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ADDITION REACTIONS OF KETENES

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CONTENTS

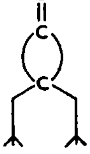
1. KETENES AS REACTIVE INTERMEDIATES

1.1. *Introduction*

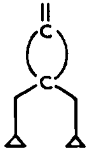
Ketenes are structurally interesting organic functional groups and over the years have been the subject of intensive study that has been frequently reviewed.[1–6a,b] Cycloaddition reactions of ketenes have been the object of particularly great attention in recent years.

Other types of ketene reactivity have also been of interest, but these reports are more scattered, although the mechanisms have been reviewed.[5,6b] One report from 20 years ago is reprinted below.[7]

> ### AMINAL-LOVERS PLEASE NOTE
>
> SIR,—Chemical nature-lovers will have been excited to find the recent reference to ketene 'animals' (*Chem. Abstr.* **62**, 1561d (1965)).
>
> We were sure that this rare species, which includes the Ket-6-ped-ene (I) and the Lesser Web-footed Ketene (II), was extinct.



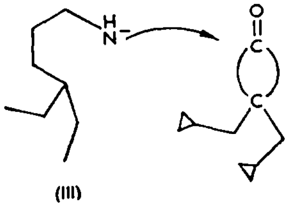
(I)



(II)

Having no arms, these creatures have limited stability and fall easy prey to their natural enemies, the Greater Hump-backed Nucleophiles.

A possible mode of attack of one of these voracious nucleophiles, *Aminus improbabilis* (III), is illustrated below.



(III)

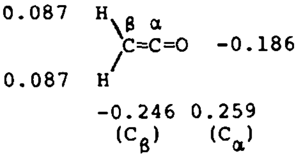
There has recently been great activity in the study of addition reactions of ketenes other than cycloadditions that has included both the synthetic and mechanistic aspects of these processes. A rich and diverse chemistry is being uncovered, and in our opinion only a bare beginning has been made. It appears to be an opportune moment to critically examine the progress in the study of ketene additions besides cycloadditions, with particular emphasis on the most recent and important developments.

After an introductory section addition reactions are considered in separate sections on radical, electrophilic, and nucleophilic additions. These mechanism-based categories are somewhat arbitrary, as it is not certain in many cases whether electrophilic or nucleophilic attack has precedence, or indeed whether a cycloaddition path, formally outside the purview of this report, may be involved. The topics have been placed using the often scanty evidence at hand, with sometimes only weak analogy as a guide. The division into mechanistic types permits the mechanistic and synthetic aspects to be discussed together to give a unified understanding of ketene chemistry, and the previous interpretations in the literature are critically examined.

The addition mechanisms of water, alcohols, thiols, phenols, carboxylic acids, and amines to ketenes were reviewed by Satchell and Satchell in 1975.[6b] Much of the work considered was done in one of the author's laboratories, and concentrated on reactions in non-hydroxylic solvents. The conclusions emphasized the existence of both nucleophilic and electrophilic routes to addition, and the role of the ketene substituents in influencing the pathway followed, and also argued for the frequent intervention of concerted additions through cyclic transition states. More recent work reviewed herein reinforces the former concepts, but in the current reviewers' opinions the arguments for concerted additions are not convincing, and such mechanisms should not be regarded as established, even in non-hydroxylic solvents.

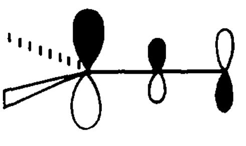
1.2. *Theoretical studies of ketene structure*

There has been a large number of theoretical studies of ketene (1) in recent years.[8–18] The net charges on the atoms in a recent study using STO-3G optimized geometries are shown.[18]

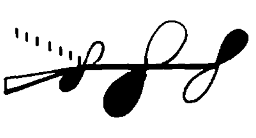


1

The position of attack by various reagents on ketenes will be determined by the energies of the different transition states for addition, but the charge distributions shown are at least indicative that the oxygen and C_β are susceptible to attack by electrophiles, while nucleophiles will be attracted to C_α just as in the case of more typical carbonyl groups. The ketene HOMO and LUMO[11] (**2a** and **2b**, respectively) further suggest that electrophilic attack will occur from above the plane of the ketene skeleton, while nucleophilic attack will occur in the plane.



2a



2b

Table 1. ^{13}C-NMR chemical shifts of ketenes $R^1R^2C{=}C{=}O$[a]

No.	R^1	R^2	C_α	C_β	No.	R^1	R^2	C_α	C_β
1[b]	H	H	194.0	2.5	**11**	Me_3Si	Me_3Si	166.8	1.7
3[b]	Me	H	200.0	10.9	**12**	Me_3Ge	H	179.4	−4.8
4[b]	Et	H	200.0	18.6	**13**	Et_3Ge	Me_3Ge	167.0	0.0
5[b]	Et	Me	206.1	26.9	**14**	Et_3Ge	Et_3Ge	165.7	−8.5
6[b]	Ph	Me	205.6	33.8	**15**	Me_3Sn	Me_3Sn	161.7	−13.9
7[b]	Ph	Et	205.6	42.1	**16**	Et_3Sn	Et_3Sn	161.3	−20.5
8[c]	Ph	Ph	201.2	47.6	**17**	Me_3Si	Me_3Ge	166.2	0.5
9	Me_3Si	H	179.2	−0.1	**18**	Me_3Si	Me_3Sn	164.4	−5.8
10	Et_3Si	H	179.2	−4.9	**19**	Me_3Ge	Me_3Sn	164.6	−6.3

[a] ppm downfield from TMS, Ref. 20 unless noted.
[b] Ref. 19.
[c] Ref. 19 reports 201.3 and 47.0, respectively.

The electronic structures of substituted ketenes have received much less theoretical attention. However, it may be anticipated that substituents at C_β can have significant effects as charge or spin density develops at this atom, or if rehybridization occurs due to attack on this atom. Steric effects of substituents at C_β will in general be larger for reactions at the LUMO **2b**, in the plane of substituents.

The presence of adjacent nucleophilic and electrophilic carbons, further subject to modification by substituents, immediately suggests that ketenes will be unusual alkenes that are reactive to both electrophiles and nucleophiles and that with a reagent consisting of electrophilic and nucleophilic halves that the initial mode of reaction may be ambiguous without detailed study.

1.3. *NMR spectra of ketenes*

The ^{13}C-NMR chemical shifts of ketenes are expected to provide at least an indication of charge densities on the carbons, and therefore a clue as to potential reactivity. Some reported values are given in Table 1.[19,20]

The chemical shifts for **1** are consistent with the calculated atomic charges noted previously.[16] Thus the low field values for C_α are typical for carbonyl groups, but the values for C_β are at very high fields compared to ordinary alkenes, which are typically in the range 100–150 ppm.

2. RADICAL ADDITIONS TO KETENES

Hydrogen atom addition to ketene (**1**) in the gas phase results in formation of methyl radical and carbon monoxide.[21–23] Initial attack on C_β to give **20** followed by fragmentation appears to be the most likely pathway for this reaction (Eq. 1), and it was suggested that if **21** is formed by attack on C_α, then it isomerizes prior to **20** dissociation (Eq. 2).[21] Ketenes **3** and **4** evidently react similarly.[22]

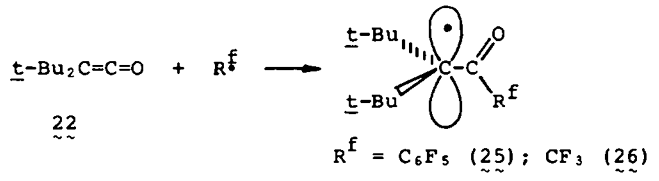
$$\underset{\mathbf{1}}{CH_2{=}C{=}O} \xrightarrow{H^\cdot} \underset{\mathbf{20}}{[CH_3\dot{C}{=}O]} \longrightarrow \dot{C}H_3 + CO \qquad (1)$$

$$\mathbf{1} \xrightarrow{H^\cdot} \underset{\mathbf{21}}{[CH_2{=}CH{-}\dot{O}]} \longrightarrow \mathbf{20} \qquad (2)$$

The addition of hydrogen atoms to di-t-butylketene (**22**) to give the radicals **23** and **24**, observable by ESR, was effected by photolysis of **22** in the presence of HI and hexamethylditin in cyclopentane solution (Eq. 3).[24]

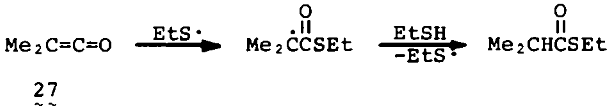
$$\underset{\mathbf{22}}{t\text{-}Bu_2C{=}C{=}O} \xrightarrow[Me_6Sn_2]{HI,\,h\nu} \underset{\mathbf{23}}{t\text{-}Bu_2CH\dot{C}{=}O} + \underset{\mathbf{24}}{t\text{-}Bu_2\dot{C}{-}CH{=}O} \qquad (3)$$

The reaction of **22** with C_6F_5 or CF_3 gave radicals **25** and **26**, respectively (Eq. 4).[24] These radicals were assigned the perpendicular conformation shown based on their ESR spectra;[24] previous alkanoxylalkyl radicals had planar conformations, but the steric bulk of the t-butyl groups evidently forced the conformations **25** and **26**.



(4)

Thiols add to ketenes to give thio esters, and kinetic studies of the reaction of dimethylketene (**27**) and ethanethiol revealed the rates to be highly irreproducible, and while the rates were apparently not affected by irradiation at 312.5 and 577 nm there was an evident acceleration by the free-radical initiator diisopropyl peroxydicarbonate.[25] The chain-reaction mechanism shown in Eq. (5) was proposed for this reaction and is consistent with the radical attack on C_α shown in Eq. (4).



$$Me_2C{=}C{=}O \xrightarrow{EtS\cdot} Me_2\dot{C}\overset{O}{\overset{\|}{C}}SEt \xrightarrow[-EtS\cdot]{EtSH} Me_2CH\overset{O}{\overset{\|}{C}}SEt \quad (5)$$

27

3. ELECTROPHILIC ADDITION

3.1. *Proton additions to ketenes*

Acylium ions **28** are long-lived species that can be directly observed by NMR in non-nucleophilic media. These species may be generated from acid anhydrides[26] and evidently ketenes as well (Eq. 6), although specific experimental details were not given for the latter reaction.[26] If ketene reactions ever produce ions from protonation at C_α or on oxygen these products are evidently unstable relative to **28**.

$$R^1R^2C{=}C{=}O \xrightarrow{H^+} R^1R^2CH\overset{+}{C}{=}O \quad (6)$$

28

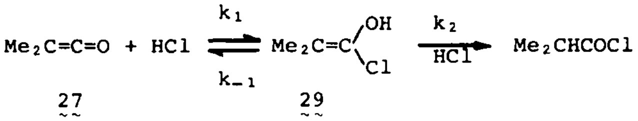
The gas phase protonation of ketene (**1**) and methylketene (**3**) has been the object of intense study, with a particular interest in the proton affinity (PA) of the ketenes.[27–37] However, the derived proton affinities are usually derived with reference to the PA of isobutene, and because of uncertainties in this latter value it has been argued that these values are not absolute.[34] However, the relative PA values of 196.2 and 202.2 kcal mol^{-1} for **1**[29] and **3**,[32] determined in the same laboratory with the same reference, are evidently reliable, and are in good agreement with the value of 197.5 kcal mol^{-1} for **1** derived without reference to isobutene.[34] The greater PA of **3** is expected because of the greater stability of the product ion.

