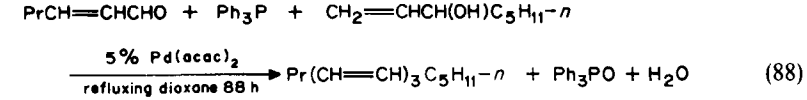


P = linear polystyrene



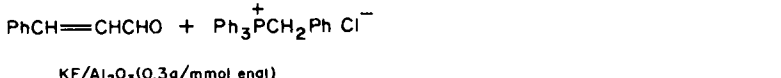
75%

Palladium-catalyzed Wittig-type olefinations have been achieved in a one-pot process by mixing allylic alcohols, enals, triphenylphosphine and palladium in the form of $Pd(acac)_2$[558] (equation 88).



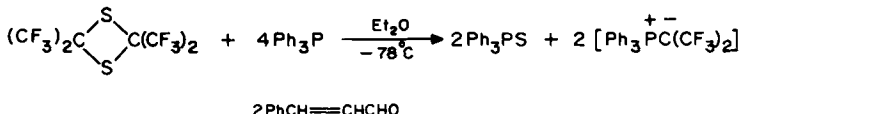
27%

Potassium fluoride supported on alumina also catalyzes Wittig reactions, without any organic solvent (equation 89)[559].



70%

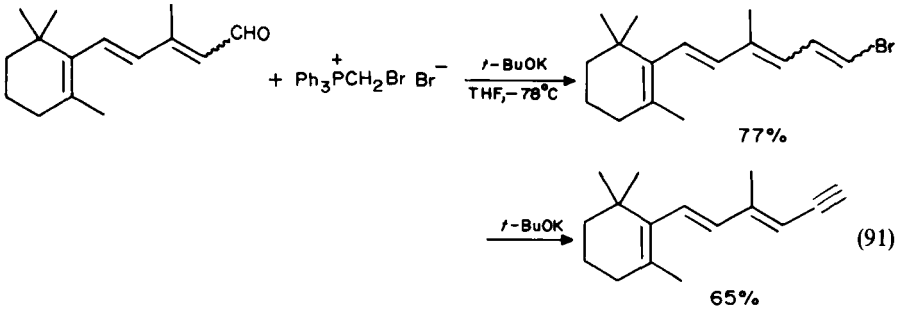
Among the new Wittig reagents, it is noteworthy that a phosphonium analog of Middleton's phosphorane is generated *in situ* from tetrakis(trifluoromethyl)-1,3-dithietane and triphenylphosphine, and reacts with cinnamaldehyde giving the resultant *bis*-trifluoromethyl olefin in 56% isolated yield (equation 90)[560]. Ketones fail to give olefins under these conditions, since decomposition of the ylide occurs faster than olefination of the ketone.



56 %

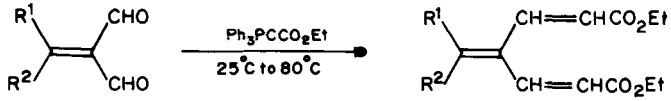
Enals are easily converted to 1-bromoolefins or terminal acetylenes by the use of Wittig

reaction of bromomethylenetriphenylphosphorane, which is prepared from bromomethyltriphenylphosphonium bromide with potassium *t*-butoxide as exemplified by reaction with β-ionilidene acetaldehyde (equation 91)[561].



(91)

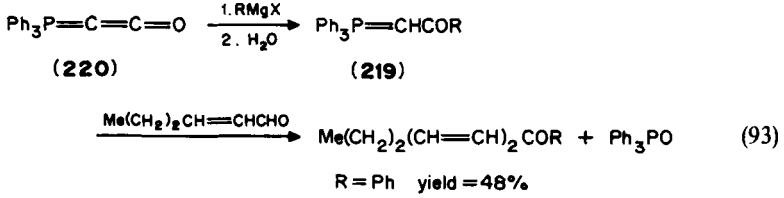
A double Wittig reaction can be performed on 2-ene-1,3-dial[562,563] with functionalized phosphorane in good yields (equation 92)[564].



(92)

R^1=H or Ph R^2=Ph or Ar

An acylylidene group can be added to enals from the Wittig reaction of phosphorane **219**, obtained from the Grignard reaction between ketenylidenetriphenylphosphorane **220** and alkyl or aryl magnesium halide (equation 93)[565].



(93)

B. Olefination with Phosphonates and Phosphine Oxides (Wittig–Horner or Horner–Emmons or Wadsworth–Emmons Reactions)

Phosphonates, are considered to react poorly with α,β-unsaturated ketones, except β-ionone[566–570], due to the smaller electrophilicity of the carbonyl carbon atom and to the competitive Michael addition. Nevertheless among other possibilities[571–578] (see Section II.A), one can perform Horner–Emmons reactions of diethyl cyanomethylphosphonate with various 3-substituted-5,5-dimethyl-2-cyclohexen-1-ones using sodium hydride as base and THF as solvent (equation 94) (Table 54)[579,580].

Under the same experimental conditions, these ketones lead to very poor yields (except when X = OEt, 79%) with triethyl phosphonoacetate, and polymerizations arise when the reaction time is increased.

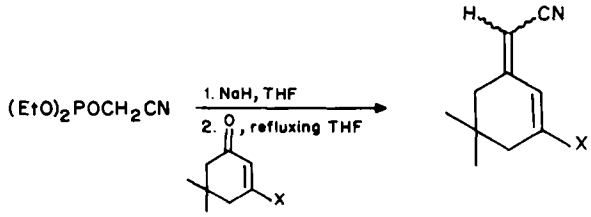
Cinnamaldehyde is converted into the corresponding α,β-γ,δ-dienic ester using triethyl phosphonate and a weaker base such as triethylamine in the presence of lithium bromide

TABLE 54. Horner–Emmons reaction between diethyl cyanomethylphosphonate and 3-substituted-5,5-dimethyl-2-cyclohexen-1-ones in refluxing THF using NaH as base[579,580]

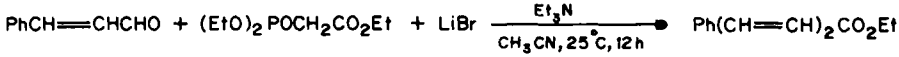
3-X substituent in the ketone	Time (h)	Isolated yield (%)	Product Z	Product E
H	18[a]	28	40	60
Me	24	56	46	54
Ph	24	55	63	37
Cl	24	47	40	60
Br	24	80	50	50
OEt	16	92	62	38
SEt	24	90	35	65
CH_2Ph	48[a]	82	44	56
p-$NO_2C_6H_4$	24	70	47	53

[a]Reactions performed at room temperature.

(equation 95)[581]. Apart from cyclohexanone, simple ketones fail to react under these conditions.



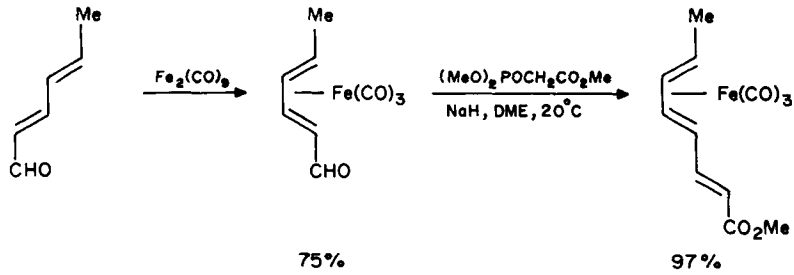
(94)



(95)

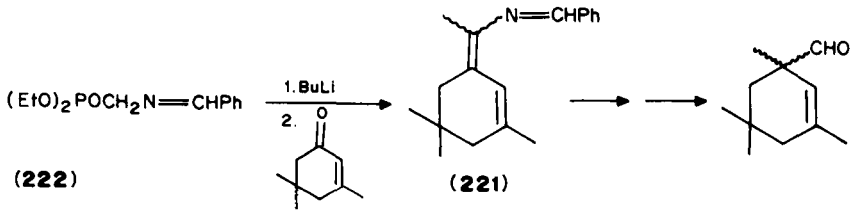
The polymer-supported phosphonate technique has also been successfully used with enals and β-ionone in THF at room temperature[582].

Sorbic aldehyde reacts in excellent yield with trimethyl phosphonoacetate in DME at 20 °C with NaH as base, when complexed by $Fe_2(CO)_9$ (equation 96)[583].



(96)

In order to perform geminal acylation-alkylation at the carbonyl carbon via regiospecifically generated metalloenimines, Martin and coworkers[584] have used the initial conversion of isophorone into the substituted 2-azatriene **221** by a Horner–Emmons reaction with diethyl N-benzylidenamino phosphonate **222** in THF (equation 97).



