Recent advances in ketene chemistry

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Dedicated to the memory of Melvin S. Newman, a pioneer in ketene chemistry

Melvin Newman (1908-1999)

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Abstract

Recent advances in ketene chemistry are reviewed, including synthetic, mechanistic, and computational studies. Topics include ketene structure determination by experimental and theoretical methods, computational studies of bonding in ketenes, spectroscopic properties of ketenes, preparation and formation of ketenes including photochemical and thermal methods, the discovery and observation of ketenes in space, and ketene reactions. The last category includes decarbonylation, cycloadditions with carbon-carbon, carbon-nitrogen, and carbon-oxygen multiple bonds, addition of oxygen, nitrogen, and carbon nucleophiles, and electrophilic additions.

Keywords: Ketenes, cycloadditions, reaction mechanisms, computations

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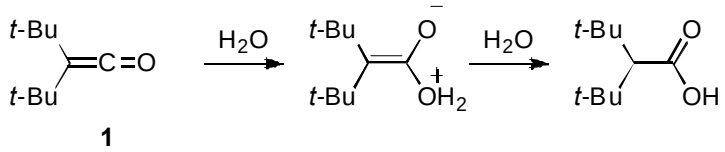
1. Introduction

The chemistry of ketenes has long been of fascination to the authors, inspired by a publication in 1960 from the laboratory of Melvin Newman at The Ohio State University reporting the preparation of di-*tert*-butylketene (**1**), which is exceptional for its indefinite stability as a neat liquid at room temperature.[1] Other alkylketenes are typically prone to dimerization and are sensitive to moisture and air, but the reactivity of **1** in aqueous solution could be measured (Scheme 1),[2] with a rate constant less that that of mono-*tert*-butylketene by a factor of 9×10^4, a result attributed to the steric protection from in-plane attack of water at the carbonyl carbon.[2]



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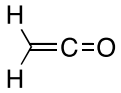
Scheme 1. Hydration of di-*tert*-butylketene.

Ketene chemistry remains a very active area of research worldwide, involving both synthetic and mechanistic studies, and has been extensively reviewed.[3-15] This review describes the most recent work in the area, which is rich in further opportunities. The organization of this review includes separate headings on ketene preparation and on ketene reactions, but since ketenes are usually short-lived intermediates ketene formation and reactivity are usually inextricably mixed, and examples of one almost invariably contain the other.

2. Structure, Bonding, and Spectroscopy

The structure and excited state of the parent ketene (**2**) have been calculated by the SCF CI method and used to interpret the excited state of the molecule.[16] Electron scattering by ketene has been studied by computational methods using the *R*-matrix method for energies ranging from 0 to 10 eV,[17] and the calculated vertical excitation energies of the first two excited states are in good agreement with experimental results. The electron scattering calculations predict two π^* shape resonant states, one core-excited shape resonant state and one Feshbach resonant state.



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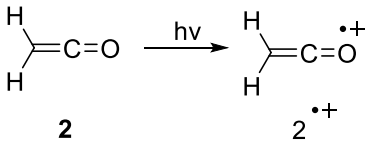
Computations of the $\tilde{X}^2B_1 \leftarrow \tilde{X}^1A_1$ photoelectron spectra of ketene (Scheme 2) and of dideuteroketene give excellent agreement with available experimental data, and the calculated structure for the ketene radical cation is shown in Figure 1.[18]



2 $2^{\bullet+}$

Scheme 2. Photoionization of ketene.

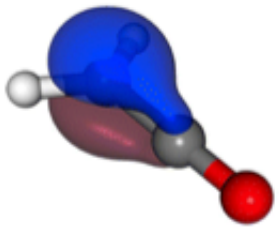
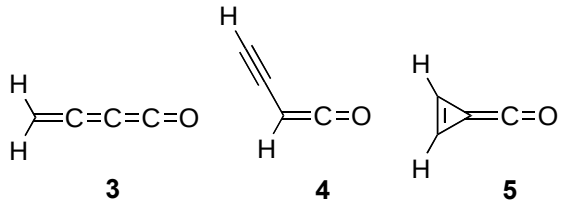


Figure 1. Singly occupied molecular orbital of the $\tilde{X}^2B_1$ ketene radical cation (Reprinted with permission of the publisher [18]).

Modeling of the ethanol/oxygen flame was interpreted as showing the presence of butatrienone (**3**) at 8.56 eV, and ethynylketene (**4**) at 8.94 eV.[19] Ketene **3**[19,20] has been reported experimentally,[21] while **4** may have been detected,[19] and substituted derivatives of **4** are known.[22] The formation of **4** by the dehydration of 3-butynoic acid has also been studied computationally,[23] as has the structure of isomer **5**.[20,24]

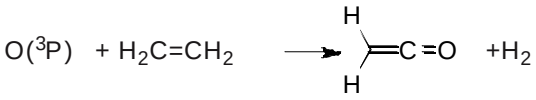


3. Preparation and Formation of Ketenes

Recent studies as described in this section reveal novel processes in which ketenes may be formed, and these add to the more traditional methods known previously.

3.1. Ketenes by oxygenation reactions

The conversion of ethylene to ketene by reaction with ground state oxygen atoms O(^{3}P) has been studied by computational and experimental methods using a crossed molecular beam apparatus with universal soft electron ionization mass spectrometric detection, which indicate almost equal contributions from the triplet and singlet surfaces to the reaction (Scheme 3).[25] The effects of added ethanol on ketene formation in ethylene flames have also been studied.[26]



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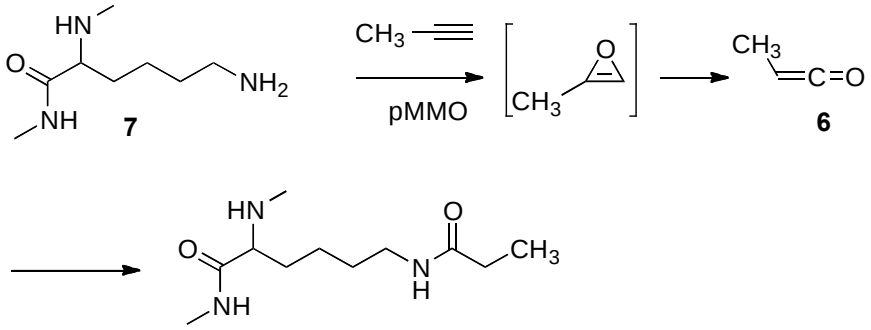
ΔH^o = -85.1[a] (-84.2)[b] kcal/mol

([a]quantum chemical, [b]experimental)

Scheme 3. Ketene formation from ground-state oxygen atom reaction with ethylene.

The formation of ketenes from alkynes occurs in particulate methane monooxygenase (pMMO) in *Methylococcus capsulatus* (Bath), which deactivates the transmembrane PmoC subunit by acetylation, as demonstrated using high-resolution MALDI-TOF mass spectrometry and computational simulation.[27] Docking of methylketene (**6**), derived from methylacetylene, forms an adduct of the transmembrane PmoC subunit **7** (Scheme 4), as illustrated in Figure 2.[27]



Scheme 4. Methylketene formation from propyne by methane monooxygenase, with transmembrane PmoC acylation.