In general the protonation of ketenes in solution or the gas phase occurred on C_β to give acylium ions (Eq. 6), but when stronger acids ($C_2D_5^+$ or CD_5^+) were reacted with **1** formation of $CH_2{=}C{=}\overset{+}{O}D$ evidently occurred, and it was argued that C_β of **1** was more basic than oxygen by 18 ± 8 kcal mol^{-1}.[28]

Theoretical studies of protonated ketene have also appeared,[9,13,35,36] and these indicate that **28** ($R^1, R^2 = H$) is more stable than the products of protonation on oxygen or C_α by 43 and 79 kcal mol^{-1}, respectively.[35]

3.2. *Hydrogen halide additions to ketenes*

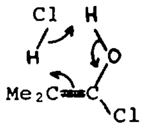
Hydrogen chloride and hydrogen bromide add to ketenes to give the corresponding acyl halides. The kinetics of the addition of these acids to dimethylketene (**27**) in ether at −20° have been measured,[38] as well as the reaction of diphenylketene (**8**) with HBr at 25°.[39] The reaction of **27** was first-order in HCl, except that below 10^{-2} M HCl with **27** some upward curvature from a linear dependence on [HCl] was noted which was ascribed to a higher order reaction in HCl.[38] The rates were fitted to a steady-state treatment of the mechanism in Eq. (7).[38]



$$Me_2C{=}C{=}O + HCl \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Me_2C{=}C(OH)Cl \xrightarrow[HCl]{k_2} Me_2CHCOCl \quad (7)$$

27 29

The conversion of the enol intermediate **29** was suggested[38] to occur through a cyclic transition state **30** involving another HCl molecule, but a more plausible path would be protonation to $Me_2CH\overset{+}{C}ClOH$. The alternative mechanism of Eq. (8) involving rate-limiting protonation on carbon was rejected because "it cannot lead to dominant second-order behaviour at low acid concentrations".[38]



30

$$R_2C{=}C{=}O + HCl \xrightarrow{slow} R_2CH\overset{+}{C}{=}O\,Cl^- \xrightarrow{fast} R_2CHCOCl \qquad (8)$$

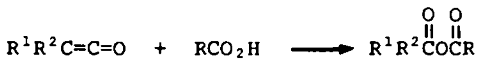
It appears that it is premature to discard the mechanism of Eq. (8). Inspection of the curvature in the k_{obs} vs [HCl] plot cited as evidence for the advent of a second-order term in HCl reveals only a small, and possibly insignificant deviation from linearity. Moreover, for 80% of the range of [HCl] studied even the authors accept that the second-order term is negligible.[38] Furthermore, even a bimolecular term in [HCl] does not necessarily imply the mechanism of Eq. (7). Thus addition of HCl to ordinary alkenes frequently depends on $[HCl]^2$, but this is interpreted as involving proton donation by HCl dimer (Eq. 9).[40]

$$>C{=}C< + (HCl)_2 \longrightarrow H{-}\overset{|}{\underset{|}{C}}{-}C^+ + HCl_2^- \qquad (9)$$

Rate-limiting protonation at C_β readily explains the observed greater reactivity of **27** compared to $Ph_2C{=}C{=}O$ (**8**), as it is known that phenyl is strongly rate-retarding toward protonation at a vinyl carbon.[41] However, there is no obvious reason to expect a much lower reactivity of **8** compared to **27** in forming an enol similar to **29**. Thus on the basis of the information now available the mechanism of Eq. (8), possibly involving $(HCl)_2$ as the proton donor, appears preferable for the addition of hydrogen halides to ketenes over most if not all observed concentrations of hydrogen halide.

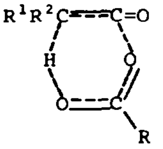
3.3. *Carboxylic acid additions to ketenes*

Carboxylic acids add to ketenes to give acid anhydrides (Eq. 10). The kinetics of the reactions of dimethylketene (**27**) and diphenylketene (**8**) in ether and of **8** and mesitylphenylketene (**31**) in *o*-dichlorobenzene with a series of carboxylic acids at 25° have been studied, and found to be first order in both acid monomer and ketene in ether.[39,42] Interestingly for **8** there was an inverse relationship between the acidity of the carboxylic acid and its reactivity, and the same trend was found for **27** except for trichloro- and dichloroacetic acids, which were the strongest acids and were also the most reactive. These results imply that except for the latter two examples that nucleophilic attack is the dominant effect.



$$R^1R^2C{=}C{=}O + RCO_2H \longrightarrow R^1R^2\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R \qquad (10)$$

A concerted reaction involving a cyclic transition state **32** was proposed for the reaction with the weaker acids, while a stepwise path involving initial protonation on carbon or oxygen was suggested to be involved for the stronger acids.[39,42] The ketene structure had a strong influence on the reactivity, and this was attributed at least in part[39,42] to the inhibition of protonation of C_β in **8**, as noted in Section 3.2. The gas phase reaction of ketene with carboxylic acids was interpreted as probably proceeding through a cyclic transition state **32**,[43a] while the reaction of ketene with phosphoric acids in solution was suggested to involve initial protonation on carbon to give a carbocation.[43b]



32

Table 2. Reaction of $CH_2{=}C{=}O$ with metal alkoxides

Compound	Product	Ref.
$Hg(OR)_2$[a]	$Hg(CH_2CO_2R)_2$	46
$Hg(CH_2COR)_2$	$Hg(CH_2CO_2CR{=}CH_2)_2$	47
$R^1_3SnOR^2$	$R^1_3SnCH_2CO_2R^2$	48, 49
$Et_2Sn(OR)_2$	$Et_2Sn(CH_2CO_2R)_2$	50
Ph_3PbOH	$(Ph_3PbCH_2CO)_2O$	51
Ph_3PbOAc[b]	$Ph_3PbCH_2CO_2Et$	51
Cl_3GeOR[c]	$Cl_3GeCH_2CO_2R$	52*a*
$Sb(OEt)_3$	$Sb(CH_2CO_2Et)_3$	53
$Zr(O{-}n\text{-}Bu)_4$[d]	$(n\text{-}BuO)_2Zr(CPh_2CO_2{-}n\text{-}Bu)_2$	54
$Ti(OR)_4$[d]	$(RO)_3TiCPh_2CO_2R$	55

[a] Reactions of different Hg(II) salts in different alcohols ROH.
[b] Reaction in ethanol.
[c] $GeCl_4$ also reacts with $CH_2{=}C{=}O$, to give $GeCl_3CH_2COCl$, Ref. 52*b*.
[d] Reaction with diphenylketene.

The principal evidence for transition state **32** in solution is the observed dependence on acid with an inverse dependence of rate on the acid strength.[39,42] Evidently it is assumed there would be charge separation in such a transition state, with positive charge on the carboxylate moiety, and hence negative charge on the ketene fragment. However, such a charge distribution would not be in accord with the observed greater reactivity of dimethylketene compared to diphenylketene,[39,42] as the latter would be better able to support negative charge build-up. The closest analog to **32** that has been well studied kinetically is in ester pyrolysis, and in this latter case there is general agreement that a cyclic transition state with considerable polar character is involved, but with negative charge on the carboxylate portion and positive charge on the alkenyl fragment,[43c,d] contrary to what is implied for **32**.

Thus it appears there is agreement that stronger acids add to ketene in stepwise processes involving initial protonation. For weaker carboxylic acids a concerted path involving the cyclic transition state **32** has been proposed,[39,42] but good analogy for this pathway is lacking and further evidence is required to substantiate this hypothesis. High quality theoretical calculations of the charge distribution in **32** may be useful in this regard.

3.4. *Carbon electrophiles*

Reaction of ketene (**1**) with α-alkoxycarbocations has been proposed to involve electrophilic attack on the ketene, as in the example of Eq. (11).[44] A similar reaction occurs with chlorodimethyl ether as the source of the electrophilic carbon.[45] Addition of Ph_3CCl to ketene was also observed (Eq. 12).[45]

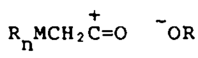
$$R(MeO)CHOR^1 \xrightarrow{ZnCl_2} R\overset{+}{C}HOR^1 \xrightarrow[2.\ OMe^-]{1.\ CH_2{=}C{=}O(1)} RCH(OR^1)CH_2CO_2Me \tag{11}$$

$$Ph_3CCl \xrightarrow{PhNO_2} Ph_3C^+ \quad Cl^- \xrightarrow{1} Ph_3CCH_2COCl \tag{12}$$

3.5. *Metal electrophiles*

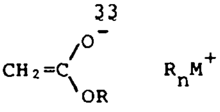
Metal alkoxides add to ketene to give the corresponding carbon metalated esters **33** (Eq. 13), as compiled in Table 2.[46–55] The mechanisms of these reactions have not been investigated but in a review Ulrich speculated that either stepwise polar additions or concerted cycloadditions might be involved.[56] The stepwise additions could involve either initial electrophilic attack by the metal or nucleophilic attack by the alkoxy group to give the intermediates **34** and **35**, respectively. It does appear that the metal accelerates the reaction[47] and so the latter intermediate can probably be excluded, at least in some cases. The reactions of mercuric salts with alkenes are generally recognized to involve initial electrophilic attack,[57] so as a working hypothesis the metal alkoxide–ketene reactions are grouped in this category, but experimental evidence for this classification is clearly required.

$$CH_2{=}C{=}O \quad + \quad R_nMOR \longrightarrow \underset{\mathbf{33}}{R_nMCH_2CO_2R} \tag{13}$$



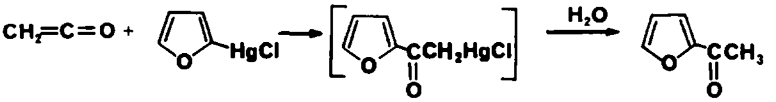
$R_nMCH_2\overset{+}{C}{=}O \quad {}^{-}OR$

34



35

Arylmercurials evidently add to ketenes; thus reaction of 2-chloromercurifuran with ketene (1) gives 2-acetylfuran after hydrolysis and presumably involves the intermediate shown (Eq. 14).[58,59] The mechanism of this reaction has also not been elucidated, and electrophilic, nucleophilic, and concerted processes can be envisaged.

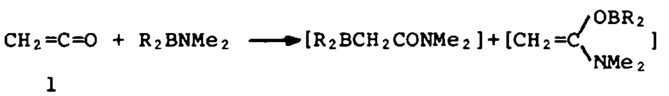


(14)

The addition of boron and aluminum derivatives to ketenes often involves O-metal bond formation, as in the examples in Eqs (15)–(19),[60–64] although in the examples of Eq. (15) the intermediate was not isolated or examined,[60] and the proposed intermediates shown in Eq. (16) reacted further.