(222) (221) (97)

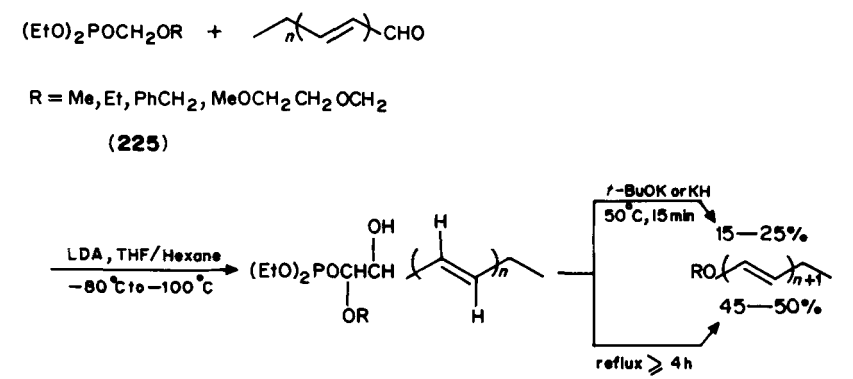
α,β-γ,δ-unsaturated sulphones and sulphoxides can be prepared via the Horner–Emmons reaction of α-enals and α-enones with α-phosphoryl sulphones **223** and sulphoxides **224** (equation 98). Selected results are presented in Table 55[585].

$$RSO_nCH_2PO(OEt)_2 + R^1COCH{=}CHR^2 \xrightarrow[THF]{BuLi} RSO_nCH{=}CR^1CH{=}CHR^2 \quad (98)$$

$n = 2$ (**223**)

$n = 1$ (**224**)

Vo-Quang and coworkers have described a convenient and highly stereoselective method for the synthesis of polyenic enol ethers by the reaction of polyenals with the carbanion of diethyl alkoxymethylphosphonate **225** (equation 99)[586].



Enals and β-ionone can be converted into their homologous ketene O,O-acetals by a Horner–Emmons reaction with dialkyloxymethyldiphenylphosphine oxides, while reactions with phosphonates usually fail (equation 100)[587].

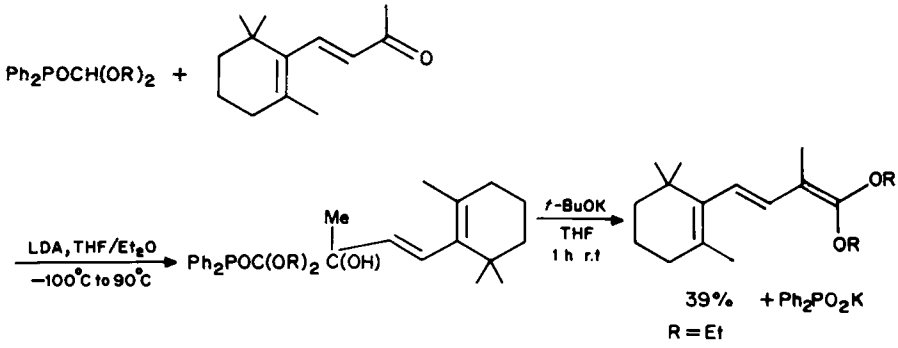
Cyanopolyenes can be prepared in a one-step route based on the Peterson reaction and the Horner–Emmons olefination of diethyl 2-cyano-2-trimethylsilylethanephosphonate **226** as exemplified by reaction with cinnamaldehyde (equation 101)[558].

Olefinations with phosphonates or phosphine oxides are seldom highly stereoselective. However, the stereochemistry with α,β-unsaturated aldehydes tends towards an *E*

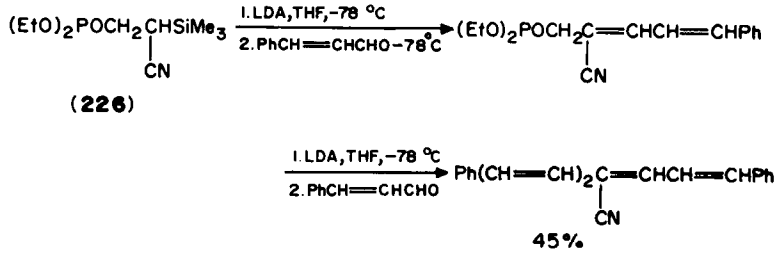
TABLE 55. Reaction of phosphoryl sulphones **223** and phosphoryl sulphoxides **224** with $R^1COCH{=}CHR^2$ at $-78\,^{\circ}C$[585]

Substrate				Isolated yield	Product	
R^1	R^2	Reagent	R	(%)	*Z*	*E*
H	H	**223**	Me	10	0	100
H	H	**223**	Ph	68	0	100
H	H	**224**	Ph	45	43	57
H	Ph	**223**	Me	80	0	100
H	Ph	**223**	Ph	80	0	100
H	Ph	**224**	Ph	64	42	58
$-(CH_2)_3-$		**223**	Me	30	61	39
$-(CH_2)_3-$		**224**	Ph	40	59	41

selectivity[582-591]. Several efforts have been made to rationalize the various factors influencing the stereoselectivity (structure of the anionic reagents and carbonyl compounds, the nature of the solvent and reaction temperature), to increase the *E* stereoselectivity or to reverse the selectivity[582-602].



(100)



(101)

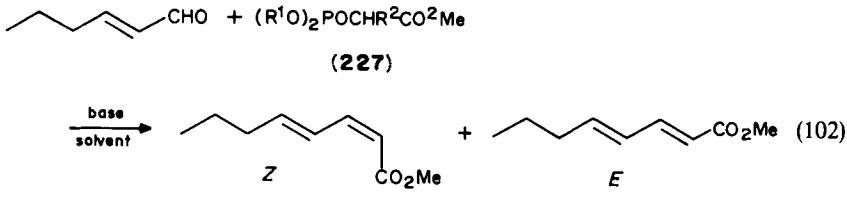
As exemplified in Table 56 with phosphonate **227**, the stereoselectivity depends upon the degree of substitution of the carbon α to phosphorus (entries a and b) as well as upon the nature of alkoxy groups bonded to phosphorus (entries a and c or d, or b and e) (equation 102)[592].

TABLE 56. Reactions between phosphonoesters **227** and 2-hexenal (*E*) under various conditions[592]

Entry	227 R^1	227 R^2	Conditions[a]	Overall yield (%)	Product *Z*	Product *E*
a	Me	H	A	50	22	78
b	Me	Me	A	59	60	40
c	CF_3CH_2	H	A	87	> 98	< 2
d	CF_3CH_2	H	B	65	94	6
e	CF_3CH_2	Me	A	79	> 98	< 2

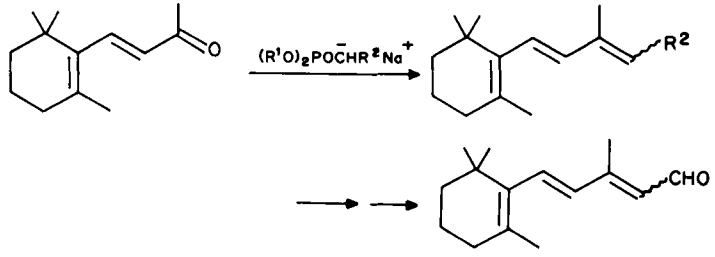
[a]Conditions: (A) KN $(TMS)_2$/18-crown-6/THF; (B) K_2CO_3/18-crown-6/Toluene.

The generally improved *Z* stereoselection with added substituents to carbon α to phosphorus is typical of Horner–Emmons olefinations[603]. As pointed out by Seyden-Penne and coworkers, the use of base system having minimally complexing counterions is important in facilitating elimination and thus maintaining *Z* stereoselection[593,595,597,598].



(102)

The influence of the nature of the phosphoric group and of the electron-withdrawing substituent bonded to the α-carbon is also demonstrated by the results observed with the intermediates used for preparation of the β-ionylideneacetaldehyde **228** (equation 103).



(103)

(228)

	Z : *E*		Ref.
R^1=Et, R^2=CN	33	67	567
R^1=Et, R^2=CO_2Et	6	94	604
R^1=*i*-Pr, R^2=CN	18	82	605

In order to perform the highest *E*-stereoselection, Etemad-Moghadam and Seyden-Penne compared the reactivities of diethyl cyanomethylphosphonate (**229**), diisopropyl

TABLE 57. Reaction of carbonyl compounds **232–236** with reagents **229–231**[606]

Carbonyl compound	Method[a] (T °C)	229			230			231		
		Yield (%)	Z	E	Yield (%)	Z	E	Yield (%)	Z	E
232	A(−78)	60	25	75	—		—		*b*	
232	A(20)	50	40	60	—		—		*b*	
233	A(−78 or 20)	70	20	80	—		—		*c*	
233	B(20)	70	20	80	60	20	80		*c*	
234	B(20)	—	—	—	—		—	85	⩽5	⩾95
235	B(20)	95	25	75	95	20	80	95	⩽5	⩾95
236	B(20)	—	—	—	90	25	75	70	5	95

[a]Methods: (A) *n*-BuLi/THF; (B) *t*-BuOK/THF.
[b]No reaction takes place; the starting materials are recovered unchanged.
[c]No olefin detected.

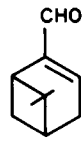
cyanomethylphosphonate (**230**) and diphenyl cyanomethylphosphine oxide (**231**) with enals **232–235** and β-ionone (**236**) in various media[606] (Table 57).