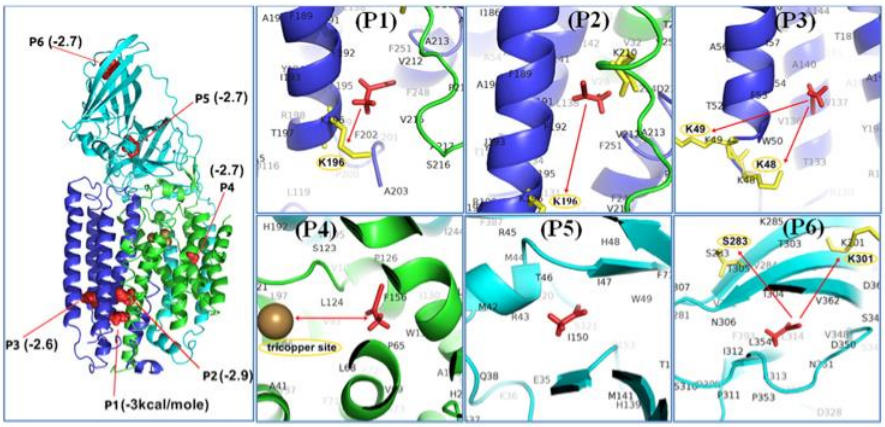
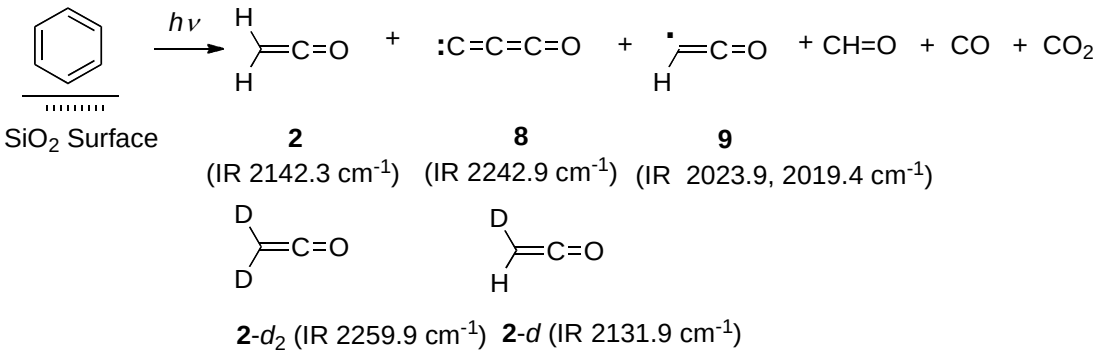


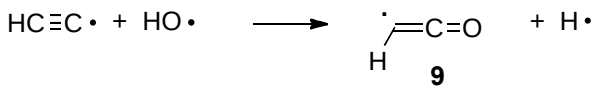
Figure 2. Molecular docking of methylketene to pMMO **(**Reprinted with permission of the publisher [27]).

Irradiation of benzene on a silica surface with a pulsed glow discharge in the presence and absence of oxygen resulted in the formation of ketene (**2**), C_3O (**8**), and ketenyl radical **9**, as detected by IR spectroscopy (Scheme 5).[28] It was suggested that oxygen in the products originated from the silica surface. Irradiation of benzene-d_6 gave dideuteroketene (**2**-d_2) and monodeuteroketenes (**2**-d_1), in which the protium arose from pentadeuterobenzene in the benzene sample.



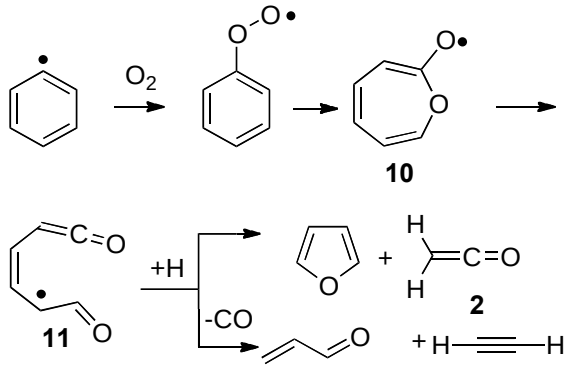
Scheme 5. Benzene photolysis on a silica surface.

The ketenyl radical (**9**) has also been observed as an abundant molecule in interstellar space, and in the cold dark clouds Lupus-1A and L486.[29] The mechanism for formation of **9** (Scheme 6) is suggested to have a much larger formation constant than used in current models.[30,31] The role of **9** in evaluating the heat release in a bluff-body combustor has also been evaluated.[32]



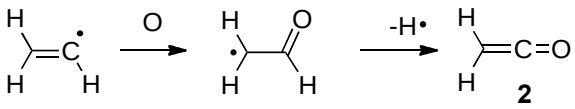
Scheme 6. Ketenyl radical formation in space.

Oxidation of phenyl radical with molecular oxygen studied experimentally with tunable vacuum ultraviolet photoionization in conjunction with a combustion simulating chemical reactor at 873 K and 1003 K showed the formation of *ortho*-benzoquinone, phenoxy radical, cyclopentadienyl radical, furan, acrolein, ketene, and acetylene.[33] The last four products arise through ring opening and fragmentation of the seven-membered ring 2-oxepinyloxy radical **10** through the intermediacy of the ring-opened ketene radical **11** [1,6-dioxo-3,5-hexadien-2-yl ($C_6H_5O_2$) radical] (Scheme 7).



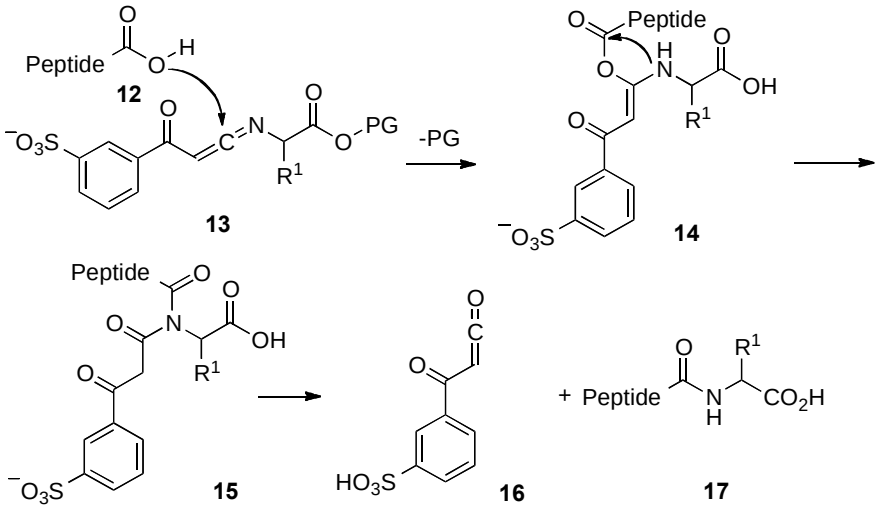
Scheme 7. Ketene formation from phenyl radical oxidation.

The formation of ketene from reaction of ground-state atomic oxygen O(^{3}P) reaction with vinyl radical has been examined using crossed-beam vacuum-ultraviolet laser-induced fluorescence spectroscopy together with *ab initio* calculations. The reaction with vinyl radical produces ketene by O addition and loss of a hydrogen atom (Scheme 8).[34,35]



Scheme 8. Ketene formation from vinyl radical reaction with atomic oxygen.

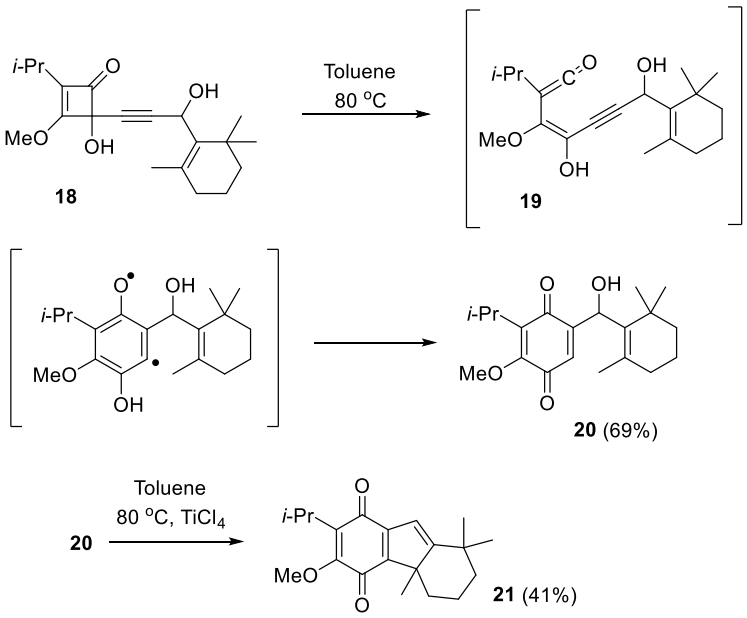
Peptide extension of doubly protonated **12** in the gas phase by reaction with ketenimine **13** is proposed to occur by acylation on carbon forming an enol ester **14** and rearrangement to **15** followed by cleavage with loss of the ketene **16** and the extended peptide **17** (Scheme 9).[36]



Scheme 9. Ketene formation by mass spectrometric ion/ion reaction.