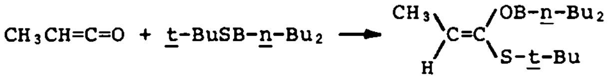
$$Ph_2C{=}C{=}O \xrightarrow[2)\ H_2O]{1)\ B(SMe)_3} Ph_2CHCOSMe \qquad (15)^{60}$$

8



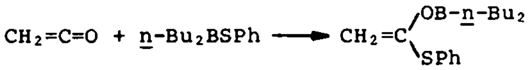
$$CH_2{=}C{=}O + R_2BNMe_2 \longrightarrow [R_2BCH_2CONMe_2] + [CH_2{=}C\begin{smallmatrix}OBR_2\\NMe_2\end{smallmatrix}] \qquad (16)^{61}$$

1

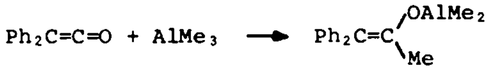


$$CH_3CH{=}C{=}O + \underline{t}\text{-}BuSB\text{-}\underline{n}\text{-}Bu_2 \longrightarrow \begin{smallmatrix}CH_3\\H\end{smallmatrix}C{=}C\begin{smallmatrix}OB\text{-}\underline{n}\text{-}Bu_2\\S\text{-}\underline{t}\text{-}Bu\end{smallmatrix} \qquad (17)^{62}$$

3



$$CH_2{=}C{=}O + \underline{n}\text{-}Bu_2BSPh \longrightarrow CH_2{=}C\begin{smallmatrix}OB\text{-}\underline{n}\text{-}Bu_2\\SPh\end{smallmatrix} \qquad (18)^{63}$$

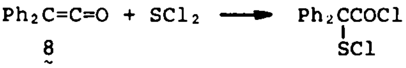


$$Ph_2C{=}C{=}O + AlMe_3 \longrightarrow Ph_2C{=}C\begin{smallmatrix}OAlMe_2\\Me\end{smallmatrix} \qquad (19)^{64}$$

3.6. *Sulfur, phosphorus, and halogen electrophiles*

Sulfenyl halides add to ketenes as shown in Eqs (20)–(23),[65–68] and these reactions evidently involve initial electrophilic attack by sulfur at C_β, although a 4-center transition state has also been suggested.[67] The fluorinated ketene **36** was inert under most conditions, as predicted by MNDO calculations,[67] but reacted with sulfenyl halides with activating solvents, of which CH_3CN was particularly effective.[67] A solid intermediate formed in the reaction of Eq. (24), and was assigned the structure shown, but this was not proven.[69]

$$CH_2{=}C{=}O \xrightarrow{ArSCl} [ArSCH_2COCl] \xrightarrow{H_2O} ArSCH_2CO_2H \qquad (20)^{65}$$

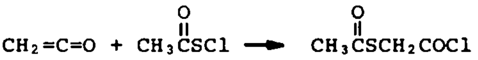


$$Ph_2C{=}C{=}O + SCl_2 \longrightarrow Ph_2\underset{\displaystyle SCl}{\underset{|}{C}}COCl \qquad (21)^{66}$$

8

$$(CF_3)_2C{=}C{=}O + PhSCl \longrightarrow PhSC(CF_3)_2COCl \qquad (22)^{67}$$

36



$$CH_2{=}C{=}O + CH_3\overset{\displaystyle O}{\overset{\|}{C}}SCl \longrightarrow CH_3\overset{\displaystyle O}{\overset{\|}{C}}SCH_2COCl \qquad (23)^{68}$$

$$Ph_2C{=}C{=}O + P(OEt)_3 \longrightarrow [Ph_2C{=}\overset{+}{C}O\overset{-}{P}(OEt)_3] \xrightarrow{EtOH} Ph_2CHCO_2Et \qquad (24)^{69}$$

The addition of bromine to **9** (Eq. 25)[70] and of H_2NCl to **8** (Eq. 26)[71] appear to involve electrophilic attack of halogen, but the result of Eq. (27)[71] appears contradictory, and reinvestigation of this latter system may be advisable.

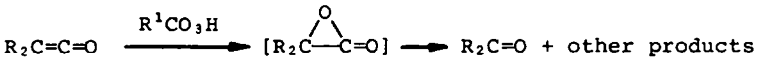
$$\underset{\mathbf{9}}{\mathrm{Me_3SiCH{=}C{=}O}} + \mathrm{Br_2} \rightarrow \mathrm{Me_3SiCHBrCOBr} \qquad (25)^{70}$$

$$\underset{\mathbf{8}}{\mathrm{Ph_2C{=}C{=}O}} + \mathrm{H_2NCl} \rightarrow \mathrm{Ph_2CClCONH_2} \qquad (26)^{71}$$

$$\underset{\mathbf{8}}{\mathrm{CH_2{=}C{=}O}} + \mathrm{H_2NCl} \rightarrow \mathrm{CH_3CONHCl} \qquad (27)^{71}$$

3.7. *Oxidation of ketenes*

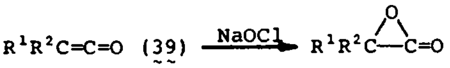
The oxidation of ketenes often involves cycloaddition, but may be considered as involving electrophilic attack. Ketenes **8**, **22**, and **37** all reacted with peracids to give the corresponding ketones and some other by-products; these reactions were all postulated to include α-lactone intermediates (Eq. 28).[72] Ketene **38** did not react with peracids but was cleaved by ozone (Eq. 29).[72] The perfluorinated ketene **39** reacted with sodium hypochlorite to give a very stable α-lactone (Eq. 30).[73]



(28)

R = Ph (**8**), *t*-Bu (**22**), *t*-BuCH$_2$ (**37**)

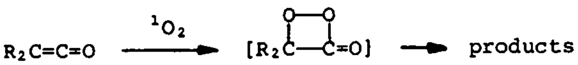
$$\underset{\mathbf{38}}{t\text{-BuC(CO}_2\text{Et)=C=O}} \xrightarrow{O_3} t\text{-BuCOCO}_2\text{Et} + t\text{-BuO}_2\text{CCO}_2\text{Et} \qquad (29)$$



(30)

$R^1 = Et^f_2Me^fC$, $R^2 = Et^fMe^fCF$

Reaction of a variety of ketenes with O_3 has been studied and proposed to also involve α-lactone intermediates.[74,75] Reaction of ketenes with singlet oxygen has been proposed to involve dioxetanone intermediates (Eq. 31),[76] and autoxidation of **8** with triplet oxygen was proposed to involve both α-lactone and dioxetanone intermediates.[77a]

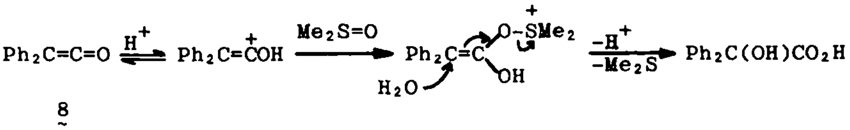


(31)

+ other intermediates

Reactions of ketenes **1**, **3**, **4**, and **27** with atomic oxygen in the gas phase have been studied, and interpreted in terms of initial attack at either carbon.[77b] Oxidation of ketenes with iodosobenzene has also been reported.[78a]

Dihydroxylation of **8** promoted by dimethylsulfoxide to form benzylic acid was observed, and was proposed to occur by the pathway shown, although no specific tests of this mechanism were carried out.[78b]



4. NUCLEOPHILIC ADDITION

4.1. *Hydride attack on ketenes*

Crowded diarylketenes have been observed to undergo reduction by hydride attack at C_α on reaction with Grignard reagents to give stable enols **42** as shown in Eqs (32) and (33).[79,80] Presumably transition states such as **44** are involved. The interesting question of the stereochemistry of the hydride attack and the product enols was not discussed.[79,80]

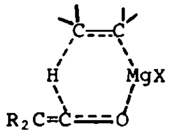
$$\underset{\textbf{31, 40, 41}}{PhRC{=}C{=}O} \xrightarrow[2.\ H_2O]{1.\ t\text{-}BuMgCl} \underset{\textbf{42}}{PhRC{=}CHOH} \qquad (32)^{79}$$

31 R = Mes (2,4,6-$Me_3C_6H_2$)

40 R = 3-BrMes

41 R = Dur(2,3,5,6-Me_4C_6H)

$$\underset{\textbf{43}}{Mes_2C{=}C{=}O} \xrightarrow[2.\ H_2O]{1.\ RMgBr\ \ (R = t\text{-}Bu,\ i\text{-}Pr,\ Et)} Mes_2C{=}CHOH \qquad (33)^{80}$$



44

The reaction of trialkylsilanes with ketenes **7**, **8**, **45**, and **46** in the presence of chloroplatinic acid as a catalyst gave the corresponding silyl enol ethers in 80–90% yield with an *E*/*Z* ratio of 1 : 1 (Eq. 34).[81] Triethylgermane and triphenylgermane reacted with **8** to give O-germylated enol ethers (Eq. 35).[82]

$$PhRC{=}C{=}O + R^1_3SiH \xrightarrow[H_2PtCl_6]{140°} PhRC{=}CHOSiR^1_3 \qquad (34)$$

R = Et (**7**), Ph (**8**), n-Pr (**45**), n-Bu (**46**)

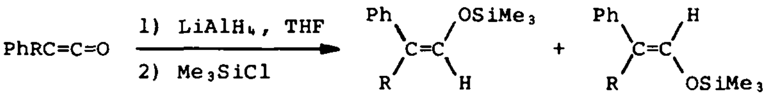
$$\underset{\textbf{8}}{Ph_2C{=}C{=}O} + R^1_3GeH \longrightarrow Ph_2C{=}CHOGeR^1_3 \qquad (35)$$

R^1 = Et, Ph

Lithium aluminum hydride treatment of **8** followed by reaction with acetyl chloride gave the enol acetate (Eq. 36).[83] Ketene **43** with $LiAlH_4$ gave the enol as in Eq. (33).[84]

$$\underset{\textbf{8}}{Ph_2C{=}C{=}O} \xrightarrow[2.\ AcCl]{1.\ LiAlH_4} Ph_2C{=}CHOAc \qquad (36)$$

Recent work in this laboratory has addressed the question of the preferred direction of attack in $LiAlH_4$ reduction of the ketenes **6** and **7**.[85] In each case on trapping with Me_3SiCl the product silyl ethers showed the *Z*-isomer was favored over the *E*-isomer by a ratio of 10 : 1 (Eq. 37).[85]

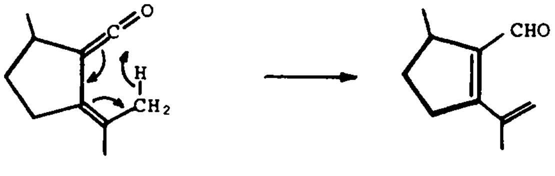


(37)

6 (R = Me) **Z** **E**

7 (R = Et)

An intramolecular hydrogen transfer with the character of hydride attack on C_α of the ketene **47** was observed on thermolysis (Eq. 38).[86]



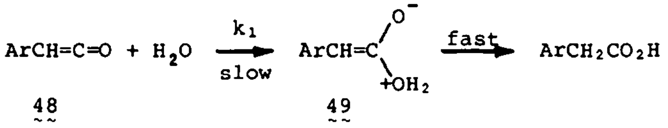
(38)

47

4.2. *Oxygen nucleophiles*

4.2.1. *Hydration of ketenes.* The hydration of ketenes has been studied experimentally in aqueous solution,[87,88] in 50% aqueous acetonitrile,[89] in organic solvents containing small amounts of water,[90,91] and in the gas phase.[92] A theoretical study of the gas phase reaction between ketene (**1**) and water dimer has also appeared.[18]

The rates of reaction of a series of arylketenes **48** in H_2O at 26° showed a 13-fold rate decrease in going from the *p*-nitro to the *p*-methyl derivative, and were correlated with σ_p^0 constants with $\rho = 1.2$.[87] Values of the solvent isotope effect k_{H_2O}/k_{D_2O} of 1.8–2 were obtained, and for the *p*-chloro compound $E_{act} = 9.3\ \text{kcal mol}^{-1}$, $\log A = 10.72$. The reaction was independent of pH in the range studied (4–10.8). These authors[87] did not propose a mechanism for the reaction but that of Eq. (39) provides a satisfactory explanation of the data.