R_2POCH_2CN

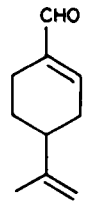
R = EtO (**229**)
R = *i*-PrO (**230**)
R = Ph (**231**)

MeCH=CHCHO (**232**)

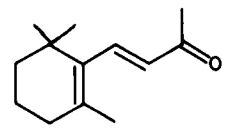
CH_2=CMeCHO (**233**)



(**234**)



(**235**)



(**236**)

PhCH=CHCHO (**237**)

Whereas the *E* stereoselectivity obtained with **231** is higher than with **229** and **230** when the olefination occurs, it appears that the phosphine oxide is less reactive than the phosphonates.

Comparable results are obtained with reaction between diethyl 1-carbomethoxyethylphosphonate (**238**), 1-carbomethoxyethylphosphine oxide (**239**) and enals **232**, **234**, **235** and **237**[607] (Table 58). On the other hand, the *E* stereoselectivity from diethyl phosphono-α-fluoroacetate (**240**) is higher than from the corresponding diphenyl phosphine oxide **241**[608] (Table 58). These results are in line with previous interpretations which take into account the electron density and steric hindrance around the phosphorus atom[608].

$(EtO)_2POCHMeCO_2Me$ (**238**)

$Ph_2POCHMeCO_2Me$ (**239**)

$(EtO)_2POCHFCO_2Me$ (**240**)

$Ph_2POCHFCO_2Me$ (**241**)

TABLE 58. Olefination reactions of enals and β-ionone with phosphonates **238**, **240** and phosphine oxides **239**, **241**[607,608]

Carbonyl compound	Method[a] (T °C)	Reagent	Yield (%)	Z	E
232	A(−78)	**238**	85	10	90
	A(20)	**239**	60	10	90
	A(−78)	**240**	76	⩽2	⩾98
	A(0)	**241**	85	83	17
234	A(20)	**238**	75	10	90
	B(20)	**239**	75	⩽5	⩾95
	A(20)	**240**	50	⩽2	⩾98
	B(20)	**241**	75	40	60
235	A(20)	**238**	90	10	90
	B(20)	**239**	65	⩽5	⩾95
	A(20)	**240**	75	⩽15	⩾85
	B(20)	**241**	75	70	30
236	A(20)	**240**	90	30	70
	B(20)	**241**	85	50	50
237	A(−78)	**238**	65	10	90
	B(20)	**239**	—	⩽5	⩾95
	A(−78)	**240**	75	⩽2	⩾98
	B(20)	**241**	80	70	30

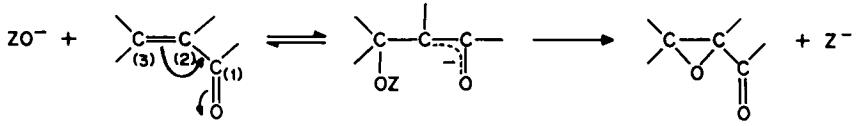
[a]Methods: (A) *n*-BuLi/THF; (B) *t*-BuOK/DMF.

VII. NUCLEOPHILIC EPOXIDATIONS

A. Formation of Epoxides from the Carbon–Carbon Double Bond

Nucleophilic epoxidation of α-enones is generally accomplished with hydrogen peroxide, *t*-butyl hydroperoxide or hypochlorite salts such as NaOCl or KOCl, where the attacking nucleophiles are respectively HOO^-, $t\text{-}BuO^-$ and ClO^-[9,609]. Hydrogen peroxide and *t*-butyl hydroperoxide are often used in protic or aprotic media with strong bases (i.e. NaOH, KOH, LiOH, Triton B)[609–613], but they can also be used in an aprotic solvent using fluorides, particularly Bu_4NF[614].

The well-established mechanism of alkaline epoxidation with H_2O_2[609,615,616] (Weitz–Scheffer reaction)[617] can be extended to *t*-butyl hydroperoxide and hypochlorite salts[609,612,618]. It proceeds by an initial nucleophilic attack of ZO^- (Z = HO, *t*-BuO, Cl) at $C_{(3)}$ in **242** to give the intermediate **243** and then the epoxide **244** by an intramolecular substitution of the carbanionic $C_{(2)}$ on the oxygen (equation 104). The reaction with Z = OH[615] or Cl[618] is first order both in α-enone and in ZO^-[619,620].



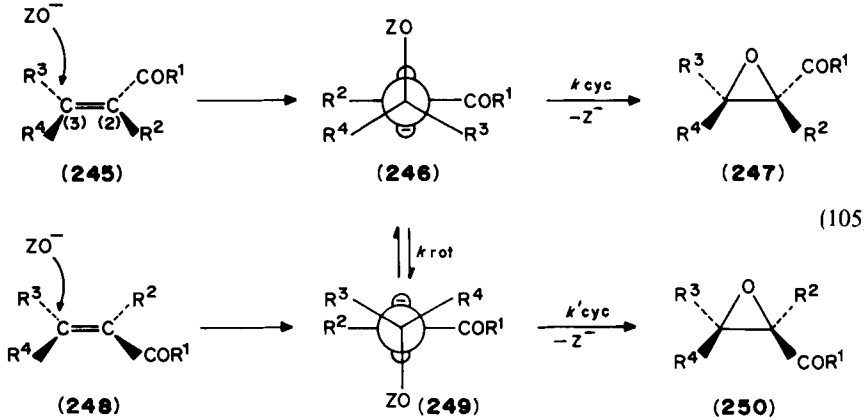
(242) **(243)** **(244)**

(104)

1. Stereochemistry of the nucleophilic epoxidation

The stereochemistry of the epoxidation depends on the nature of both the nucleophile and the enone. Acyclic enones and cyclic enones should be distinguished.

a. Stereochemistry of epoxidation of acyclic enones. Oxidation of acyclic enones with alkaline H_2O_2 is usually stereoselective but not stereospecific, giving the same single epoxide from both *E* and *Z* precursors[609,616,621,622]. For *t*-butyl hydroperoxide, the stereochemistry seems similar to that with hydrogen peroxide[614] whereas epoxidation with the hypochlorite ion is mostly stereospecific giving a high proportion of the retained epoxide[623,624]. In the two-step carbanionic mechanism, the ZO^- nucleophile approaches the enone **245** or **248** in a plane perpendicular to the molecular plane. The carbanion is therefore formed initially in a perpendicular conformation **246** or **249** where the 2p(C^-)-C-OZ hyperconjugation is maximal[625] (equation 105).



Usually, the stereochemistry of nucleophilic epoxidation is determined by the relative activation energies for rotation around the $C_{(3)}$-$C_{(2)}$ bond and for cyclization. The reaction is highly stereospecific if internal rotation in **246** or **249** (cf. k_{rot}) is significantly slower (i.e. the rotation barrier is high) than nucleophilic displacement of Z^- (cf. k_{cyc}, k'_{cyc}). A pair of *E* and *Z* enones should then give two different retained isomeric epoxides (i.e. **245** → **247**, **248** → **250**). However, if the rotation **246** ⇄ **249** is faster than ring closure and the **246** ⇄ **249** equilibrium is established before nucleofuge expulsion, then complete stereoconvergence (i.e. formation of identical **247**:**250** mixtures from either **245** or **248**) should be observed.

The rotation barriers **246** ⇄ **249** are determined by the hyperconjugating ability (HCA) of the C—OZ, C—R^3 and C—R^4 bonds, by the nature of COR^1 and R^2 and by the eclipsing steric interactions of the α- and β-substituents[625]. If steric effects are relatively small, then the stereochemistry of nucleophilic epoxidation can be explained by the following points:

(i) The higher the stereospecificity of epoxidation for a particular set of substituents R^1, R^2, R^3, R^4, the higher the HCA of the C—OZ bond. The dependence of stereospecificity on the nucleofuge decreases in the order $ClO^- > HOO^- \sim t\text{-}BuO^-$.

(ii) α-Substituents R^2 that stabilize the carbanion, reduce the rotation barrier in **246** or **249**, increase k_{rot}, and decrease the stereospecificity of epoxidation with a particular nucleophile.

(iii) The better the nucleofugality of *Z*, the higher is k_{cyc} and the higher is the stereospecificity. Both HCA (C—OZ) and the nucleofugality of Z are related to the electronegativity of Z and in most cases they change in a parallel fashion[625]. HO^- is a poor

nucleofuge as compared to Cl^-, $k_{rot} > k_{cyc}$ and the product ratio is determined exclusively by the relative energies of the transition states leading to the diastereomeric epoxides. Stereoselectivity but not stereospecificity is often observed[609,621]. If HCA(C—OOBu-*t*) ~ HCA(C—OOH), *t*-BuO^- is a poor nucleofuge as compared to HO^- due to electron donation by the alkyl group. Lower stereospecificity is therefore observed in epoxidation with *t*-$BuOO^-$ comparatively to HOO^-[614].

(iv) The degree of stereospecificity is in most cases nearly independent of the alkyl or aryl substituents R^3 and R^4 (except when they are very bulky) because HCA(C—OZ) ≫ HCA(C—R^3), HCA(C—R^4).