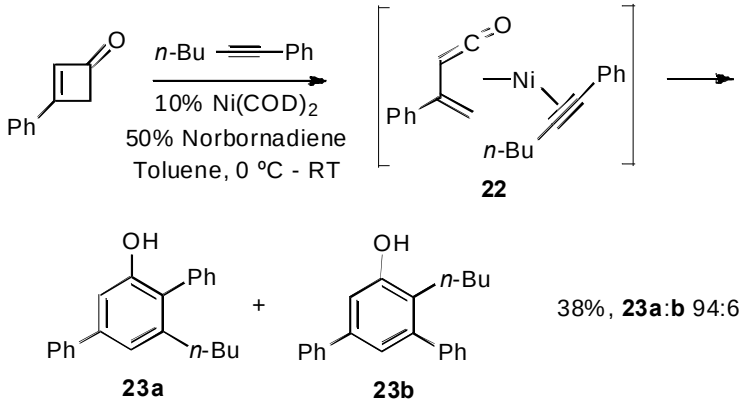
3.2. Ketenes by ring opening of cyclobutenones

Thermal and photochemical ring openings of cyclobutenones are widely used methods for generation of vinylketenes, and applications of these reactions have been reviewed.[3] Thermolysis of cyclobutenone **18** in toluene gave the quinone **20** in 69% yield via intramolecular [4+2] cycloaddition of the ene-yne ketene **19** (Scheme 10).[37] Treatment of the crude product with $TiCl_4$ led to (–)-taiwaniaquinone (**21**) (Scheme 8).[38]



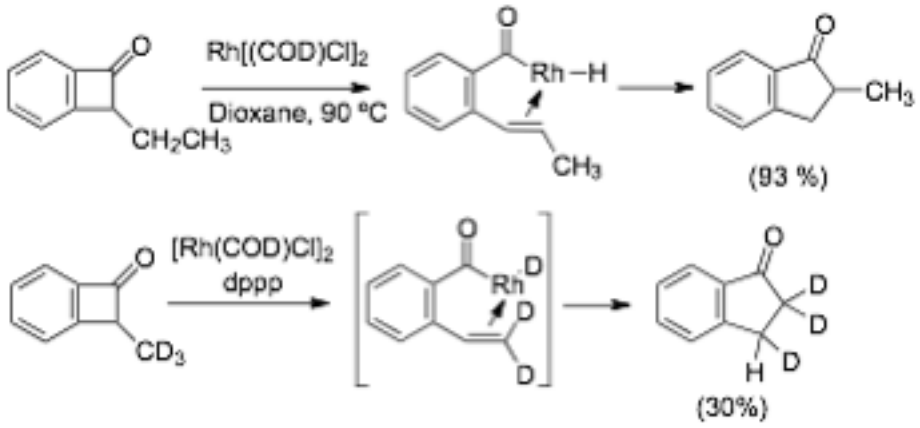
Scheme 10. Quinones by ene-yne ketene cycloaddition.

Cyclobutenone ring opening catalyzed by $Ni(COD)_2$ gave net [4+2] vinylketene cyclo-addition with 1-phenylhexyne in a reaction interpreted as proceeding through complex **22**, leading to the isomeric phenols **23** (Scheme 11).[39]



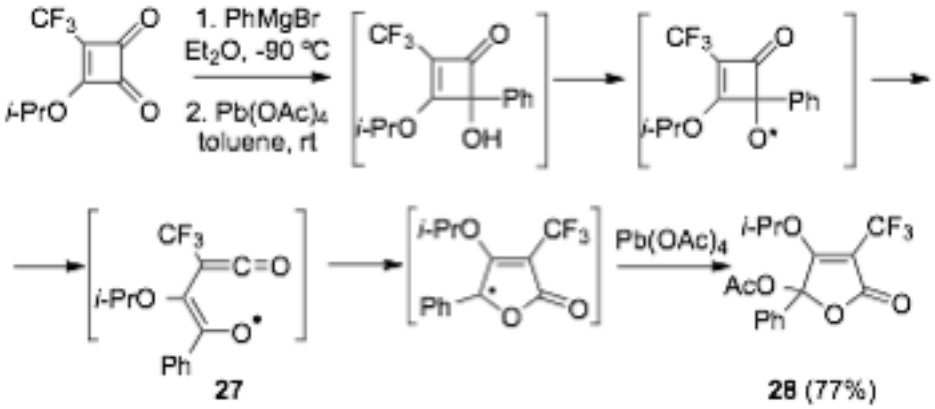
Scheme 11. Phenol formation by vinylketene/alkyne cycloaddition.

Rhodium-catalyzed benzocyclobutenone ring expansion with DPPP ligand [1,3-bis-(diphenylphosphino)propane] was tested in the presence of nucleophiles, but this did not capture a ketene intermediate. Therefore it was concluded that the reaction proceeded through a rhodium-bridged intermediate leading to the product, and a ketene intermediate was not involved. This mechanism was tested with deuterium labeling (Scheme 12).[40]



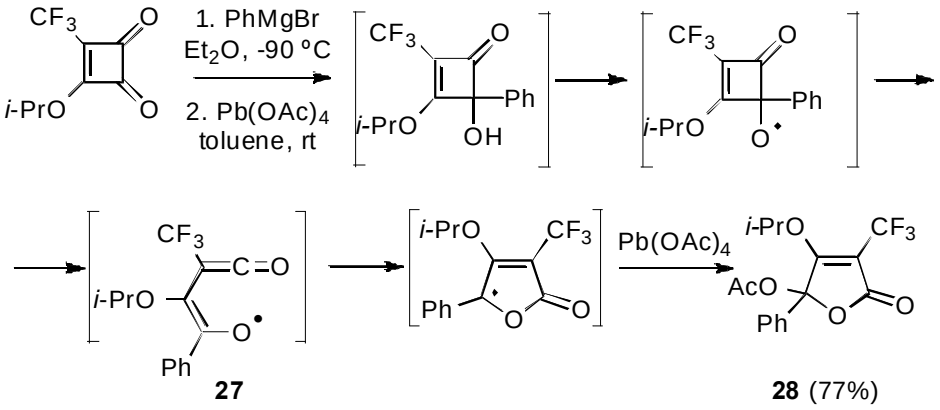
Scheme 12. Rhodium catalyzed benzocyclobutenone ring expansion.

The trifluoromethyl-substituted cyclobutenone **24** upon thermolysis undergoes ring opening to trifluoromethyl(arylvinyl)ketene **25**, which after cyclization and oxidation gives the product naphthoquinone **26** (Scheme 13).[41]



Scheme 13. Cyclization of a trifluoromethyl(oxyvinyl)ketene intermediate.

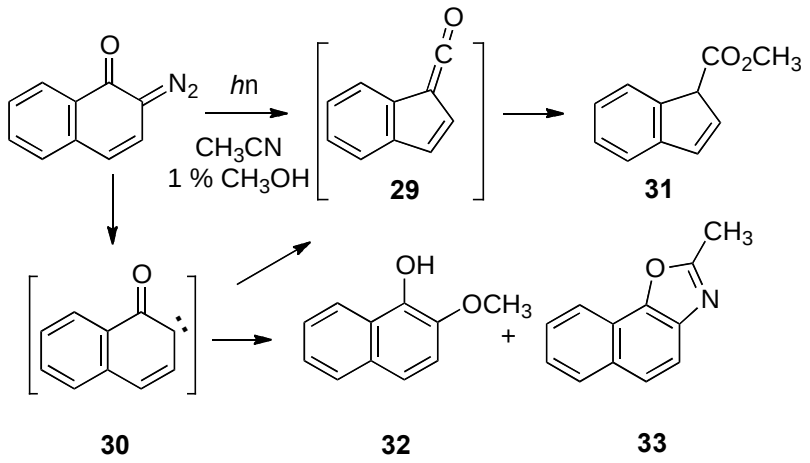
Lead tetraacetate oxidation of the aryl Grignard adducts from the same cyclobutenedione forms ketenyl radicals **27** which cyclize to furanones such as **28** (Scheme 14).[41]



Scheme 14. Ketenyl radical formation by hydroxycyclobutenol oxidation with lead tetraacetate.