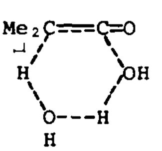


$$\underset{48}{ArCH{=}C{=}O} + H_2O \xrightarrow[slow]{k_1} \underset{49}{ArCH{=}C(O^-)(\overset{+}{O}H_2)} \xrightarrow{fast} ArCH_2CO_2H \qquad (39)$$

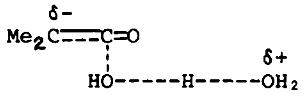
Thus the rather small positive ρ value indicates some development of negative charge next to the aryl group. This would be expected for a transition state leading to **49**, as the reactions are very fast ($T_{1/2} = 1.4\text{–}18.4 \times 10^{-5}$ s) and presumably have early transition states, and much of the negative charge developed will be on oxygen rather than carbon. This magnitude of the solvent isotope effect was suggested[88] to be in the range expected for rate-limiting attack of H_2O on the carbonyl group (*vide infra*).

The hydration of ketene itself in H_2O at 25° had a rate constant of 44 s^{-1},[88] or a factor of 86 less than *p*-tolylketene, the least reactive in the series of Eq. (39). The reaction rate was independent of pH in the range 4.4–9.85, gave a solvent isotope effect $k_{H_2O}/k_{D_2O} = 1.9$, $\Delta H^* = 10.3\ \text{kcal mol}^{-1}$ and $\Delta S^* = -16$ eu.[88] Dilution of the water with acetonitrile or dioxane resulted in a linear decrease of the rate constant with the percentage organic cosolvent, so that in 25% H_2O the rate constant had decreased by a factor of 3. These results were interpreted in terms of rate-limiting attack of H_2O as in Eq. (39). The significantly faster rate of the arylketenes in comparison to **1** is particularly strong evidence for a polar transition state.

Satchell and co-workers[90,91] measured the rates of hydrolysis of dimethylketene (**27**) and diphenylketene (**8**) in ether solution containing up to 0.351 M H_2O. The rate for **8** was 5–40 times greater than for **27**, depending upon the water concentration, and whereas the reaction of **27** was catalyzed by added carboxylic acids **8** was not, up to 0.093 M acetic acid. The non-catalyzed rate of **27** was second-order in water concentration, whereas the rate of **8** was third order. These results were interpreted in terms of concerted additions involving cyclic transition states, depicted as **50** for **27**. The open transition state **51** was considered but not favored.[90]



50



51

The principal argument against transition state **51** was that monomeric water, which was reported to be unreactive, ought to be able to participate in a transition state such as **51** with ether as the non-nucleophilic catalytic partner, but no strong justification for this assumption was advanced. The greater reactivity of **8** compared to **27** is however supportive of a polar transition state as in **51** as dimethyl substitution would retard carbanion formation relative to phenyls, and as pointed out by these investigators[91] phenyl is known[41] to inhibit proton transfer to the adjacent vinyl carbon, and would tend to cause reaction of **8** by a concerted path slower than **27**, contrary to experiment. Analogy with additions of other reagents (anilines, alcohols, carboxylic acids, and hydrogen halides) to ketenes by concerted cycloadditions were also cited as support for **50**, but as discussed in separate sections significant doubts exist as to the generality of the cycloaddition path in these reactions as well.

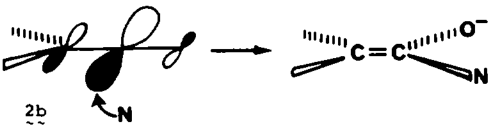
For dimethylketene in ether strong catalysis of hydration by BF_3 was observed. This was interpreted as involving rate-limiting protonation as in Eq. (40).[91]

$$Me_2C{=}C{=}O + H_2O{:}BF_3 \xrightarrow{\text{slow}} Me_2CH\overset{+}{C}{=}O\ HOBF_3^- \xrightarrow[\text{fast}]{-BF_3} Me_2CHCO_2H \tag{40}$$

Di-t-butylketene (**22**) is quite stable to non-catalyzed hydration but acid-catalyzed hydration kinetics were measured in 50% H_2O–acetonitrile at 25°.[89] The observation of general acid catalysis and a solvent isotope effect k_{H_2O}/k_{D_2O} of 2.8 were taken as strong evidence for the mechanism of Eq. (41),[89] analogous to that of Eq. (40).

$$\underset{\mathbf{22}}{t\text{-}Bu_2C{=}C{=}O} \xrightarrow[\text{slow}]{H^+} t\text{-}Bu_2CH\overset{+}{C}{=}O \xrightarrow[\text{fast}]{H_2O} t\text{-}Bu_2CHCO_2H \tag{41}$$

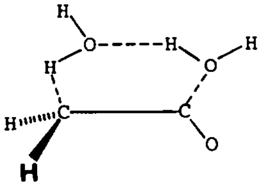
The low reactivity of **22** in the uncatalyzed hydration also argues that such a reaction would involve a nucleophilic attack of water to give an enolate-like species and not a cycloaddition. Nucleophilic attack on a ketene would involve the LUMO **2b** (Eq. 42), so that a strong steric interaction of the incoming nucleophile with the ketene substituents would be expected, and as discussed in Section 4.4 this steric interaction has been convincingly demonstrated for other nucleophiles.



(42)

A cycloaddition of water dimer to the C=C double bond would appear to be much less susceptible to steric effects, as the attack would occur from above the plane of the ketene. The STO-3G optimized geometry shown in **52** has been calculated for the reaction of ketene with water dimer,[18] and steric interactions would not appear to be large even if the ketene hydrogens are replaced by t-butyls. Furthermore, the acid-catalyzed hydrolysis of $t\text{-}Bu_2C{=}CHOMe$, which involves proton transfer to a vinyl carbon substituted with two t-butyl groups (Eq. 43), is 11 times faster than the reaction of $Me_2C{=}CHOMe$,[93] providing further evidence for the lack of a significant steric barrier to such a proton transfer. Steric retardation of attack of bulky electrophiles above the plane of t-butylalkenes has been observed, but not in protonation.[94]

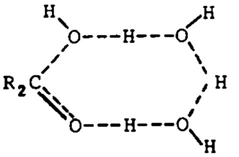
Transition state structures for the addition of monomeric H_2O to the C—C bond of ketene have been calculated using MINDO/3.[17]



52

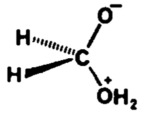
$$t\text{-}Bu_2C{=}CHOMe \xrightarrow[\text{slow}]{H^+} t\text{-}Bu_2CH\overset{+}{C}OMe \xrightarrow[\text{fast}]{H_2O} t\text{-}Bu_2CHCH{=}O \tag{43}$$

The possibility of rate-limiting protonation of the carbonyl oxygen of ketenes can probably be excluded, as proton transfers to oxygen are generally quite rapid. However, the uncatalyzed hydration of ketenes may be compared to the hydration of ketones and aldehydes, which has continued to be the object of kinetic study.[95–98] The experimental results for the uncatalyzed reaction with H_2O of acetaldehyde show $\Delta H^* = 9$ kcal mol^{-1}, $\Delta S^* = -38$ eu, $T_{1/2}$ (25°) = 88 s, and $k_{H_2O}/k_{D_2O} = 3.6$.[95] Results for ketones are comparable both in aqueous solution and in dioxane or acetonitrile containing small amounts of water.[96,97] There is support from all these authors for a hydration transition state involving three water molecules with the general structure **53**.



53

A recent theoretical study at the STO-3G level of formaldehyde hydration is also supportive of a cyclic transition state involving three water molecules for reaction in aprotic solvents.[98] In aqueous solution it was concluded that a choice could not be made between a concerted reaction involving the cyclic transition state **53** or a stepwise mechanism with a zwitterionic transition state resembling **54** with additional hydrogen bonded water molecules.[98]



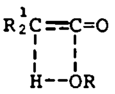
54

Calculations at the STO-3G and 4-31G levels for the hydration of ketene by water dimer led to the conclusion that the preferred path for this reaction involved a concerted addition across the $C{=}O$ bond, rather than $C{=}C$.[18] Thus this result favors a path parallel to that found for aldehyde and ketone hydration. However, as pointed out[18] this pathway does not account for the experimentally demonstrated major effects of ketene substituents on the reactivity, which appear to be of both electronic and steric origin.

In summary it is clear that uncatalyzed ketene hydration is a prime topic for further experimental and theoretical study, particularly with a systematic change in ketene structure. At present it does not appear that the roles of $C{=}C$ and $C{=}O$ addition through stepwise and concerted processes can be reliably differentiated. For the strong acid-catalyzed reaction there is agreement[89,91] that rate-limiting proton transfer to carbon is involved (Eqs 40 and 41).

4.2.2. *Alcohol and acid anhydride additions.* The addition of alcohols to ketenes forming esters is a familiar reaction and earlier reviews[3,4] of much of the previous work are not repeated here. There is also evidence that in some examples the acylation of alcohols with acyl chlorides and *tertiary* amines that ketenes are generated *in situ* and they react with the alcohol to give the ester,[99a] and alcoholysis of vinyl ketene has recently proven of value for the preparation of esters $CH_2{=}CHCH_2CO_2R$.[99b] As discussed below the mechanism of the reaction of ketenes with alcohols has been studied for the system without added catalysts, as well as with acid and base catalysis.

The kinetics of the reactions of alcohols with ketenes were reported by different groups to be first order in alcohol concentration,[100] from first to second and higher order depending on the temperature,[101] and third order.[90] Based on these results and several indications that the reaction rate was not enhanced by polar effects in the ketene or the solvent, these groups proposed the reactions involved cyclic transition states with four (**55**), six (**56**), or eight (**57**) members, respectively.