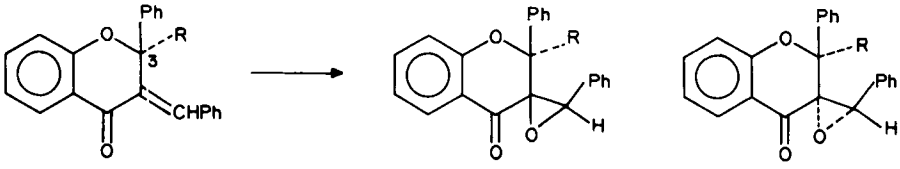
b. Stereochemistry of epoxidation of cyclic enones. The stereochemistry of epoxidation of cyclic enones has been extensively studied for the Weitz–Scheffer reaction. In the case of an enone with an exocyclic double bond, the stereochemistry is comparable to those of acyclic enones due to the possibility of rotation of the hydroperoxyalkyl side-chain in the intermediate carbanion. The hydroperoxy group is capable of fulfilling the stereoelectronic requirements for the maximum orbital overlap at both sides of the carbanionic sp^2 carbon. The stereochemistry is then dependent on the relative conformational stabilities of the two conformers of the carbanionic intermediate. A mixture of diastereomeric epoxides is obtained, the sterically more favoured and therefore the more stable isomer being dominant (Table 59)[626,627].

The exclusive formation of epoxide **252** from *cis* and *trans* enones **251** (equation 106)[628] and of the mixture of **254** and **255** from *cis* and *trans* **253** (equation 107)[629] with basic H_2O_2 agrees with the rule that the keto-epoxide with the least-hindered carbonyl group is preferentially obtained. When the interaction between the side-chain phenyl and the substituents on $C_{(3)}$ becomes too large (e.g. **256**) epoxidation is not observed.

(106)

cis and *trans*

(251) **(252)**



cis and *trans*

(253) R = H

(256) R = Ph

(254) R = H **(255)** R = H

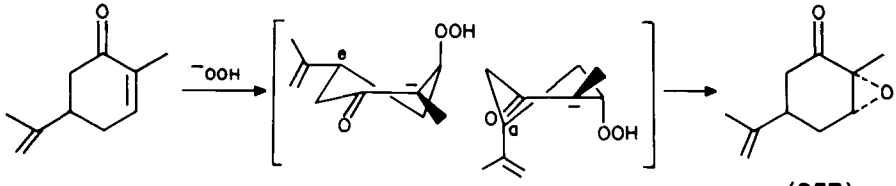
(107)

In the case of an enone with an endocyclic double bond, the alkaline H_2O_2 epoxidation can be entirely stereoselective. Thus, carvone gives only epoxide **257**[626] and 4-menthen-3-one gives only **258**[630] (equations 108 and 109). This is in accordance with the fact that the hydroperoxy group must be as close to axial as possible near the transition state for the cyclization step. Of the two axial conformations of the anions derived from carvone, the

TABLE 59. Stereochemistry of the Weitz–Scheffer reactions of cyclic enones[626,627]

Enone	Product isomers	*trans/cis* ratio
(+)-(1*R*)-Pulegone	(−)-(1*R*:4*R*)-*trans*	64.5
	(+)-(1*R*:4*S*)-*cis*	35.5
(+)-(1*S*:5*R*)-Pinocarvone	(−)-(1*R*:2*S*:5*R*)-*trans*	35.5
	(+)-(1*R*:2*R*:5*R*)-*cis*	64.5
(+)-(1*R*:2*S*)-isopropylidene camphor	(−)-(1*R*:3*S*:4*S*)-*trans*	67
	(+)-(1*R*:3*R*:4*S*)-*cis*	33

one with the equatorial isopropenyl group (leading to **257**) will be definitely more reactive than the one with the axial isopropenyl group[627].



(257)

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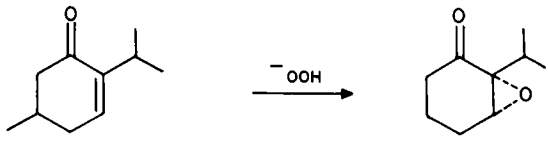

(258)

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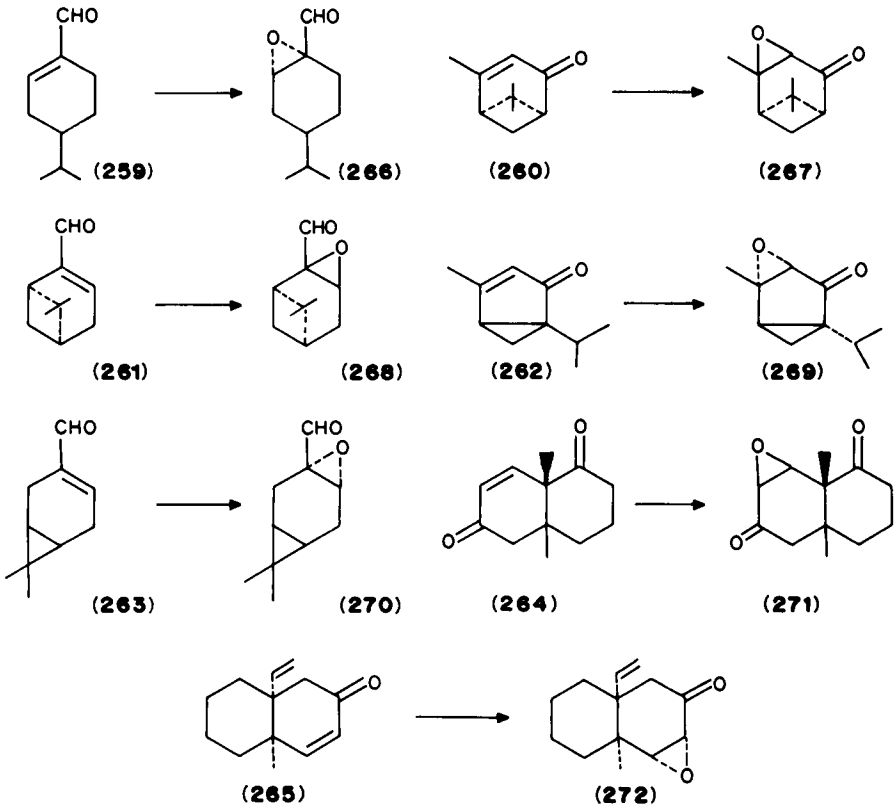
For the terpenic enals and enones **259**–**261**[626], **262**[631], **263**[632] and the decalones **264**[614], **265**[633], the exclusive formation of epoxides **266**–**272** can be explained by the theory of overlap control[627], as for carvone and 4-menthen-3-one (Scheme 4).

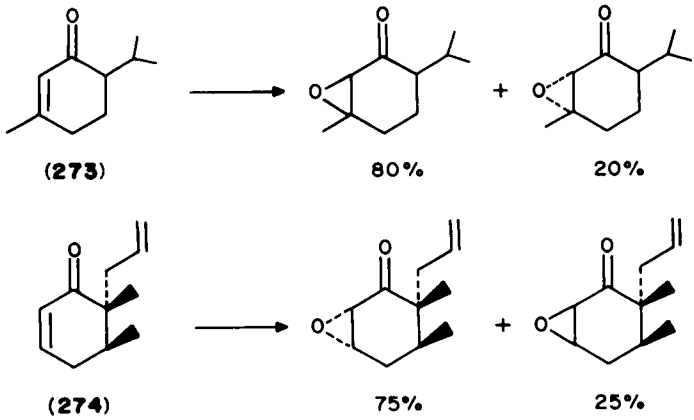
In the case of the epimerizable piperitone **273**[627] and 5,6,6-trisubstituted cyclohexenone **274**[634], a mixture of diastereomeric epoxides is obtained, but the product distributions are in agreement with the relative conformational stabilities of the intermediates (Scheme 5).

For the few cases studied, the stereochemistry of cyclic enone epoxidation with *t*-butyl hydroperoxide and with hydrogen peroxide are similar[614].

The stereochemistry of epoxidation with ZOH (Z = OH or *t*-BuO) in the steroid series has been explained in terms of the above mechanism for simple mono or bicyclic enones[609,612,635]. In some cases, the use of *t*-butyl hydroperoxide instead of hydrogen peroxide permits an increase of stereoselectivity, probably due to increase of the steric effect of Z[612], as exemplified in peroxide oxidation of 17-substituted Δ^4-3-ketosteroids **275** (equation 110) (Table 60).