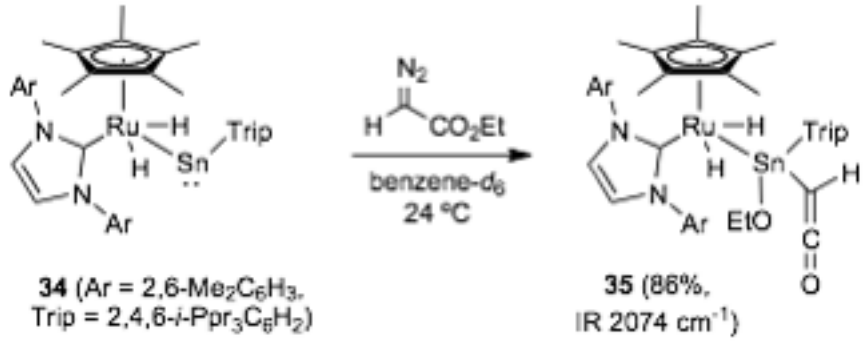
3.3. Ketenes from diazo-ketones

Photolysis of 2-diazo-1,2-naphthoquinone in methanol or acetonitrile/methanol is interpreted by Stern-Volmer analysis as occurring by formation of ketene **29** by concerted Wolff rearrangement, and by a stepwise reaction involving a carbene intermediate **30**. The ketene is captured by methanol forming the ester **31**, with partial capture of the carbene by methanol forming the phenol **32**; capture by acetonitrile forming 2-methylnaphth[2,1-*d*]oxazole (**33**) is also observed (Scheme 15).[42] It was concluded that a substantial part of the hot nascent carbene **30** formed by photolysis rearranges to the ketene **29** during its vibrational relaxation.



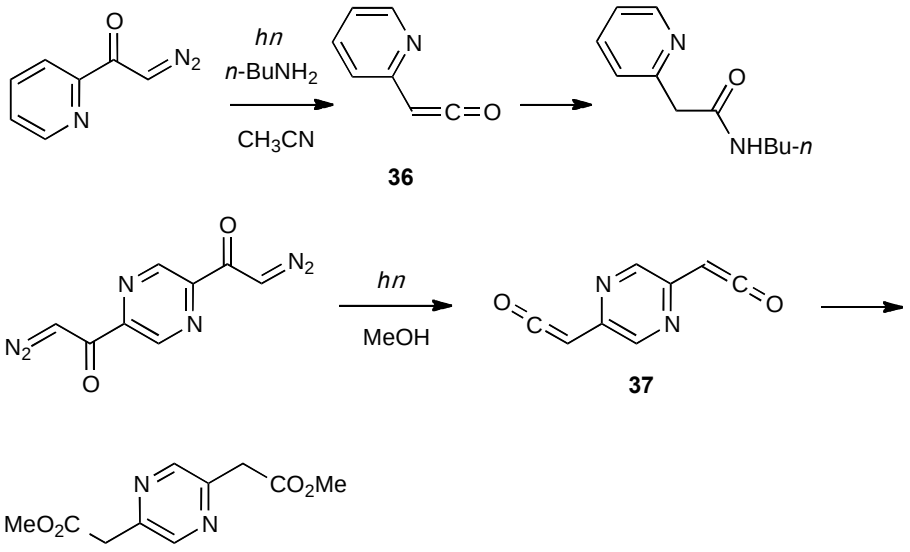
Scheme 15. Ketene formation by photochemical Wolff rearrangement.

Reaction of the ruthenium complex **34** with ethyl diazoacetate gave stannylketene **35**, characterized by X-ray and the distinctive ketenyl IR absorption at 2074 cm^{-1} (Scheme 16).[43]



Scheme 16. Stannylketene formation from ruthenium complex **34** with ethyl diazoacetate.

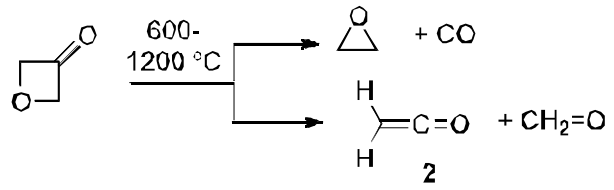
2-Pyridylketene (**36**) is formed by Wolff rearrangement of the corresponding diazo ketone, observed by IR at 2127 cm^{-1}, and captured by nucleophiles (Scheme 17).[44] Ketenes substituted with pyrrolyl,[45] pyrazinyl,[46] and pyrimidinyl groups are also formed by Wolff rearrangements of the relevant diazoketones,[46] and similar bisketenes are generated by ring opening of bis(diazoacetyl) precursors (Scheme 17).[46] The formation of **37** was confirmed by observation of the ketenyl IR absorption at 2123 and 2133 cm^{-1} in acetonitrile.[46]



Scheme 17. Formation of 2-pyridylketene (**36**) and of pyrazinylbisketene (**37**) by Wolff rearrangement.

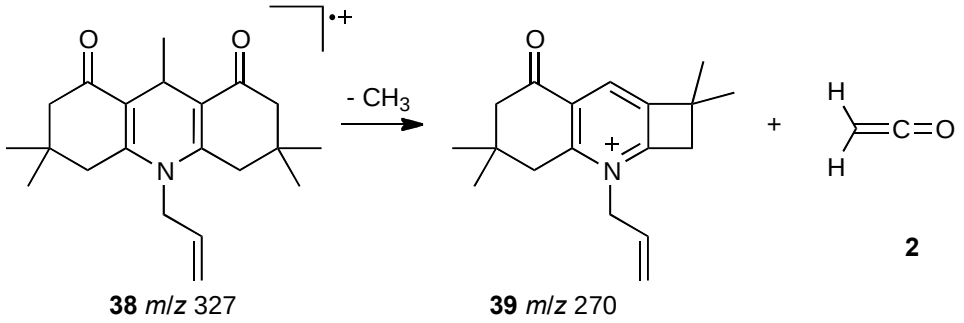
3.4. Ketenes by other photolytic, thermolytic and mass spectral methods

Gas-phase pyrolysis of 3-oxetanone in a hyperthermal nozzle begins at 600 ºC, and proceeds with cleavage to ethylene oxide and carbon monoxide, as well as ketene and formaldehyde (Scheme 18).[47]



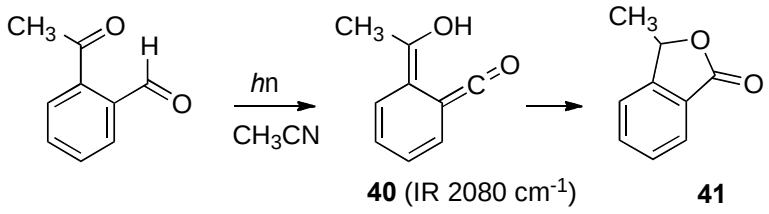
Scheme 18. Ketene formation by 3-oxetanone pyrolysis.

The 9-methylhexahydroacridinedione radical cation **38** is proposed to give mass spectral fragmentation to the fused 5-oxoquinolinium ion **39** with loss of a methyl radical and ketene (Scheme 19).[48]



Scheme 19. Ketene formation by acridinedione radical ion decomposition.