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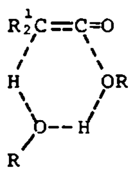

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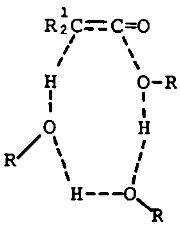
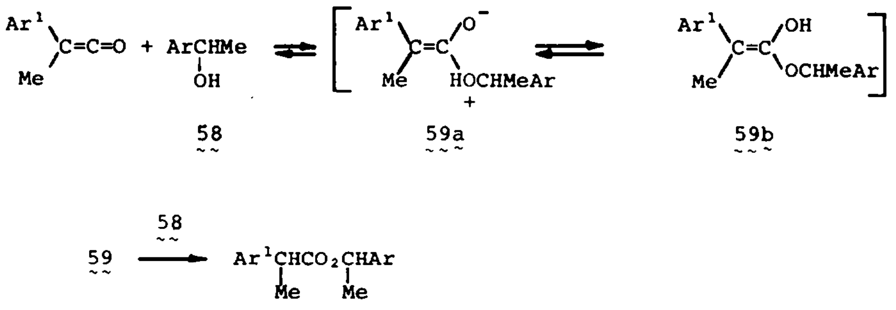


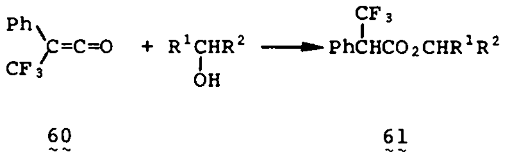
57

More recently an alternative explanation of the reaction of ketenes with alcohols has been provided by Jähme and Rüchardt[102,103] who studied the effect on the reactivity of changes in concentration, temperature and the structure of the alcohol and ketene, and deuterium isotope effects.[102] Particularly remarked were the observation of an inverse dependence of rate on temperature, small activation enthalpies, and very large negative entropies of activation. The mechanism in Eq. (44) was suggested to explain the observed reactivities of arylmethylketenes with 1-arylethanols. Thus it was proposed that there is an equilibrium formation of a small concentration of **59a** or **b** which is ketonized in a slow step by reaction with a second molecule of alcohol.[102]



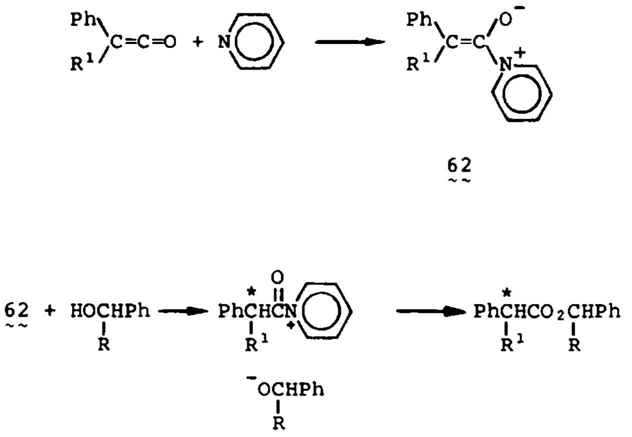
(44)

The stereochemistry of the esterification of ketenes was examined in the reaction of phenyltrifluoromethylketene (**60**) with a series of chiral secondary alcohols to give esters **61** of α-trifluoromethylphenylacetic acid. Ratios of the two diastereomeric esters ranged from 50 : 50 to 68 : 32 (Eq. 45).[104] There was a greater preference for one diastereomer when there was a large difference in size between the two groups on the secondary alcohol, and the stereoselectivity was correlated with a previously proposed rule.[104]



(45)

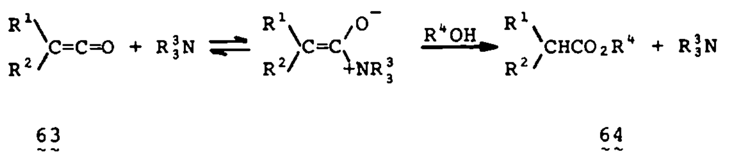
Stereoselectivity was also observed in the reactions of Eq. (46) and was found to be greatly enhanced in the presence of achiral bases such as pyridine and 1,4-diazabicyclo[2.2.2]octane.[103,105] This process was interpreted as involving initial attack of pyridine to give **62**, which is then protonated by the alcohol in the stereochemically determining step to give an ion pair which then undergoes fast conversion to product (Eq. 46).[103]



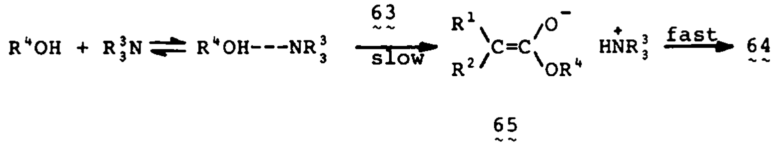
(46)

In the case where R^1 = Et and R = t-Bu (Eq. 46) a preference as high as 99 : 1 for a single diastereomer could be obtained under certain conditions. The selectivity was dependent upon the structure, solvent, and temperature, so caution was urged in terms of explaining the observed selectivities in terms of transition state models.[105]

The catalysis by tertiary amines of the addition of alcohols to ketenes has been extensively studied by Pracejus and co-workers,[101,106–110] who studied the effect of changing the temperature, base, solvent and alcohol as well as the kinetic isotope effect for alcohols ROH and ROD. These authors considered two possible reaction schemes (Eqs 47 and 48) and favored that shown in Eq. (48) involving initial formation of an amine–alcohol complex which reacts with ketene in the slow step of the reaction to give an ion-pair which gives a fast collapse to product.



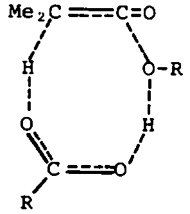
(47)



(48)

In the presence of chiral amines as catalysts asymmetric addition of the achiral alcohols to unsymmetrical ketenes occurred. This stereoselectivity was proposed to occur in the collapse of the ion pair **65**. As already noted later workers favored a process similar to Eq. (47),[103] but a definitive basis for choosing between these alternatives does not appear to be available, and restraint in the use of these models has been advised.[105]

The kinetics of the carboxylic acid catalyzed addition of a series of alcohols to dimethylketene (**27**) in ether at 25° was studied by Lillford and Satchell.[90] As already noted these authors proposed that in the absence of acid catalysis of the reaction that an 8-membered cyclic transition state **56** was involved. In the presence of carboxylic acid catalysts the reaction was first order in monomeric alcohol, the acid, and the ketene and another 8-membered transition state **66** was proposed.[90]



66

As noted above the role of a concerted addition in the uncatalyzed reaction has been disputed with the proposal of a non-concerted process shown in Eq. (44),[102] and the role of **66** is open to question as well. The primary argument for **66** was that "an inverse relationship exists between catalytic power and acid strength (pK_a)".[90] That is, the weaker acids were better catalysts, so both protonating and nucleophilic functions were proposed for the acid. However, as discussed above for carboxylic acid addition to ketenes, the closest structural analog to this latter reaction which had been thoroughly studied, namely ester pyrolysis, displays the characteristics of a negatively charged carboxylate moiety in the transition state, contrary to the implied role for carboxylate in ketene additions.[90] Transition state **66** is similarly without good analogy, and suffers the further liabilities of being termolecular and involving an 8-membered ring, and should not be regarded as established without further corroborating evidence. Other possibilities for the reaction of Eq. (49) would be stepwise processes or a concerted addition not involving a cyclic transition state, but further evidence is needed to clarify the unique catalytic role of carboxylic acids. The strongest acid studied reacted rapidly to form an anhydride, presumably according to Eq. (50).

$$\underset{\mathbf{27}}{Me_2C{=}C{=}O} + HOR + R^1CO_2H \longrightarrow Me_2CHCO_2R \tag{49}$$

$$\underset{\mathbf{27}}{Me_2C{=}C{=}O} + CCl_3CO_2H \xrightarrow{slow} Me_2CH\overset{+}{C}{=}O \xrightarrow[fast]{} Me_2CHCO_2O_2CCCl_3 \tag{50}$$

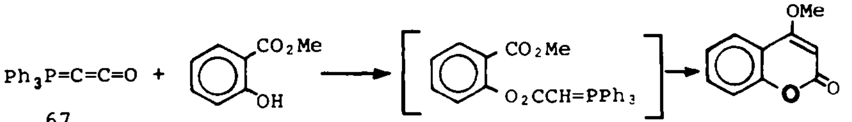
The addition of alcohols to **27** in Et_2O ether was also catalyzed by BF_3, and rate-limiting proton transfer from an $ROH \cdot BF_3$ adduct was invoked (Eq. 51).[111]

$$\mathbf{27} + ROH \cdot BF_3 \xrightarrow{slow} Me_2CH\overset{+}{C}{=}O \;\; ROBF_3^- \xrightarrow[-BF]{fast} Me_2CHCO_2R \tag{51}$$

The acylation of diphenylketene (**8**) with diphenylacetic anhydride (Eq. 52) has been reported.[112] Mechanisms involving initial attack of either the carbonyl or the ethereal oxygen of the anhydride on C_α of the ketene, or of the carbonyl carbon of the anhydride on the ketene oxygen, can be imagined for this transformation, but evidence to differentiate these possibilities has not been published. As noted in Section 4.4 nucleophilic attack by carbon of the enolized anhydride also occurs.

$$\underset{\mathbf{8}}{Ph_2C{=}C{=}O} + (Ph_2CHCO)_2O \longrightarrow Ph_2C{=}C(O_2CCHPh_2)_2 \qquad (52)$$

The nucleophilic addition of phenols and alcohols to the unique triphenylphosphoranylideneketene (**67**)[113] has recently been applied for the synthesis of a variety of heterocycles. For example, methyl salicylate evidently adds to **67** to form an intermediate phosphorane which undergoes an internal Wittig reaction to give 4-methoxycoumarin in 43% yield (Eq. 53).[114] Similarly the steroid **68** reacts with **67** to give the corresponding cardenolide **69** in 84% yield (Eq. 54).[115]



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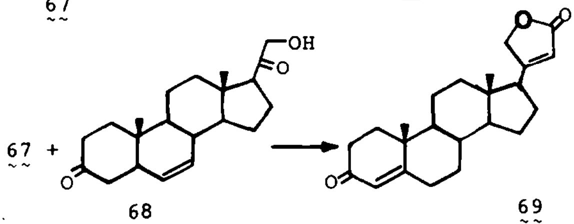
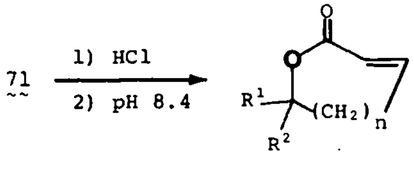


68 **69**

(54)

In a new synthesis of macrocyclic lactones, the alcohol **70** containing a protected aldehyde group reacted with **67** to give **71** which cyclized after deprotection (Eq. 55).[116]

$$\underset{\mathbf{70}}{(RO)_2CH(CH_2)_nCR^1R^2OH} \xrightarrow[95\%]{\mathbf{67}} \underset{\mathbf{71}}{(RO)_2CH(CH_2)_nCR^1R^2O_2CH{=}PPh_3} \qquad (55)$$



4.3. *Nitrogen nucleophiles*

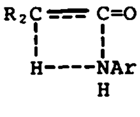
The reaction of ketenes with primary amines such as aniline to give amides is a reaction that has long been known.[1]

$$Ph_2C{=}C{=}O + PhNH_2 \longrightarrow Ph_2CH\overset{\overset{O}{\|}}{C}NHPh$$

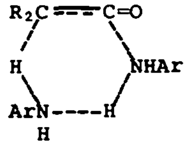
The kinetics of this progress have been studied by Satchell and co-workers for the reactions of ketene (**1**) dimethylketene (**27**), and diphenylketene (**8**) with anilines in ether or benzene.[117–119] These authors reported that

$$\text{rate} = (k_1[ArNH_2] + k_2[ArNH_2]^2)[\text{ketene}]$$

was followed by this reaction and proposed there were two different cyclic transition states involved, with 4- (**72**) and 6-members (**73**), respectively.[119]

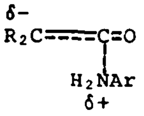


72

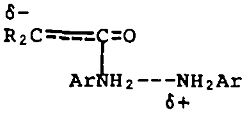


73

Earlier Lillford and Satchell[118] had proposed the transition states **74** and **75** for this reaction. These structures explain the increase in reactivity with increasing basicity of the aniline, and also the relative order of reactivity $Ph_2C{=}C{=}O > CH_2{=}C{=}O > Me_2C{=}C{=}O$,[117,118] in that the negative charge build up would be stabilized in this order. Evidence cited for the importance of **72** and **73** included Hückel molecular orbital calculations of the ground states of $CH_2{=}C{=}O$ and $Me_2C{=}C{=}O$, which showed significant negative charge on C_β of these ketenes,[119] in agreement with the more advanced calculations noted in Section 1.2. Lillford and Satchell concluded "The calculated charge distributions strongly suggest that the slow processes involve proton transfer to the β-carbon atom."[119] However, this argument is not persuasive, as a calculated charge density in the reactant does not give a reliable indication as to the preferred transition state. The low catalytic activity of the much more strongly basic Et_3N relative to aniline was also cited as evidence for the proton transfer role in **73**,[119] but the high reactivity of $Ph_2C{=}C{=}O$ argues that the open transition states **74** and **75** originally proposed by Lillford and Satchell[118] give the best account of the data.