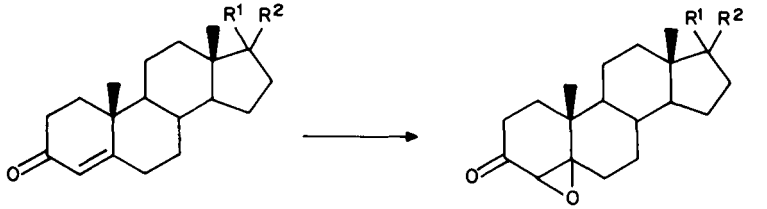
SCHEME 4



SCHEME 5

TABLE 60. Product distribution of peroxide oxidations of 17-substituted Δ^4-3-ketosteroids **275**[612]

275				Epoxides **276**	
R^1	R^2	Oxidant	Base	α	β
β-C_8H_{17}	α-H	H_2O_2	NaOH	1	5
		H_2O_2	LiOH	1	6
		t-BuO_2H	LiOH	β only	
β-$COCH_3$	α-H	H_2O_2	NaOH	1	2.5
		H_2O_2	LiOH	1	3
		t-BuO_2H	LiOH	β only	
β-OH	α-H	H_2O_2	NaOH	1	2.3
		t-BuO_2H	LiOH	β only	
=O		H_2O_2	NaOH	1	3
		t-BuO_2H	LiOH	β only	

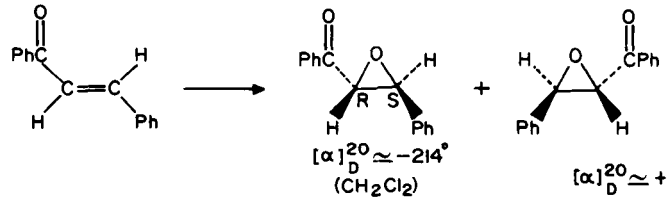


(110)

(275) α or β **(276)**

2. Catalytic asymmetric induction in nucleophilic epoxidation

In order to optimize the optical yields of enantioselective epoxidation of enones, several attempts have been carried out with *trans*-chalcone, principally by two groups: Wynberg and coworkers using phase-transfer conditions, and Julia, Colonna and coworkers using three-phase systems (equation 111).



(111)

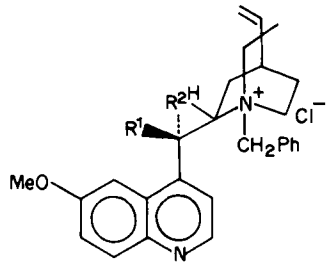
Owing to the many factors involved in the asymmetric epoxidation (structure and amount of the catalyst, solvent, temperature and nature of the oxidant), it is difficult to rationalize the occurrence of asymmetric induction. Nevertheless, some inferences can be made.

As exemplified by the Weitz–Scheffer reaction with hydrogen peroxide and the most efficient catalysts **277**–**283** (Table 61), appropriate poly-α-amino acids, such as poly(*S*)alanine **279** or poly(*S*)leucine **280** and poly(*S*)isoleucine **281**, lead to a high

TABLE 61. Enantioselective oxidation of *trans*-chalcone with alkaline H_2O_2 in toluene

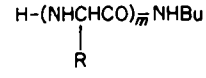
Catalyst	Yield (%)	$[\alpha]_D^{20}$ in CH_2Cl_2 (deg)	e.e. (%)	Ref.
277	99	−51	24	636,637
278	—	+49	23	636,637
279 $m = 10$ (L)	75	−199.5	93	638,639
279 $m = 10$ (D)	53	+193.5	90	638,639
279 $m = 30$ (L)	77	−205.4	96	638,639
280 $m = 10$ (L)	60	−182.2	84	638,639
280 $m = 30$ (L)	44	−189.8	88	638,639
281 $m = 10$ (L)	76	−204.5	95	638,639
282	69	−79	37	640
283	81	+4	2	640

stereospecificity. Other polypeptides such as poly(*S*)valine, polyglutamate or polyaspartate lead to lower chemical and optical yields[639,641].



(**277**) $R^1 = OH$, $R^2 = H$

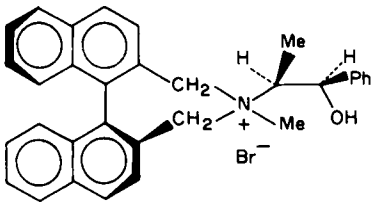
(**278**) $R^1 = H$, $R^2 = OH$



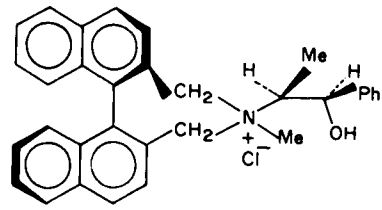
(**279**) R = Me

(**280**) $R = CH_2CHMe_2$

(**281**) $R = CHMeCH_2Me$



(**282**) (1*R*,2*S*,*S*)



(**283**) (1*R*,2*S*,*R*)

The opposite specific rotations of epoxychalcone obtained from the two antipodes (L and D) of **279** are easily comprehensive. By contrast, results obtained from the diastereomeric quininium and quinidinium benzyl chlorides (**277** and **278**), and the ephedrinium salts **282** and **283** are unaccountable.

Other catalysts such as quininium salts anchored to a polystyrene matrix in toluene[642], α and β cyclodextrins[643,644] or bovine serum albumin (BSA)[645] have been tested with alkaline hydrogen peroxide. They give poor chemical yield and enantiomeric excess. In the

TABLE 62. Effect of the oxidants on the asymmetric induction in chalcone epoxidation

Oxidant	Catalyst	Solvent	$[\alpha]_D^{20}$ in CH_2Cl_2 (deg)	e.e. (%)	Ref.
30% H_2O_2/NaOH	**277**	PhMe	−51	24	636
85% *t*-BuO_2H/NaOH	**277**	PhMe	+24	14	636
28% NaOCl	**277**	PhMe	+53	25	646
30% H_2O_2/NaOH	**279** $m = 10$ (L)	PhMe	−199.5	93	638,639
80% *t*-BuO_2H/NaOH	**279** $m = 10$ (L)	PhMe	+38.5	18	647
30% H_2O_2/NaOH	BSA[a]	H_2O, pH 11	−25.5	12	645
80% *t*-BuO_2H/NaOH	BSA[a]	H_2O, pH 11	+27	13	645

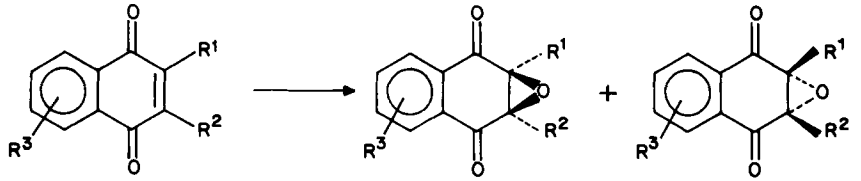
[a]BSA = Bovin Serum Albumin.

case of cyclodextrins, the use of sodium hypochlorite instead of hydrogen peroxide leads to 10% enantiomeric excess (e.e.) of epoxychalcone (0% e.e. with H_2O_2). This result can be explained through the initial formation of cyclodextrin hypochlorite[643].

With the catalysts for which the three usual oxidative reagents (hydrogen peroxide, *t*-butyl hydroperoxide, sodium hypochlorite) lead to an optical activity of epoxide mixture, optical activity is very dependent on the oxidant (Table 62).

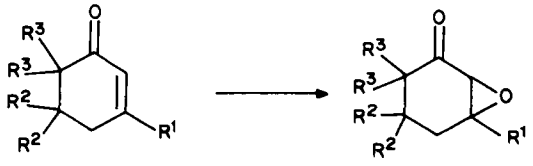
The degree of asymmetric induction in epoxidation of chalcone or substituted chalcones is influenced by the solvent. Toluene or carbon tetrachloride seems to be the solvents of choice when quininium benzyl chloride or poly-α-amino acids are used as catalysts[638,647,648]. However, no direct correlation exists between the classical solvent parameters such as the dielectric constant, and the enantiomeric excess[647,649].

The enantioselectivity is also very sensitive to minor structural variation in the substrates, as exemplified (i) by the reactions of mono or disubstituted 1, 4-naphthoquinones **284** in the presence of BSA[639,645] or quininium benzyl chloride[636,637,650–652] (equation 112) (Table 63), and (ii) by the epoxidation reaction of substituted cyclohexenones **285**[636,639,653] (equation 113) (Table 64).



(**284**) (+)(2*S*,3*R*) (**286**) (−)(2*R*,3*S*) (**287**)

(112)



(**285**) (**288**)

(113)

TABLE 63. Substituent effects on enantioselective epoxidation of mono and disubstituted 1,4-naphthoquinones **284**[a]

284						
R^1	R^2	R^3	Oxidizing agent	Catalyst	[α]	e.e. (%)
Me	H	H	H_2O_2	BSA	(+)	3
			H_2O_2	**277**	(−)	9
			t-BuO_2H	BSA	(−)	20
			t-BuO_2H	**277**	(−)	6
Et	H	H	H_2O_2	BSA	(+)	15
			H_2O_2	**277**	(−)	10
			t-BuO_2H	BSA	(+)	5
i-Pr	H	H	H_2O_2	BSA	(+)	15
			H_2O_2	**277**	(−)	31
			t-BuO_2H	BSA	(+)	21
i-Bu	H	H	H_2O_2	BSA	(+)	8
			H_2O_2	**277**	(−)	16
			t-BuO_2H	BSA	(−)	77
t-Bu	H	H	H_2O_2	BSA		0
			H_2O_2	**277**	(+)	23
			t-BuO_2H	BSA		0
Ph	H	H	H_2O_2	BSA	(−)	~0
			H_2O_2	**277**	(−)	45
			t-BuO_2H	BSA	(−)	50
			t-BuO_2H	**277**	(+)	78
4-$MeO_2CC_6H_4$	H	H	*t*-BuO_2H	**277**	(+)	78
CH_2Ph	H	H	H_2O_2	BSA	(−)	15
			H_2O_2	**277**	(−)	23
			t-BuO_2H	BSA	(−)	12
n-Hex	H	H	H_2O_2	BSA	(+)	2
			H_2O_2	**277**	(+)	39
			t-BuO_2H	BSA	(−)	70
Me	Et	H	H_2O_2	BSA	(−)	11
			H_2O_2	**277**		0
			t-BuO_2H	BSA	(−)	54
Me	*n*-Bu	H	H_2O_2	BSA		0
			H_2O_2	**277**	(−)	~0
			t-BuO_2H	BSA	(−)	48
Me	H	5-Me	H_2O_2	**277**	(−)	18
Me	H	5-OMe	H_2O_2	**277**	(+)	12

[a]Reactions with Bovin Serum Albumine (BSA) are performed in pH 11 buffer solution and those with **277** under phase-transfer conditions with toluene.