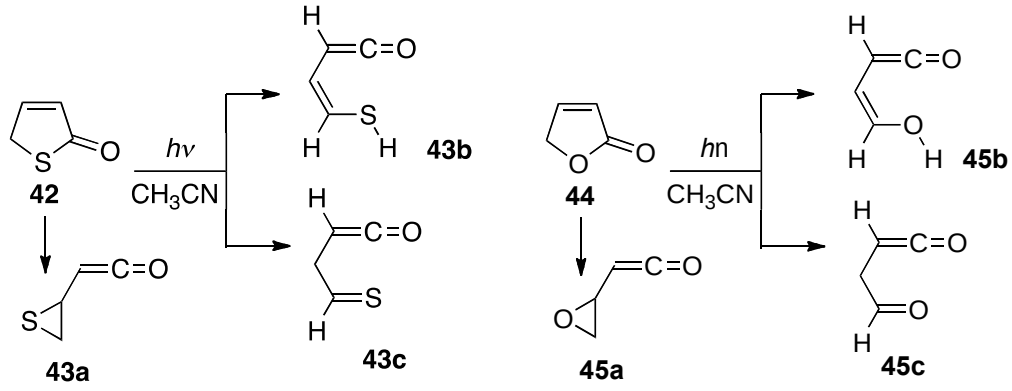
Photolysis of 2-acetylbenzaldehyde forms the ketene intermediate **40**, with IR absorption at 2080 cm^{-1}, which is suggested to form from an initial biradical intermediate within 2-3 ps, as observed by femtosecond stimulated Raman spectroscopy. The ketene has a lifetime of 1.4 μs and leads to 3-methylphthalide **41** with a quantum yield of 30% (Scheme 20).[49]



Scheme 20. Ketene formation by photolysis of 2-acetylbenzaldehyde.

Thiophenone **42** upon photolysis in CH_3CN gives IR absorption in the range 2000-2220 cm^{-1}, ascribed to ring opening forming ketenes **43** (Scheme 21) which revert to **42** with 60% efficiency.[50] Furanone **44** reacts similarly giving IR absorption in the range 2020-2180 cm^{-1}, ascribed to ketenes **45** (Scheme 21), which gives less than 10% reformation of **44**.[50] *Ab initio*

calculations of the reaction mechanism suggest an important role for dissociative (n/π)σ* states in these reactions (Figure 3).



Scheme 21. Ketene formation by thiophenone and furanone photolysis.

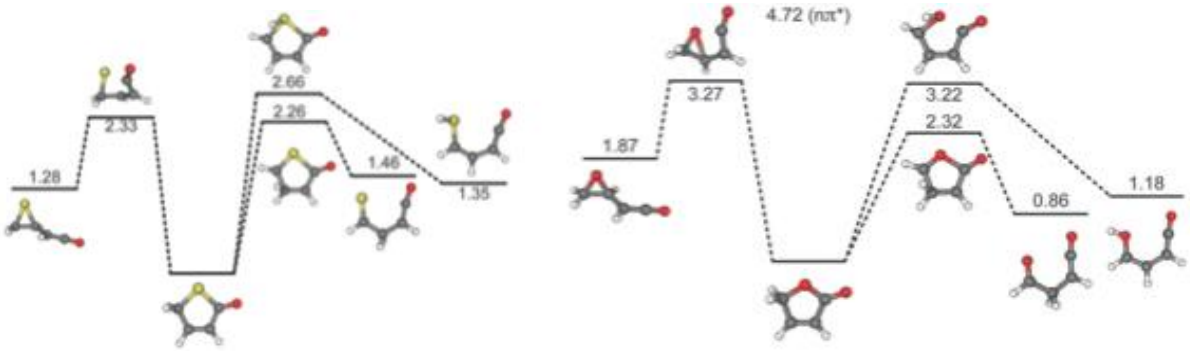


Figure 3. Calculated ketene formation from thiophenone and furanone (Reprinted with permission of the publisher [50]).

Computations based on electronic structure calculations and dynamics simulations of photoinduced reactions of 2-formyl-2*H*-azirine and isoxazole reveal that isoxazole (**46**) gives an excited state **47** which forms HCN and the CHCHO diradical **48** through the transition state TS_{CC}_VN_S0 (Fig. 4), and the diradical forms ketene through a 1,2-hydrogen shift reaction (Scheme 22).[51]

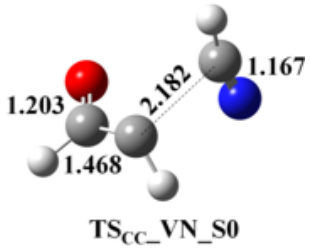
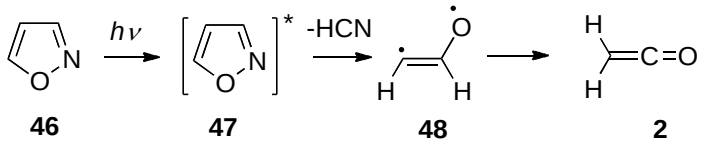
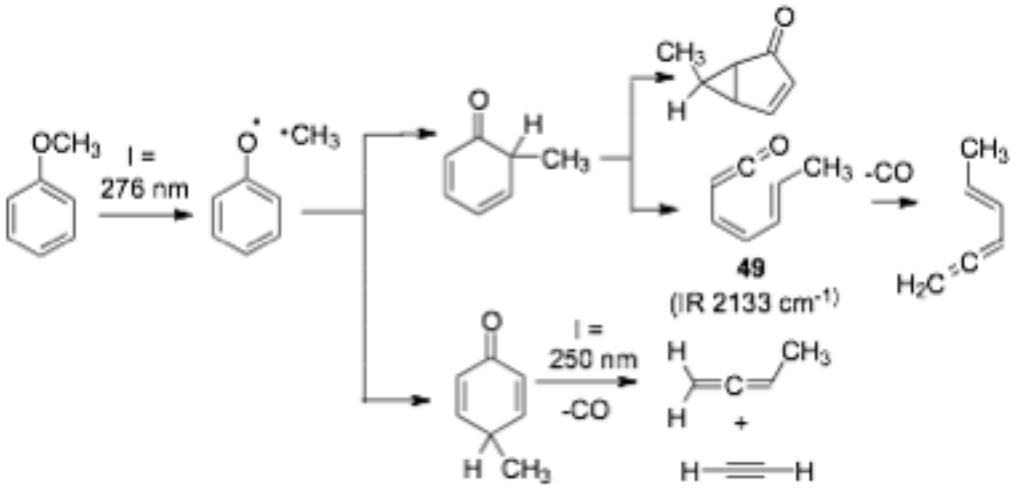


Figure 4. Calculated structure of TS_{CC}_VN_S0 **(**Reprinted with permission of the publisher [51]).



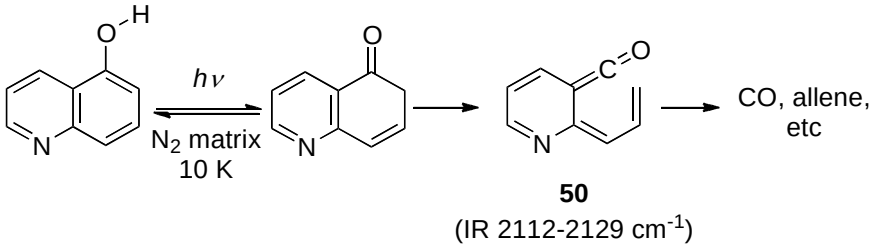
Scheme 22. Ketene formation by isoxazole photolysis.

Matrix photolysis of anisole results in formation of a radical pair followed by recombination at the 2- and 4-positions forming isomeric cyclohexadienones, which lead to the open-chain ketene **49** and other products (Scheme 23).[52]



Scheme 23. Matrix photolysis of anisole.

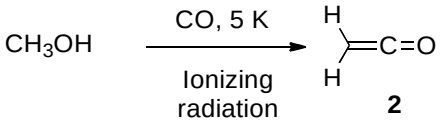
Photolysis of 5-hydroxyquinoline, forming ketene **50**, was studied by matrix isolation spectroscopy and computations (Scheme 24).[53] The ketene was identified by its characteristic IR absorption in the region 2112-2129 cm^{-1}.



Scheme 24. Ketene formation by 5-hydroxyquinoline photolysis.