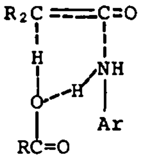


74



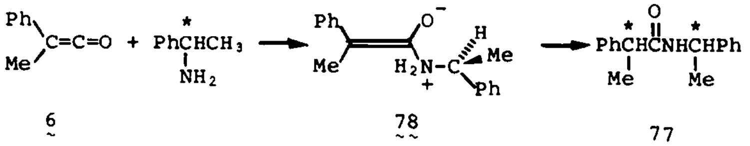
75

Catalysis by carboxylic acids of the reaction with anilines with ketenes was also reported, although for the two acids studied the stronger acid was the less effective catalyst.[118] The cyclic transition state **76** was proposed[118] for this process, but it would appear that further study of this process would be required before a firm conclusion could be reached.



76

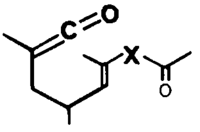
Asymmetric induction was observed in the addition of (*S*)-(−)-1-phenylethylamine to phenylmethylketene (**6**) to give the amide **77** (Eq. 56).[120,121] The stereoselectivity varied with the temperature and solvent and a stepwise process was proposed in which the intermediate **78** was formed which then gave the diastereomeric products through two different transition states. The intermediate **78** resembles that which would result from the transition state **74** initially proposed[118] on the basis of the reaction kinetics.



6 78 77

(56)

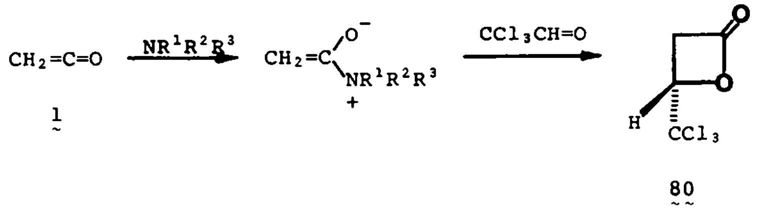
More recently the asymmetric induction in the reaction of a photogenerated ketene **79** with several chiral amines was studied.[122] Interestingly with this ketene the stereoselectivity was invariant with temperature but did depend upon the particular amine and solvent.



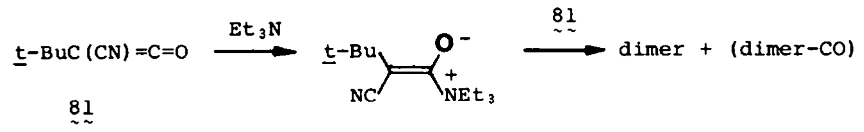
X = O, CH₂

79

Some reactions of ketenes catalyzed by tertiary amines evidently involve initial nucleophilic attack of nitrogen on the ketene. A noteworthy example is the reaction of ketene (**1**) with chloral catalyzed by optically active amines to give the lactone **80** in up to 98% enantiomeric excess. This reaction was proposed to involve a ketene–amine complex which is attacked by chloral by the least hindered path to give the product as shown in Eq. (57).[123] Another example involving t-butylcyanoketene (**81**) is shown in Eq. (58).[124]

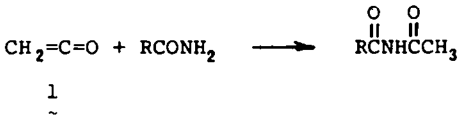


(57)

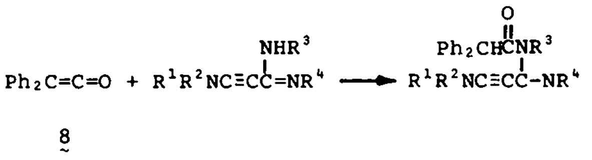


(58)

Preparative reactions of ketenes have been reported that involve a variety of other nitrogen nucleophiles including amides (Eq. 59)[125] and a carbodiimide derivative (Eq. 60).[126] The product of the latter process sometimes reacted further.

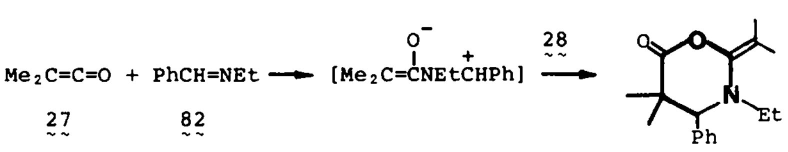


$$\underset{\mathbf{1}}{CH_2{=}C{=}O} + RCONH_2 \longrightarrow R\overset{O}{\overset{\|}{C}}NH\overset{O}{\overset{\|}{C}}CH_3 \tag{59}$$



$$\underset{\mathbf{8}}{Ph_2C{=}C{=}O} + R^1R^2NC{\equiv}C\overset{NHR^3}{\overset{|}{C}}{=}NR^4 \longrightarrow R^1R^2NC{\equiv}C\overset{Ph_2CH\overset{O}{\overset{\|}{C}}NR^3}{\overset{|}{C}}{-}NR^4 \tag{60}$$

In reactions with imines combination of **82** with dimethylketene (**27**) evidently involved initial nucleophilic attack on the ketene, followed by addition of a second ketene molecule and cycloaddition (Eq. 61).[127] Reaction of **8** with N-trimethylsilyl benzophenonimine gave addition (Eq. 62), although some other silyl imines gave cycloaddition.[128] This example could proceed by initial attack of silicon or nitrogen, or by a concerted path.

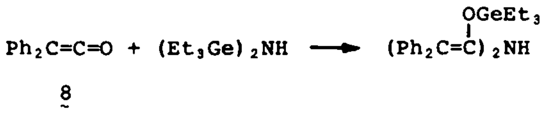


(61)

$$\underset{\mathbf{8}}{Ph_2C{=}C{=}O} + Ph_2C{=}NSiMe_3 \longrightarrow Ph_2C{=}C(OSiMe_3)N{=}CPh_2 \tag{62}$$

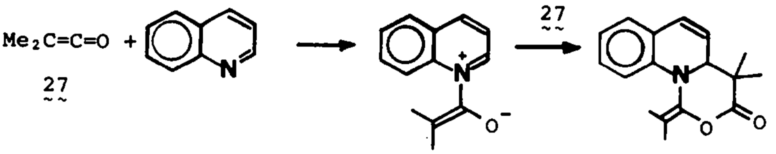
Ketene (**1**) reacted with triethyl(dimethylamino)silane at − 15° to give **83** (Eq. 63), but the initial product was unstable and rearranged to the α-silylamide.[129] Hexaethyldigermazane added 2 mol of **8** (Eq. 64).[130]

$$\underset{\mathbf{1}}{CH_2{=}C{=}O} + Et_3SiNMe_2 \longrightarrow \underset{\mathbf{83}}{CH_2{=}C(OSiEt_3)NMe_2} \tag{63}$$



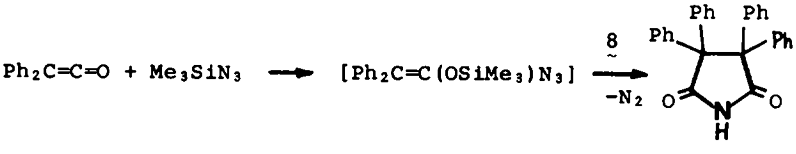
$$\underset{\mathbf{8}}{Ph_2C{=}C{=}O} + (Et_3Ge)_2NH \longrightarrow (Ph_2C{=}\overset{OGeEt_3}{\overset{|}{C}})_2NH \tag{64}$$

Many nitrogen heterocycles react with ketenes. These reactions have been proposed to proceed in general with nucleophilic attack by nitrogen on the ketene, followed by further reactions, as illustrated for the case of dimethylketene (**27**) and quinoline (Eq. 65).[131,132]



(65)

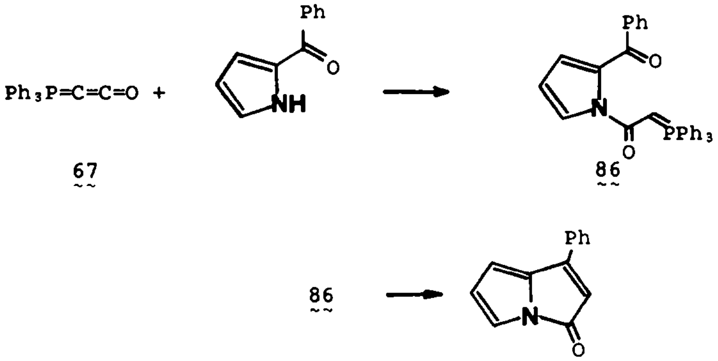
Trimethylsilyl azide reacted with **8** to give **84** as the major product.[133] This reaction was proposed to involve initial formation of **85** (or the C-silylated isomer) (Eq. 66).



85 84

(66)

Reaction of the phosphoranylideneketene **67**[113] with pyrroles and other nucleophiles evidently involves an initial nucleophilic attack by nitrogen on the ketene to give a phosphorane intermediate which in suitable cases undergoes cyclization by an intramolecular Wittig reaction as in the example of Eq. (67).[114,134–136]



67 86

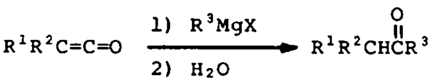
(67)[136]

4.4. *Carbon nucleophiles*

The reaction of **8** with PhMgBr was studied very early,[137] and the enolate which was trapped by benzoyl chloride to give the enol benzoate (Eq. 68) in 79% yield by Gilman and Heckert.[138]

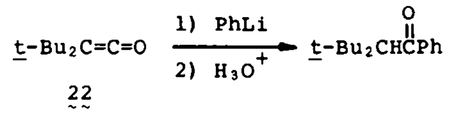
$$\underset{\mathbf{8}}{Ph_2C{=}C{=}O} \xrightarrow{PhMgBr} Ph_2C{=}C(OMgBr)Ph \xrightarrow{PhCOCl} Ph_2C{=}C(O_2CPh)Ph \qquad (68)$$

The reaction of ketenes with Grignard reagents followed by hydrolysis to give the ketone (Eq. 69) has been extensively studied, as summarized in Table 3. The alkyl ketenes are prone to dimerization and polymerization and the yields of ketones are not high, so these procedures have been only rarely utilized in organic synthesis. However, the additions to the hindered ketenes **31**, **43** and **90** provide a unique route to products which exist as the enol tautomers.

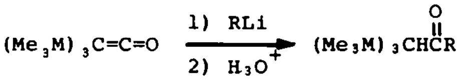


$$R^1R^2C{=}C{=}O \xrightarrow[2)\ H_2O]{1)\ R^3MgX} R^1R^2CH\overset{O}{\overset{\|}{C}}R^3 \qquad (69)$$

The first addition of an organolithium to a ketene involved PhLi and paralleled Eq. (68).[148] Later examples are given in Eqs (70)–(73). Bis(trimethylstannyl)ketene (**93**) evidently reacted by attack on Sn (Eq. 72).