TABLE 64. Substituent effects on enantioselective epoxidation of substituted cyclohexenones **285**

Cyclohexenone			Oxidizing		Chemical	$[\alpha]^{RT}$	e.e.	
R^1	R^2	R^3	agent	Catalyst	yield (%)	in CH_2Cl_2	(%)	Ref.
H	H	H	H_2O_2	**279** $m = 10$	100	0	0	639
H	H	H	t-BuO_2H	**277**	54	−39	20	653
H	Me	H	t-BuO_2H	**277**	59	+9	16	653
Me	Me	H	NaOCl	**277**	23	−4	—	636
H	H	Me	t-BuO_2H	**277**	60	−15	15	653

3. *Epoxidation by electrogenerated superoxide*

Excellent yields of the epoxides of enones are obtained by treating the enones contained in the cathode chamber of an electrochemical cell with *in situ* electrogenerated superoxide in the presence of an auxiliary carbon acid, such as diphenylacetonitrile or diethyl methylmalonate (the nucleophilic species are $Ph_2C(CN)OO^-$ and $MeC(CO_2Et)_2OO^-$)[654] (Table 65).

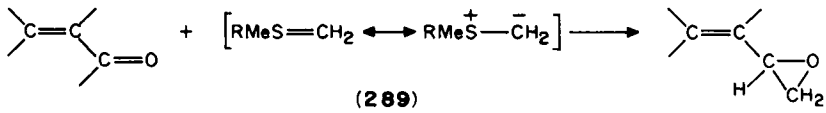
TABLE 65. Epoxidation of α-enones with electrogenerated superoxide and carbon acids[654]

Enone (5 mmol)	Carbon acid (mmol)		Faradays/ mol of enone	Yield of epoxide (%)	Recovered enone (%)
2-Cyclohexen-1-one	Ph_2CHCN	(5)	0.90	67	18
	Ph_2CHCN	(10)	1.80	89	trace
4,4-Dimethyl-2-cyclohexen-1-one	Ph_2CHCN	(10)	1.80	trace	85
	Ph_2CHCN	(10)	0.45	31	59
	$MeCH(CO_2Et)_2$	(20)	0.88	56	38
	$MeCH(CO_2Et)_2$	(40)	1.80	90	trace
4,4,6,6-Tetramethyl-2-cyclohexen-1-one	Ph_2CHCN	(10)	1.80	0	85
Mesityl oxide	Ph_2CHCN	(5)	0.90	15	64
	Ph_2CHCN	(10)	1.90	42	35
	Ph_2CHCN	(20)	3.70	85	trace
Chalcone	Ph_2CHCN	(5)	0.70	23	65
	Ph_2CHCN	(10)	1.60	42	39
	Ph_2CHCN	(20)	3.20	84	trace

B. Formation of Epoxides from the Carbon–Oxygen Double Bond

The carbonyl group of unsaturated aldehydes and ketones is converted into the unsaturated oxirane in good yields by methylene insertion with sulphur ylides **289**, generated from alkyl dimethylsulphonium salts such as trimethylsulphonium halides[655,656], dodecyl dimethylsulphonium chloride or dodecyl dimethylsulphonium methyl sulphate and base[657] (equation 114).

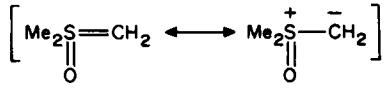
For enones containing other base-sensitive groups, the original conditions developed by Corey and Chaykovsky[655], using dimethyl sulphonium methylide (R = Me) prepared



(289) (114)

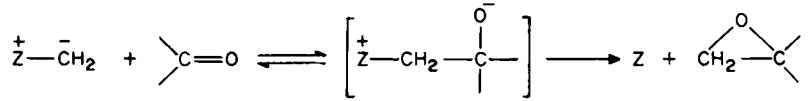
from trimethylsulphonium iodide and sodium hydride in dry dimethyl sulphoxide, are preferred. Thus, several compounds were converted to the corresponding oxiranes by selective addition of methylene to the carbonyl group, for instance benzalacetophenone (87% yield), carvone (89%), eucarvone (93%), pulegone (90%)[655], 2,5,6-trimethyl-2-cyclohexen-1-one (79%)[656], β-ionone (94%) and 3,7-dimethyl-2,6-octadienal (79%)[657]. Phase-transfer conditions using trimethylsulphonium chloride or fluoride, or dodecyldimethyl sulphonium salts (chloride or methyl sulphate), are more convenient when the substrates and products are base stable[657].

It is noteworthy that saturated ketones give oxirane formation with dimethyl oxosulphonium methylide **290**, whereas α,β-unsaturated ketones give only cyclopropanes (see Section VIII).

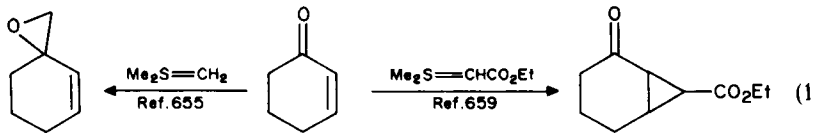


(290)

The stereochemical difference in the behaviour of **289** and **290** is attributed to formation of the betaine **291** (equation 115), being reversible for $Z = Me_2S{=}O$ but not for the less stable alkyldimethyl sulphonium methylide, so that the more hindered product is the result of kinetic control and the less hindered product results from thermodynamic control[658]. The stability of the sulphur ylide is an important factor in formation of the vinyl oxirane from enones. Substitution of a carboethoxy group on the methylene of dimethylsulphonium methylide dramatically increases ylide stability; consequently reversion of any kinetically favoured betaine to ylide and substrate is enhanced and cyclopropanation is observed (equation 116). As for the oxosulphonium ylides, the carbonyl stabilized ylide is a better 'leaving group'[658].



(289) Z = RMeS
(290) Z = $Me_2S{=}O$
(291) (115)

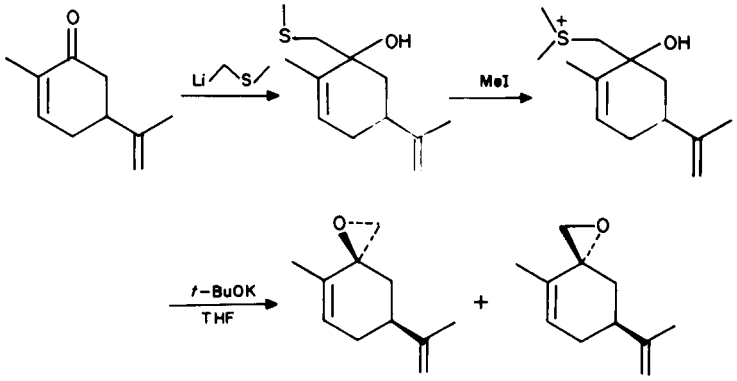


(116)

In the same way as for dimethylsulphonium methylide epoxidation, the oxirane formation is performed from an unstabilized arsonium ylide. The reaction can be highly

stereoselective; for instance, with 2-butenal and triphenylarsonium *n*-butylide, the *E* epoxide is obtained in 75% yield[660].

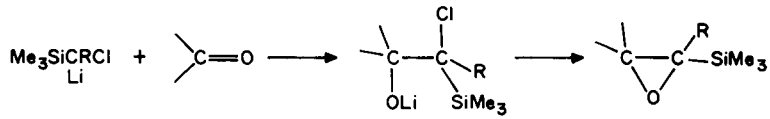
An alternative to the sulphur ylide route for the vinyl spiro epoxide formation from cyclenones, using sulphur compounds as starting materials, is the addition of [(methylthio)methyl] lithium on the carbonyl group, followed by methylation and closure of the hydroxysulphonium salt. Using this method, 2-methyl-2-cyclopenten-1-one, 2-cyclohexen-1-one and piperiton **273** might give single spiro epoxides in excellent yields (80–90%). Carvone gives a mixture of epoxides in 92% yield (equation 117)[661].