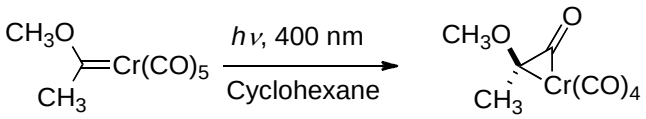
3.5. Ketenes from carbonylation processes

A radiation-induced process of methanol-carbon monoxide ices produces ketene among other small molecules (Scheme 25).[54] Ketene IR bands using isotope-labeled ices of methanol–carbon monoxide were also identified at 2107 cm^{-1} ($H_2C=C=^{18}O$) and at 2067 cm^{-1} ($H_2{}^{13}C=^{13}C=O$).[54]



Scheme 25. Ketene formation from irradiation in methanol-carbon monoxide ice.

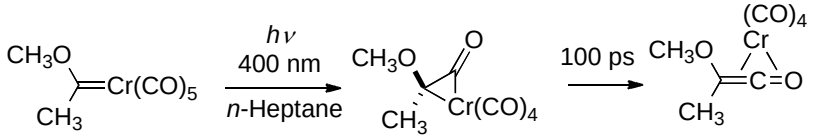
Photolysis of the Fischer chromium complex **51** using low temperature matrix isolation with picosecond time resolved observation indicated the formation of the chromium ketene complex **52**, as detected by IR absorption at 1777 and 1990 cm^{-1}, consistent with time-dependent density function calculations (Scheme 26).[55]



51 **52** (IR 1777, 1990 cm^{-1})

Scheme 26. Chromium ketene complex formation by carbene complex photolysis.

An independent study[56] of this system as well as of the corresponding tungsten complex found that, in contrast to the previous work, which indicated triplet states in the case of the chromium complex, no evidence for the formation of triplet states was observed. The later investigators preferred the reaction path forming structures **53** and **54** (Scheme 27).[56]

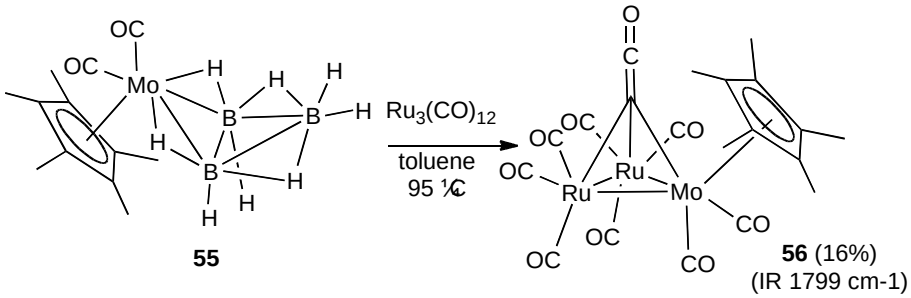


51 **53** (IR 1770 cm^{-1}) **54** (1945 cm^{-1})

Scheme 27. Alternative interpretation of chromium ketene complex formation by carbene complex photolysis.

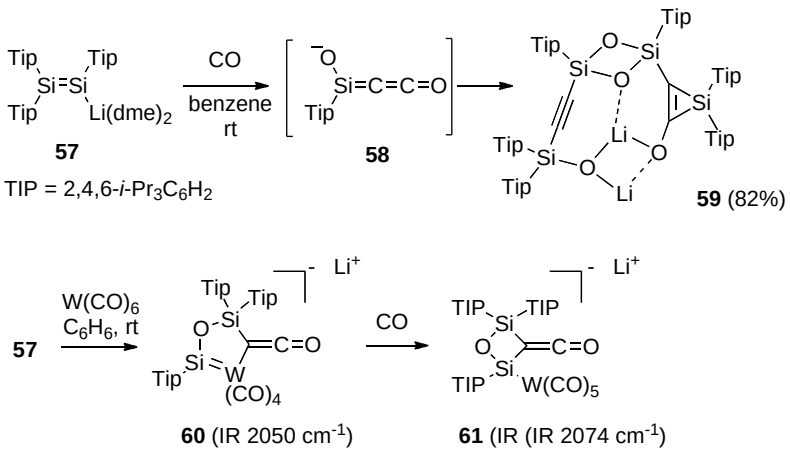
Reaction of cluster arachno-[Cp*Mo$(CO)_2B_3H_8$] (**55**) with [$Ru_3(CO)_{12}$] gave the stable heterometallic ketenylidene cluster [Cp*Mo$(CO)_2$(μ-H)$Ru_2(CO)_6$(μ3-η1-CCO)] **56** (Scheme 28)

as red crystals, IR (C=C=O, 1799 cm^{-1}), together with [Cp*Mo(CO)$_2${Ru(CO)$_3$}$_4$B], with the structure of **56** established by single-crystal X-ray crystallographic analysis.[57]



Scheme 28. Formation of a ketenylidene molybdenum-ruthenium complex.

Carbon monoxide reduction by lithium disilenide **57** forms a silanone dimer **59** proposed to form through the ketenyl intermediate **58**.[57] Related ketenyl species **60** (Figure 5)and **61** were also prepared from **57** (Scheme 29) and characterized.[57]



Scheme 29. Silanone formation by carbon monoxide reduction of a lithium disilenide.

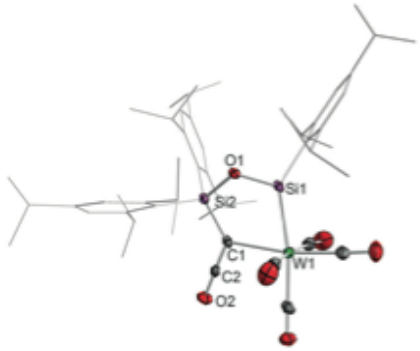
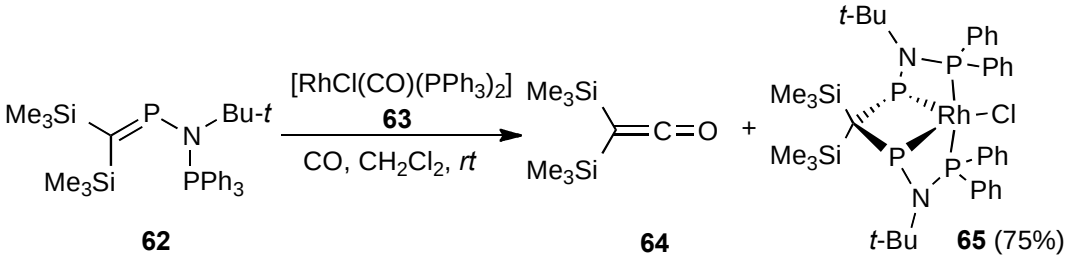


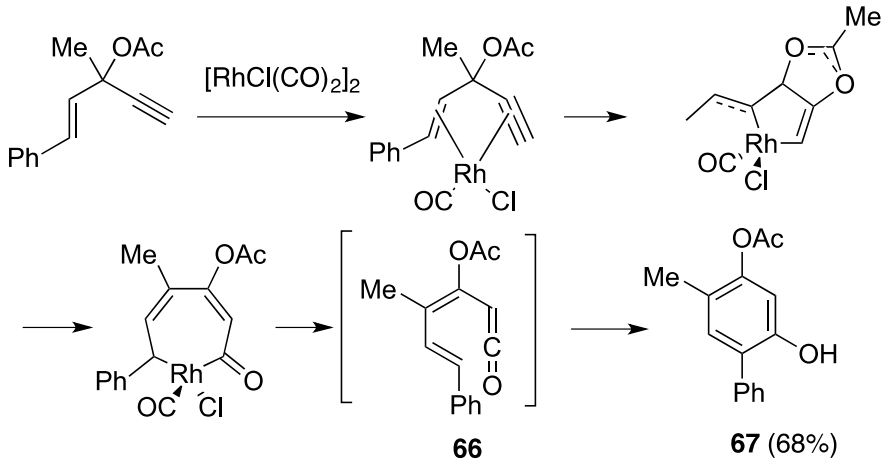
Figure 5. X-ray structure of ketenylene **60 (**Reprinted with permission from the publisher [58]).

Bis(trimethylsilyl)ketene (**64**) is proposed to be expelled during preparation of the rhodium complex **65** from reaction of **62** with the phosphine ligand **63** the presence of carbon monoxide (Scheme 30).[59] Ketene **64** was identified by the distinctive ^{13}C NMR of the reaction product.