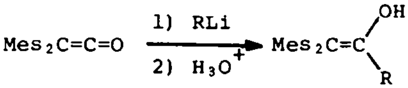
$$\underset{\mathbf{22}}{t\text{-}Bu_2C{=}C{=}O} \xrightarrow[2)\ H_3O^+]{1)\ PhLi} t\text{-}Bu_2CH\overset{O}{\overset{\|}{C}}Ph \qquad (70)^{149}$$



$$(Me_3M)_3C{=}C{=}O \xrightarrow[2)\ H_3O^+]{1)\ RLi} (Me_3M)_3CH\overset{O}{\overset{\|}{C}}R \qquad (71)^{150,151}$$

91 (M = Si), **92** (M = Ge), R = Me, n-Bu, Ph

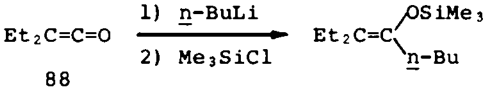
$$\underset{\mathbf{93}}{(Me_3Sn)_2C{=}C{=}O} \xrightarrow{RLi} Me_3SnR \qquad (72)^{151}$$



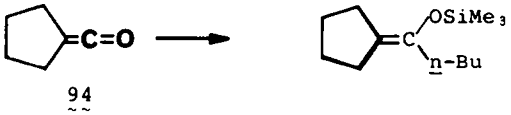
$$\underset{\mathbf{43}}{Mes_2C{=}C{=}O} \xrightarrow[2)\ H_3O^+]{1)\ RLi} Mes_2C{=}C(OH)R \qquad (73)^{80}$$

R = i-Pr, t-Bu

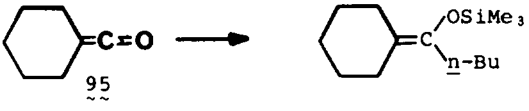
Treatment of the enolate solutions from reaction of ketenes and organolithiums with Me_3SiCl gave directed formation of only a single silyl enol ether in each case (Eqs 74–77).[152] The procedures are advantageous as enolization–silylation of the corresponding ketones gave mixtures of isomers in every case, and usually a preference for a different isomer than obtained from the ketene.[152] The addition of t-BuLi to **22** is particularly useful, as the corresponding enolate could not be prepared from the ketone with t-BuOK, KH, or $i\text{-}Pr_2NLi$ (Eq. 78).[152]



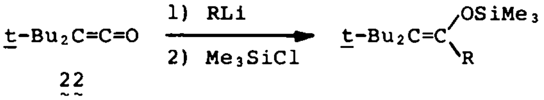
$$\underset{\mathbf{88}}{Et_2C{=}C{=}O} \xrightarrow[2)\ Me_3SiCl]{1)\ n\text{-}BuLi} Et_2C{=}C(OSiMe_3)(n\text{-}Bu) \qquad (74)$$



94 (75)

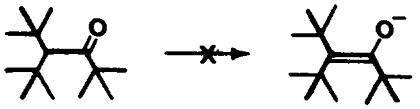


95 (76)



$$\underset{\mathbf{22}}{t\text{-}Bu_2C{=}C{=}O} \xrightarrow[2)\ Me_3SiCl]{1)\ RLi} t\text{-}Bu_2C{=}C(OSiMe_3)R \qquad (77)$$

R = n-Bu, t-Bu



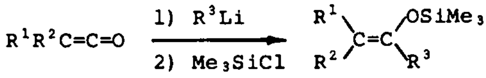
(78)

Reaction of organolithiums with unsymmetrical ketenes followed by silylation proceeds stereospecifically in the examples shown in Eqs (79) and (80).[153] The reactions are interpreted as proceeding through nucleophilic attack from the least hindered side in the plane of the ketene on the LUMO **2b** (Eq. 42), and give the silyl ethers shown as the only observed isomers. The stereoselectivity shown is unique as enolization–silylation of the corresponding ketones showed a strong tendency to prefer the opposite stereochemistry from that favored by the ketene route.[153]

Table 3. Preparation of ketones according to Eq. (69)

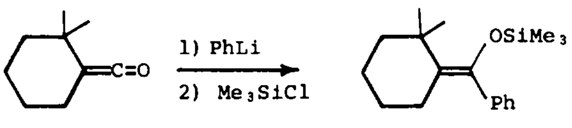
Ketene	R^1	R^2	R^3	Yield (%)	Ref.
1	H	H	Ph	35	139, 141
1	H	H	Et	35	140
1	H	H	*E*-MeCH=CH	30	142
1	H	H	$Me_2C{=}C$	40	142
1	H	H	PhC≡C	30	142
1	H	H	n-Bu	35	140, 142
87	Et	CO_2Et	Ph	45	143
88	Et	Et	n-Bu	45	142
89	n-Bu	n-Bu	n-Bu	50	142
6	Me	Ph	Et	55	142
7	Et	Ph	Et	60	142
8	Ph	Ph	Et	30	142
8	Ph	Ph	*E*-MeCH=CH	65	142
8	Ph	Ph	$Me_2C{=}CH$	65	142
8	Ph	Ph	PhC≡C	40	142
31	Mes[a]	Ph	Mes	33	144
43	Mes	Mes	Me	80	145
43	Mes	Mes	9-Anthryl	9	146
43	Mes	Mes	$2,6\text{-}Me_2C_6H_3$	31	146
90	Ar[b]	Mes	Mes	—	146
43	Mes	Mes	Mes	51	146, 147

[a] $2,4,6\text{-}Me_3C_6H_2$.
[b] $2,6\text{-}Me_2\text{-}4\text{-}t\text{-}BuC_6H_2$.



(79)

No.	R^1	R^2	R^3
96	t-Bu	H	t-Bu
6	Ph	Me	n-Bu
7	Ph	Et	n-Bu
97	Me_3Si	Et	n-Bu, $CH_2{=}CH$, HC≡C

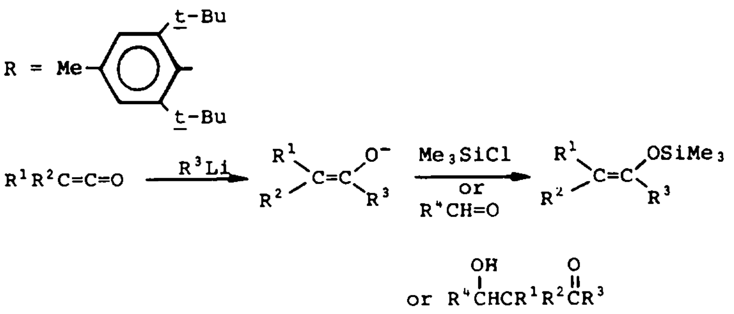


(80)

98

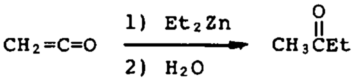
A new method for the *in situ* generation of ketenes and their reaction with organolithiums involves the reaction of n-BuLi with 2,6-di-t-butyl-4-methylphenyl esters **99** to give the ester enolates, which cleave to the ketenes above −20° (Eq. 8).[154] The ketenes were trapped *in situ* with organolithiums to give ketone enolates which were either silylated or reacted with aldehydes to give aldols (Eq. 82) as summarized in Table 4.[154] For the unsymmetrical ketenes the *E*/*Z* selectivities in forming the silyl enol ethers and the diastereoselectivities in forming the aldols are included in Table 4. A reaction pathway for formation and nucleophilic attack on ketenes based on X-ray structures of enolates[155] was also presented.[154]

$$\underset{\mathbf{99}}{R^1R^2CHCO_2R} \xrightarrow[\text{THF}]{\text{n-BuLi}} R^1R^2C{=}C(OLi)OR \xrightarrow{-20^\circ} R^1R^2C{=}C{=}O \qquad (81)$$



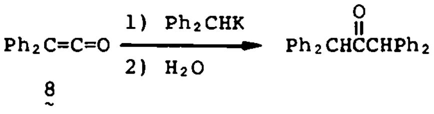
(82)

Reactions of some other organometallic species and carbon nucleophiles with ketenes are shown in Eqs (83)–(91). Addition of Me_3SiCN to ketenes (Eq. 87) was proposed[157] to involve a $\pi^2+\pi^2+\sigma^2$ cycloaddition pathway.



$$CH_2{=}C{=}O \xrightarrow[2)\ H_2O]{1)\ Et_2Zn} CH_3\overset{O}{\overset{\|}{C}}Et$$

(83)[156]

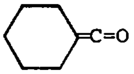
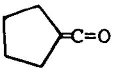
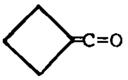
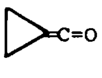


$$\underset{\underset{\sim}{8}}{Ph_2C{=}C{=}O} \xrightarrow[2)\ H_2O]{1)\ Ph_2CHK} Ph_2CH\overset{O}{\overset{\|}{C}}CHPh_2$$

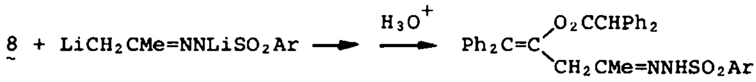
(84)[157]

(85)[64]

Table 4. Ketene generation and reaction according to Eqs (81) and (82)

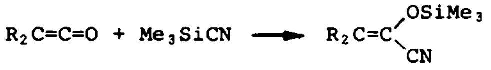
Ketene	No.	R^3	Ketene reactant	Product selectivity (Z/E or % ds)[a]
EtMeC=C=O	5	Me	Me_3SiCl	1.7
		$PhCH_2$	PhCH=O	60
i-PrMeC=C=O	100	Me	Me_3Si	7.0
		n-Bu	PhCH=O	84
		$PhCH_2$	PhCH=O	>97
		$PhCH_2$	n-PrCH=O	83
t-BuMeC=C=O	101	Me	Me_3SiCl	>99
		n-Bu	PhCH=O	>99
		$PhCH_2$	PhCH=O	>99
		$PhCH_2$	n-PrCH=O	84
$Me_2C{=}C{=}O$	27	Me	PhCH=O	
		PhC≡C	PhCH=O	
$Et_2C{=}C{=}O$	88	n-Bu	PhCH=O	
	95	$PhCH_2$	PhCH=O	
		$PhCH_2$	n-PrCH=O	
		Et_2N	n-PrCH=O	
		Ph	PhCH=O	
	94	$PhCh_2$	PhCH=O	
		$PhCH_2$	n-PrCH=O	
	102	$PhCH_2$	PhCH=O	
		$PhCH_2$	n-PrCH=O	
		n-Bu	PhCH=O	
	103	$PhCH_2$	PhCH=O	
		Ph	PhCH=O	

[a] *Z/E* is the product ratio for silylation and % ds is the percentage of the major diastereomer of the aldol reaction for the unsymmetrical ketene.



$$\mathrm{8 + LiCH_2CMe{=}NNLiSO_2Ar \longrightarrow \xrightarrow{H_3O^+} Ph_2C{=}C(O_2CCHPh_2)CH_2CMe{=}NNHSO_2Ar}$$

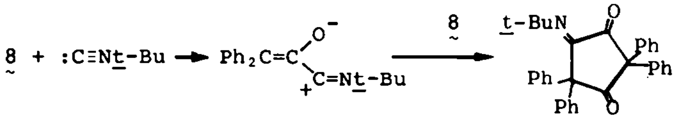
(86)[158]