(117)

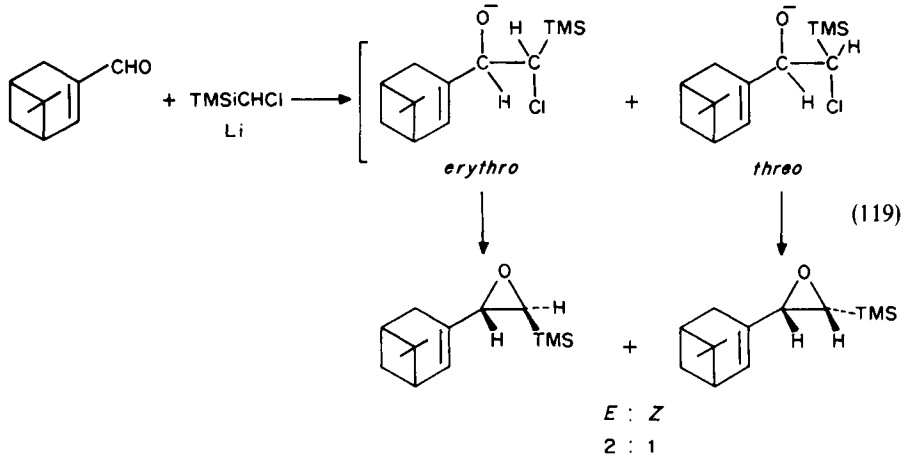
The Darzens reaction[609], i.e. the base-induced addition of a compound of type X-CHR-Y bearing halogen X and an electron-withdrawing substituent Y on the same carbon atom, to a carbonyl group, can be applied to enones to obtain α-functionalized vinyl oxiranes[609,662,663]. Taking into account the ambident electrophilic nature of α-enones, the choice of reagent is as important as that of the sulphur ylide. When the carbanion XC^-RY is pyramidal (hard), the 1,2-addition is preferred and the oxirane is obtained, whereas an inverted regioselectivity is observed with delocalized negative-charge carbanions leading to 1,4-addition and cyclopropanation. 4-phenyl-3-buten-2-one reacts with the anions derived from methyl chloroacetate and chloroacetonitrile (which are of the charge localized type, 'hard') at the carbonyl group to give equal amounts of the corresponding *Z* and *E* oxiranes. The same ketone reacts with the anions derived from methyl phenylchloroacetate and phenylchloroacetonitrile (the negative charge of which is delocalized) to give cyclopropanes by attack at the carbon–carbon double bond[20,664].

Another alternative to the Darzens reaction is the addition of reagents of the form **292** to aldehydes or ketones (equation 118)[665]. The product **293** is an α,β-epoxysilane which is a masked carbonyl group. 2-cyclohexen-1-one, carvone and myrtenal lead to the corresponding unsaturated oxiranes in 52, 76 and 95% yield, respectively. When the α,β-epoxytrimethylsilanes are formed as epimers at the carbon bearing the trimethylsilyl group (TMS), the epimer having the TMS group in the least sterically encumbered environment is predominant (equation 119)[666].



(292) (293)

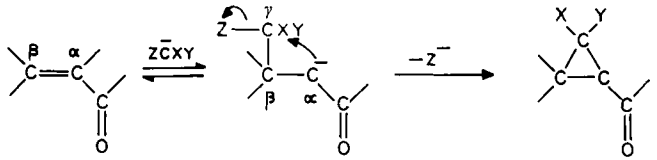
(118)



(119)

VIII. NUCLEOPHILIC CYCLOPROPANATION

Nucleophilic cyclopropanation of the carbon–carbon double bond of α-enones closely parallels nucleophilic epoxidation both in the mechanism and the reagent of type ZC^-XY, where Z is a nucleofuge. It is established that cyclopropanation proceeds via the carbanion **294**, which cyclizes to **295** by an internal S_N2 reaction with expulsion of Z, which may be a neutral leaving group when the nucleophile is an ylide, or a halogen (equation 120)[20,625].

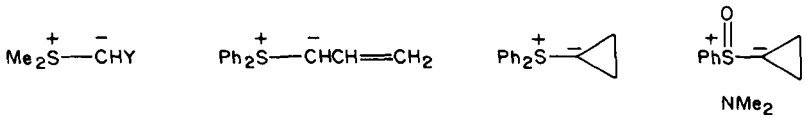


(294) (295)

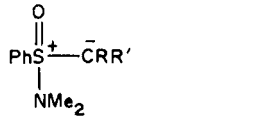
(120)

A more common nucleophilic cyclopropanation involves nucleophilic ylides, especially sulphur ylides, where intermediate **294** is a zwitterion and the nucleofuge is neutral[658]. Of the sulphonium ylides which permit methylene insertion on the ethylenic double bond of α-enones, dimethyloxosulphonium methylide **290** is the most useful[655,667]. It presents a convenient balance between reactivity and stability. Furthermore, the precursor, trimethyloxosulphonium iodide, is easily available by the S methylation of dimethyl sulphoxide. Unfortunately, S-alkylation of sulphoxides is not a general reaction, and with trivial exceptions[668] it is not possible to obtain salts in the trialkyloxosulphonium series. This limits the ylides in the series to methylide, and other sulphur ylides, e.g. **296** (Y = acyl[669–671], carboethoxy[659]), **297**[672] and **298**[673], which transfer CHY, CH-vinyl and cyclopropylidene, respectively, have also been used. CHR and CRR′ can be added in a similar manner with certain nitrogen-containing compounds[674]. For example, the ylides **299**[675], **300**[676], **301**[677] and **302**[678], and the carbanions **303** and **304**[675], have been used.

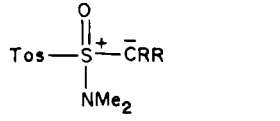
Similar reactions have been performed with nitrogen ylides such as cyanotrimethylammonium methylide[679] and substituted pyridinium phenacylides[680]. Many substituted cyclopropanes can also be made by treatment of α-enones with ZC^-XY in which Z is Cl or



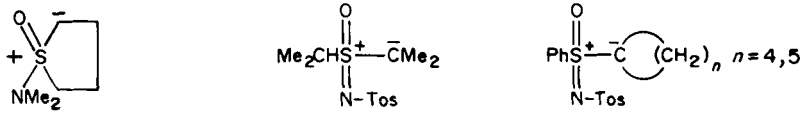
(296) (297) (298) (299)



(300) R = H, R' = Me; R = R' = Me

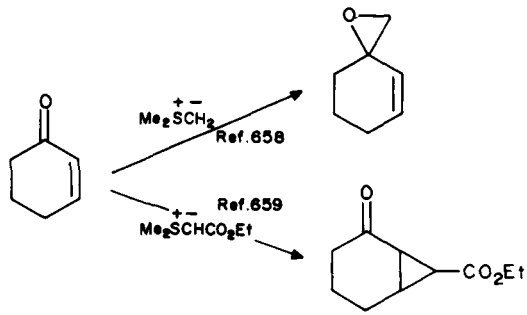


(301) R = H, R' = Me; R = R' = Me

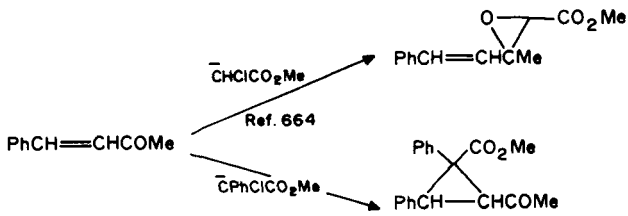


(302) (303) (304)

Br, X = Ph, Cl or CO_2R and Y = CO_2R, CN or COR[20,681-684]. As for sulphonium methylide[658], the stability of the ZC^-XY carbanion is very important for cyclopropanation. When X = H or alkyl, cyclopropane formation by a Michael-type addition competes with oxirane formation by 1,2-addition, since the charge-localized pyramidal carbanion (hard) ZC^-H(or alkyl)Y preferentially attacks the carbonyl group (equations 121 and 122).



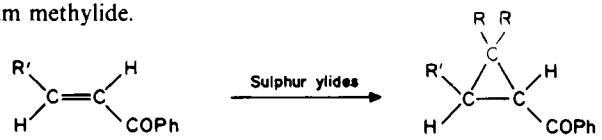
(121)



(122)

The stereochemistry of cyclopropanation with the reagents cited above is illustrated by three cases:

(*i*) *A CH_2 or CR_2 insertion into acyclic enones.* This is the case of sulphur ylides, in which intermediate **294** is a zwitterion. In most cases, a single isomeric precursor (e.g. *trans*-chalcone **8**, or *trans*-1,4-diphenyl-2-butene-1,4-dione (**305**) gives a single cyclopropane in an apparent stereoselective reaction (**8** → **306**, **305** → **307**) (equation 123)[668,673,675-677,685,686]. In contrast to these studies, Corey and Chaykovsky[655] observed a *cis–trans* mixture of cyclopropanes from *trans*-chalcone and dimethyloxosulphonium methylide.