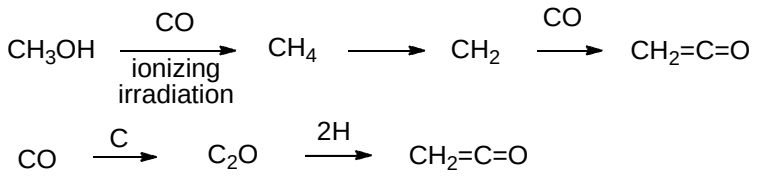
Scheme 30. Expulsion of bis(trimethylsilyl)ketene in preparation of a Rh(III)-coordinated tetradentate ligand.

Rhodium catalyzed reaction of 3-acyloxy-1,4-enynes leads to resorcinol products by a mechanism calculated by DFT methods to involve a [5 + 1] cycloaddition with successive 1,2-acyloxy migration, CO insertion, and reductive elimination to ketene intermediate **66**, 6π-electrocyclization, and aromatization to **67** (Scheme 31).[60]



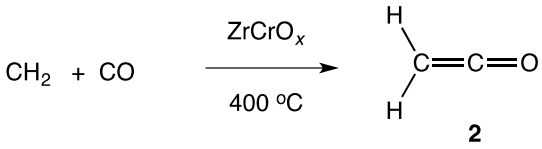
Scheme 31. Ketene formation during rhodium catalyzed reaction of 3-acyloxy-1,4-enynes.

In a study of the chemical evolution and the origin of oxygen-containing organic molecules in space, photolysis of methanol/carbon monoxide ices at 5.5 K using single photoionization reflection time-of-flight (ReTOF-PI) mass spectrometry detected ketene formation in $^{13}CH_3OH$ and $CH_3{}^{18}OH$ ices via the observation of the ν_2 fundamental at 2067 cm^{-1} ($^{13}CH_2{=}{}^{13}C{=}O$) and 2107 cm^{-1} ($CH_2{=}C{=}{}^{18}O$).[54] Two possible suggested routes to ketene are shown in Scheme 32.[54]



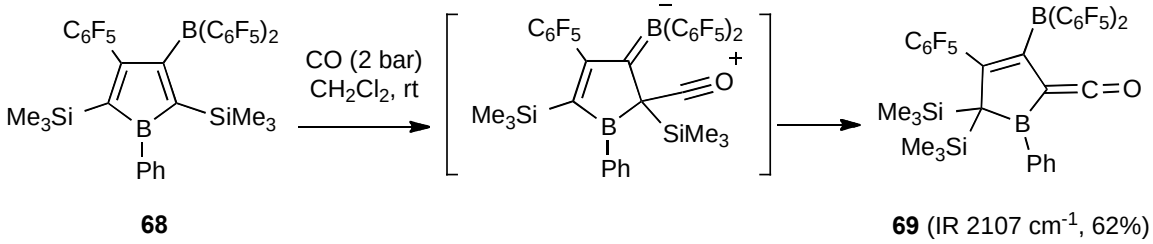
Scheme 32. Possible ketene formation from photolysis of methanol/carbon monoxide ices in space.

A particularly interesting finding is that ketene formation by the combination of CH_2 with carbon monoxide is implicated in the conversion of synthesis gas to olefins in the Fischer-Tropsch process (Scheme 33).[61,62]



Scheme 33. Ketene formation in the Fischer-Tropsch process.

Reaction of the anti-aromatic borole **68** with carbon monoxide gives the boron substituted ketene **69** in a process proposed to occur by addition of CO followed by migration of a trimethylsilyl group (Scheme 34).[63] The structure of **69** was confirmed by determination of the X-ray structure (Figure 6).



68 **69** (IR 2107 cm^{-1}, 62%)

Scheme 34. Ketene formation from reaction of an antiaromatic borole with carbon monoxide.

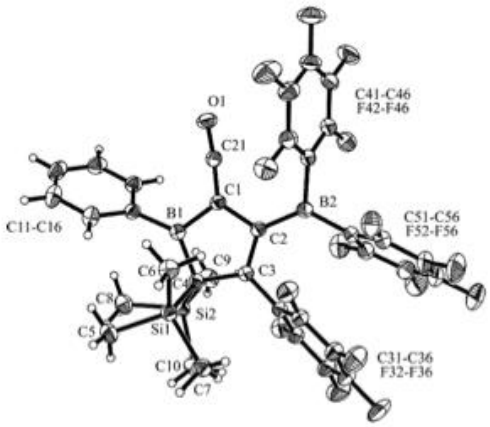


Figure 6. X-ray structure of ketene **69** (Reprinted with permission of the publisher [63]).

Intramolecular coupling of carbenes with CO in metal carbonyl radicals leading to ketene complexes has been examined by computational methods, and a variety of pathways are obtained for $M(CH_2)(CO)_3$ (M = Co, Rh, Ir) (Figure 7).[64]

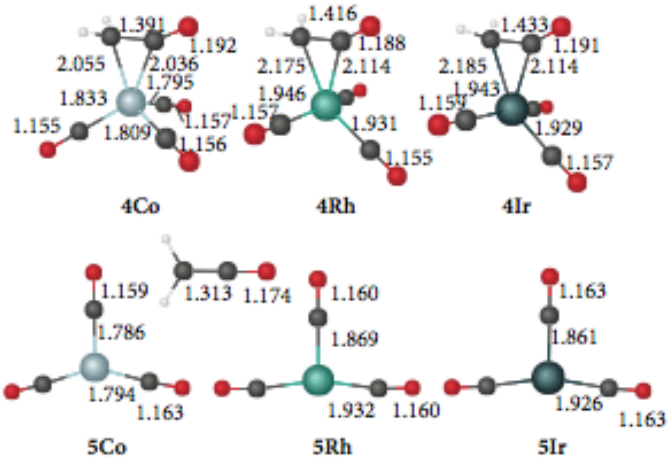
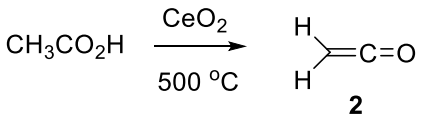


Figure 7. Coordinatively saturated ketene complexes with carbenes (Reprinted with permission of the publisher [64]).

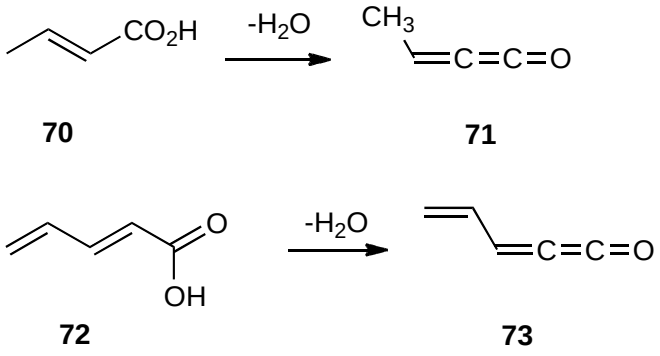
3.6. Ketenes from carboxylic acids and their derivatives

Acetic acid decomposition on Pt(III) gave ketene and acetaldehyde formation as the major decomposition pathway,[65] while acetic acid on CeO_2 formed ketene above 500 K (Scheme 35).[66]



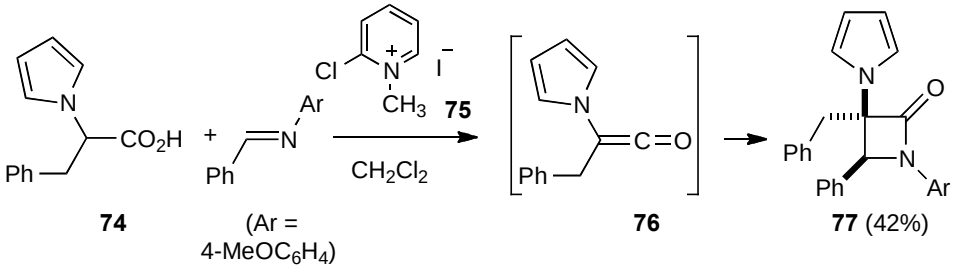
Scheme 35. Ketene formation from acetic acid on CeO_2.