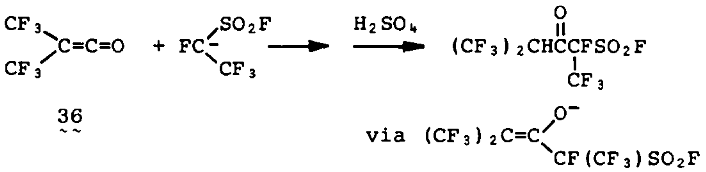
$$\mathrm{R_2C{=}C{=}O + Me_3SiCN \longrightarrow R_2C{=}C(OSiMe_3)CN}$$

(87)[159]

R = H(1), Ph(8), CF_3(36)



(88)[160]

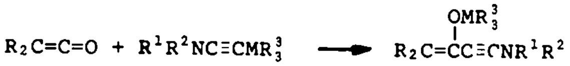


$$\mathrm{(CF_3)_2C{=}C{=}O + FC^-(SO_2F)CF_3 \longrightarrow \xrightarrow{H_2SO_4} (CF_3)_2CHC({=}O)CF(CF_3)SO_2F}$$

36

via $\mathrm{(CF_3)_2C{=}C(O^-)CF(CF_3)SO_2F}$

(89)[161]



$$\mathrm{R_2C{=}C{=}O + R^1R^2NC{\equiv}CMR^3_3 \longrightarrow R_2C{=}C(OMR^3_3)C{\equiv}CNR^1R^2}$$

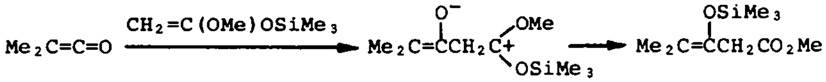
(90)[162,163]

6-8, 88 M = Si, Ge

(91)[164]

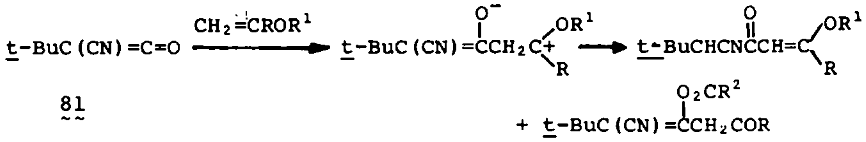
R = Me, Ph

Reactions of electron-rich alkenes with ketenes sometimes involve initial nucleophilic attack on the ketene to give a zwitterion, which then partitions among several product forming pathways (Eqs 92–96). A concerted path was proposed[165] for the reaction of Eq. (92), and the stepwise path shown is only speculative. The reaction of Eq. (96) may involve attack of an enol of acetic anhydride on **8**.



$$\mathrm{Me_2C{=}C{=}O \xrightarrow{CH_2=C(OMe)OSiMe_3} Me_2C{=}C(O^-)CH_2C^+(OMe)OSiMe_3 \longrightarrow Me_2C{=}C(OSiMe_3)CH_2CO_2Me}$$

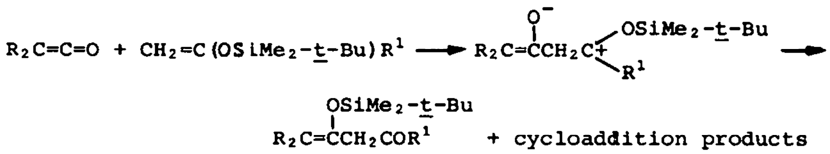
(92)[165]



$$\mathrm{\underline{t}\text{-}BuC(CN){=}C{=}O \xrightarrow{CH_2=CROR^1} \underline{t}\text{-}BuC(CN){=}C(O^-)CH_2C^+(OR^1)R \longrightarrow \underline{t}\text{-}BuCHCNC({=}O)CH{=}C(OR^1)R + \underline{t}\text{-}BuC(CN){=}C(O_2CR^2)CH_2COR}$$

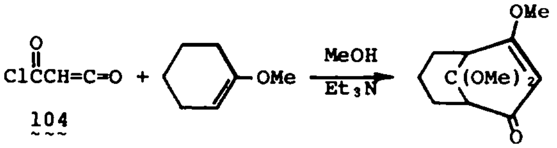
81

(93)[166]

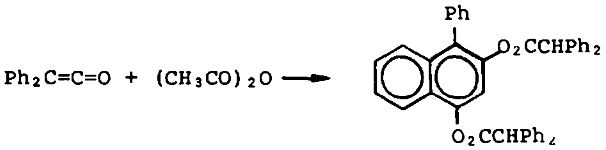


$$\mathrm{R_2C{=}C{=}O + CH_2{=}C(OSiMe_2\text{-}\underline{t}\text{-}Bu)R^1 \longrightarrow R_2C{=}C(O^-)CH_2C^+(OSiMe_2\text{-}\underline{t}\text{-}Bu)R^1 \longrightarrow R_2C{=}C(OSiMe_2\text{-}\underline{t}\text{-}Bu)CH_2COR^1}$$ + cycloaddition products

(94)[167]

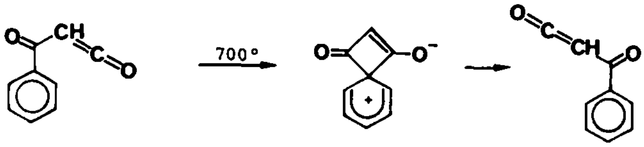


(95)[168]



(96)[112]

The interesting rearrangement of Eq. (97) may be envisaged as involving an intramolecular nucleophilic attack on carbon.[169]



10

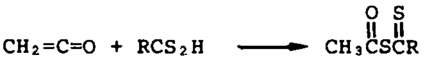
(97)

4.5. *Sulfur and phosphorus nucleophiles*

As noted in Section 2 there is some evidence for the radical addition of dimethylketene (27) with ethanethiol (Eq. 5),[25] but this reaction is also catalyzed by isobutyric acid in what is evidently a non-radical reaction.[25] Some recent reports of the reaction of several different ketenes with sulfur nucleophiles are illustrated in Eqs (98)–(100). The additions of some boron–sulfur compounds to ketenes were classified as electrophilic reactions (Eqs 15, 17 and 18).

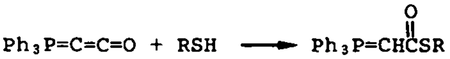
$$(CF_3)_2C{=}C{=}O + RSH \longrightarrow (CF_3)_2CHCOSR \qquad (98)^{170}$$

36 R = PhCH₂, *t*-Bu



$$CH_2{=}C{=}O + RCS_2H \longrightarrow CH_3\overset{O}{\overset{\|}{C}}S\overset{S}{\overset{\|}{C}}R \qquad (99)^{171}$$

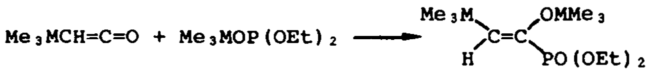
R = Me, Ph



$$Ph_3P{=}C{=}C{=}O + RSH \longrightarrow Ph_3P{=}CH\overset{O}{\overset{\|}{C}}SR \qquad (100)^{135}$$

67 R = Me, Ph

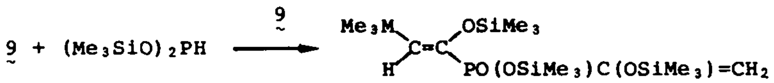
Some reactions of silyl and germylketenes with phosphorus nucleophiles are shown in Eqs (101)–(103). All these reactions were proposed to proceed with initial nucleophilic attack of phosphorus from the least hindered side of the ketene to give the adducts shown following migration of one group from oxygen.[172] In the case of Eq. (103) two molecules of ketene reacted.[172]



(101)[172]

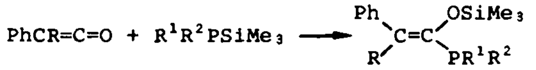
M = Si(9), Ge(12)

(102)[172]



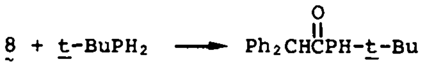
(103)[172]

Reactions of some other ketenes with phosphorus nucleophiles are shown in Eqs (104)–(107). The stereochemistry of the product of Eq. (106) was not assigned but that of Eq. (107) was reported to be a mixture of *E* and *Z* isomers.[175]

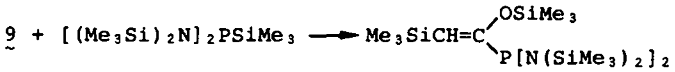


$$\mathrm{PhCR{=}C{=}O} + \mathrm{R^1R^2PSiMe_3} \longrightarrow \mathrm{(Ph)(R)C{=}C(OSiMe_3)(PR^1R^2)} \qquad (104)^{173}$$

R = Ph(8); R = MeO$_2$C(106)



$$\mathbf{8} + t\text{-}\mathrm{BuPH_2} \longrightarrow \mathrm{Ph_2CHC({=}O)PH}\text{-}t\text{-}\mathrm{Bu} \qquad (105)^{173}$$

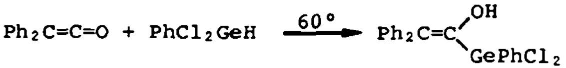


$$\mathbf{9} + \mathrm{[(Me_3Si)_2N]_2PSiMe_3} \longrightarrow \mathrm{Me_3SiCH{=}C(OSiMe_3)P[N(SiMe_3)_2]_2} \qquad (106)^{174}$$

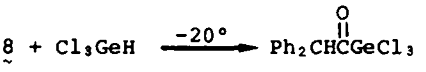
$$\mathbf{9} + \mathrm{(R_2N)_2C{=}PSiMe_3} \longrightarrow \mathrm{Me_3SiCH{=}C(OSiMe_3)P{=}C(NR_2)_2} \qquad (107)^{175}$$

R = Me, Et

Reaction of $Ph_2C{=}C{=}O$ with some germanium hydrides also has been reported to occur with what appears to be nucleophilic attack of germanium (Eqs 108 and 109).[82]



$$\underset{\mathbf{8}}{\mathrm{Ph_2C{=}C{=}O}} + \mathrm{PhCl_2GeH} \xrightarrow{60^\circ} \mathrm{Ph_2C{=}C(OH)GePhCl_2} \qquad (108)$$

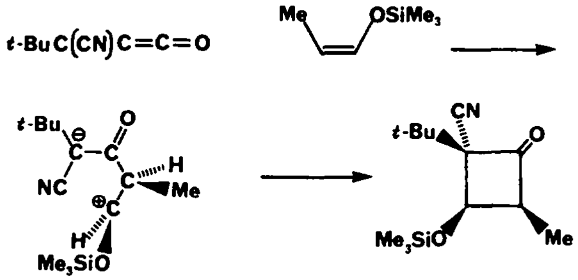


$$\mathbf{8} + \mathrm{Cl_3GeH} \xrightarrow{-20^\circ} \mathrm{Ph_2CHC({=}O)GeCl_3} \qquad (109)$$

5. CONCLUSION

Ketenes are fascinating and versatile reactive intermediates, but even though an authoritative monograph on their chemistry was published in 1912[1] we believe their full study has just begun. New syntheses of ketenes are being developed, and new structural types and new reactions of ketenes are being examined. We hope to participate in these exciting developments.

Interestingly among numerous recent articles[176–183] on [2+2] cycloadditions of ketenes there are several cases[177–179] in which these reactions are suggested to proceed by non-concerted pathways, as in the example of Eq. (110).[179] It has even been suggested that this behavior may be general.[178] The initial step of this process is similar to that of many of the other ketene reactions described herein and indicates a possibly widespread unity of mechanism in diverse reactions of ketenes.



(110)

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