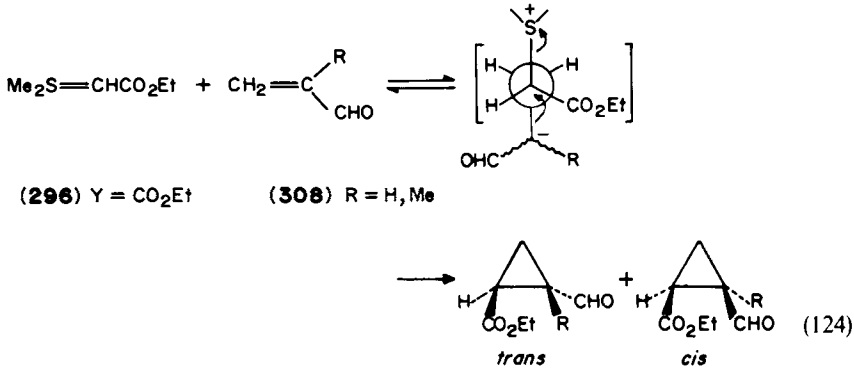
(123)

(**8**) R′ = Ph
(**305**) R′ = COPh

(**306**) R′ = Ph
(**307**) R′ = COPh

In fact, there are not sufficient data to distinguish between stereospecific and stereoselective behaviour. Computation results using the hyperconjugating ability (HCA) concept show that cyclopropanation with sulphur ylides may exhibit stereospecificity. However, this prediction is expected *a priori* to be less reliable than prediction for epoxidations of the ethylenic double bond of enones. This is because the computational experience with zwitterions is very limited, and because the extrapolation of the gas-phase results to solution is less reliable, since solvation is probably more important for zwitterions than for carbanions[625].

(*ii*) *β-Unsubstituted unsaturated aldehydes or ketones, $CH_2{=}CR^2COR^1$; sulphur ylides $\geq S{=}CR^3R^4$ and halogenocarbanions ZC^-XY.* The stereochemistry of the cyclopropane formed reflects both steric and electronic substituent factors and solvent effects. With sulphur ylides, this can be exemplified with acrolein **308** (R = H) and methacrolein **308** (R = Me) as substrates and **296** (Y = ethoxycarbonyl) as reagent (equation 124, Table 66).



(**296**) Y = CO_2Et (**308**) R = H, Me

(**309**) R = H, Me

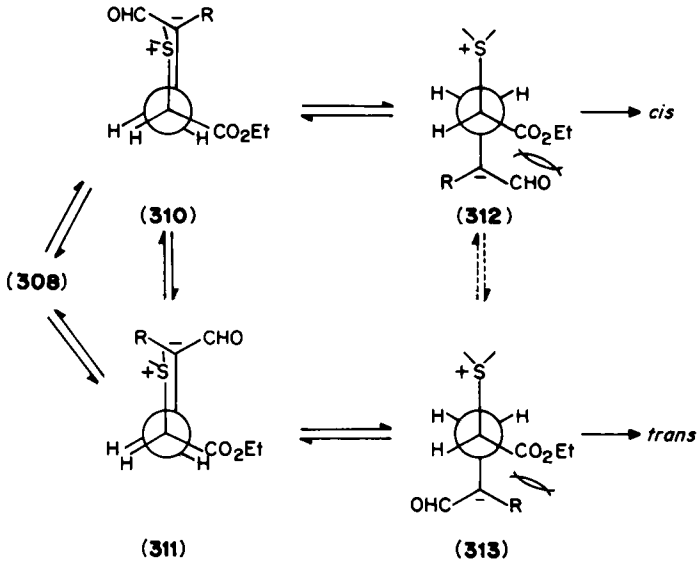
(124)

In all cases, predominant *trans* cyclopropanation to give **309** was observed. Electrosta-

TABLE 66. Stereochemistry of cyclopropanation of **308** by ethyl (dimethysulphuranylidene) acetate

R in **308**	Solvent	Product distribution		Ref.
		cis	*trans*	
H	PhH	8.5	91.5	671
H	Me_2CO	17	83	659
Me	PhH	32	68	671
Me	Me_2CO	45	55	659

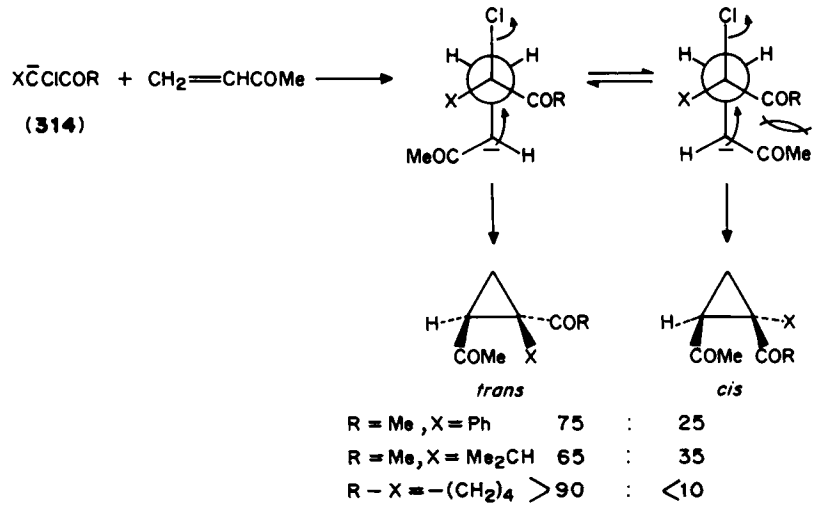
tic interactions favour initial formation of the eclipsed betaines **310** and **311** (equation 125)[550,625].



(125)

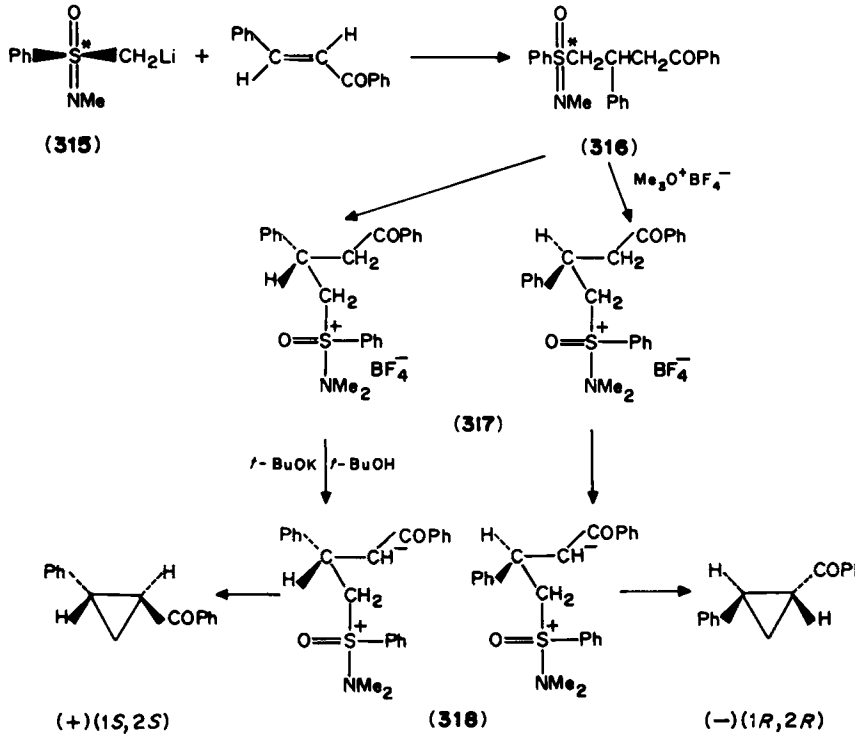
Subsequent collapse to cyclopropanes *via anti* conformers **312** and **313** is retarded in solvents of low dielectric constant such as benzene, that are less capable of solvating the proposed internal ion-pair. These solvents promote the equilibration of **310** and **311**, resulting in preferential formation of the favoured *trans* product. In solvents of higher dielectric constant such as acetone, the rate of cyclopropane formation increases. The betaine equilibration is precluded and increasing proportion of *cis* cyclopropane is formed. Comparatively to acrolein, the *trans* stereoselectivity of methacrolein decreases, due to the competitive steric interactions between the methyl and aldehyde groups and the ethoxycarbonyl group in **312** and **313**[671].

This interpretation also accounts for the stereoselectivity of cyclopropanations using carbanions ZC^-XY, as exemplified by the reaction of methyl vinyl ketone and carbanion **314** derived from α-chloroketones with NaH in benzene/HMPA (equation 126)[684].



(126)

When acyclic enones are β-substituted (e.g. chalcone), the stereochemistry of cyclopropanation with both ylides and carbanions is difficult to explain due to the presence of several factors[20,669,672,679].



(127)

(iii) A CH_2 or CR_2 insertion into substituted cyclic enones. Few data are available for discussing the stereochemistry of cyclopropanation[655,673,686,687]. With carvone, a single isomer is obtained with dimethyloxosulphonium methylide[655], whereas *cis* and *trans* (40:60) isomers are observed with pulegone and (diethylamino)methyloxosulphonium methylide[686].

Some attempts to synthesize optically active cyclopropanes have been made by Johnson and coworkers with *trans*-chalcone and *trans*-1,4-diphenyl-2-buten-1,4-dione and chiral oxosulphonium methylides derived from sulphoximines salts. Usually the optical purities are low[676,677]. In contrast, the two pure enantiomers of *trans*-1-benzoyl-2-phenylcyclopropane are obtained by a conjugate addition of the lithium anion of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulphoximine **315** to *trans*-chalcone. After separation, the two diastereomeric adducts **316** are methylated with trimethyloxonium fluoroborate, and the betaines **318**, generated by treatment of **317** with potassium *t*-butoxide-*t*-butyl alcohol, collapse to give the optically pure cyclopropanes (equation 127)[688].

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