Computations have been used to study the dehydration of unsaturated acids such as **70** forming the extended ketene **71**,[67] as well as of other unsaturated acids to the corresponding ketenes.[67] In a separate investigation dehydration of the dienyl acid **72** to the vinyl extended ketene **73** was included (Scheme 36).[68]



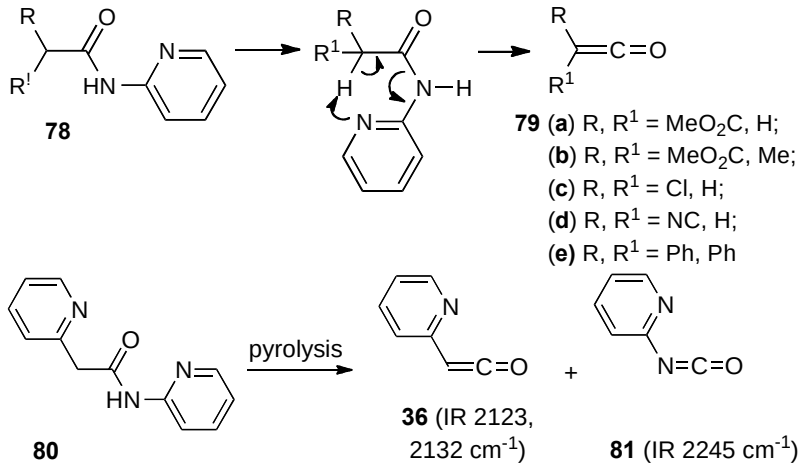
Scheme 36. Computational studies of extended ketene formation.

Mukaiyama's reagent (**75**) is used for the dehydration of 3-phenyl-2-(1*H*-pyrrol-1-yl)-propanoic acid (**74**), forming ketene **76**, which in the presence of benzylidene-*p*-anisidine reacts by [2+2] cycloaddition giving the β-lactam **77** (Scheme 37).[69]



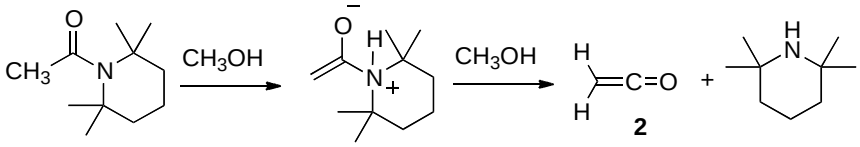
Scheme 37. Ketene formation by carboxylic acid dehydration with Mukaiyama's reagent.

Flash vacuum pyrolysis of *N*-(2-pyridyl)acetamides **78** generates ketenes **79** by elimination, and these are trapped by argon matrix isolation of the products, with characterization of the ketene products by IR absorption between 2106 and 2156 cm^{-1} (Scheme 38).[70] Similar pyrolysis of **80** gave 2-pyridylketene (**36**) as well as the isocyanate **81**, and the isocyanate formation is attributed to hydrogen elimination by the second pyridyl group.[70]



Scheme 38. Ketene formation by pyridyl ester pyrolysis.

The rather facile reaction of *N*-(2,2,6,6-tetramethylpiperidinyl) amides with methanol was studied by DFT computational methods, and it was concluded the lack of conjugation in the twisted geometry of the amide permitted hydrogen transfer from methanol to nitrogen which promoted dissociation to ketenes (Scheme 39, Figure 8).[71]



Scheme 39. Ketene formation from twisted amides.

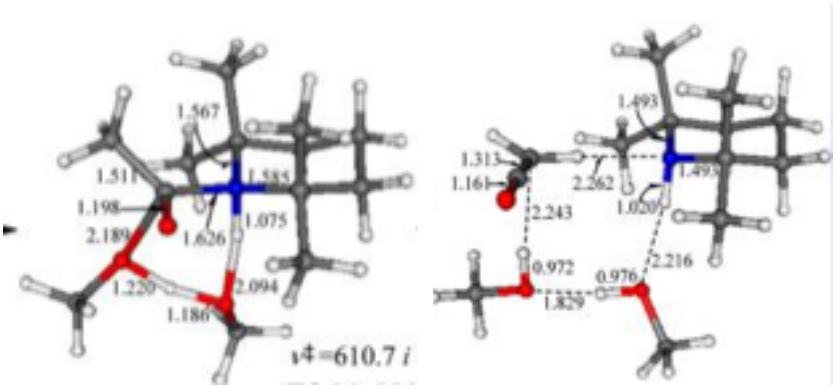
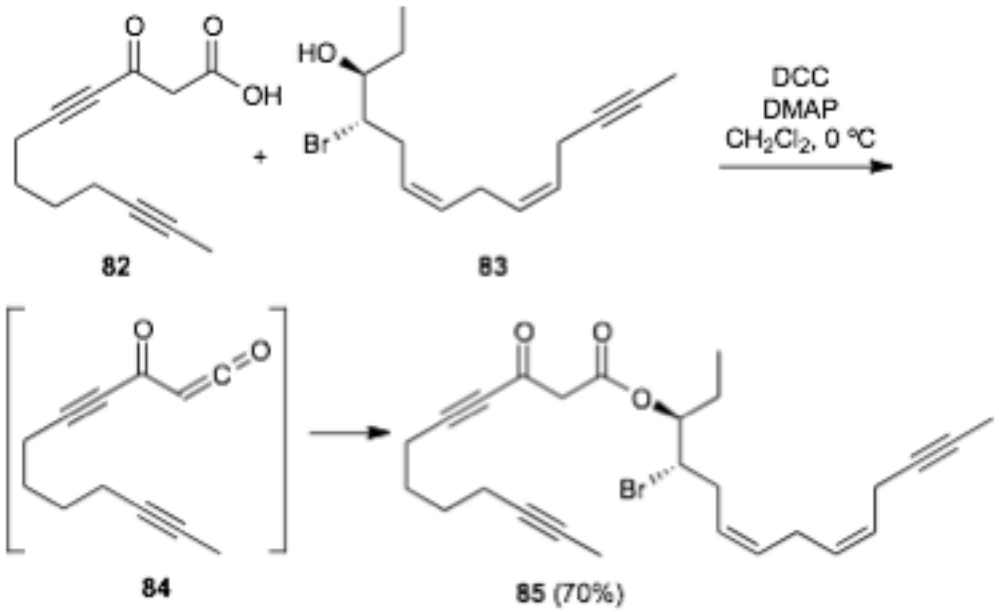


Figure 8. Facile amide methanolysis with ketene elimination (Reprinted with permission from the publisher [71]).

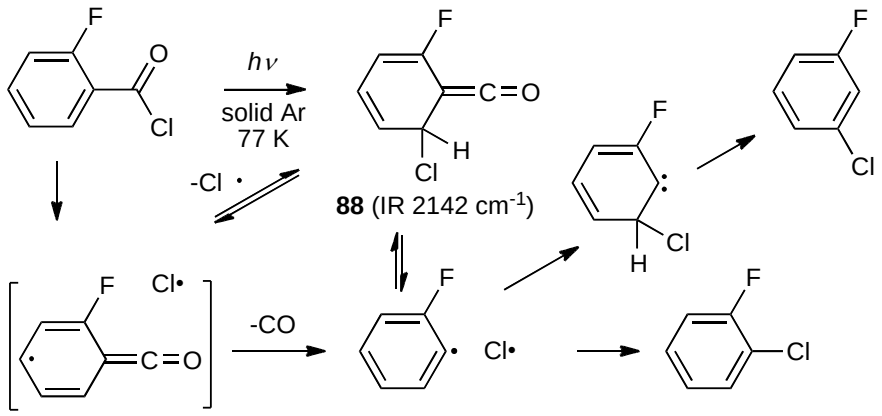
Acyl ketene **84** generated from carboxylic acid **82** by dehydration with dicyclohexyl-carbodimide reacts with the alcohol **83** forming ester **85**, which is used in macrolide synthesis (Scheme 40).[72]



Scheme 40. Ketene generation by carboxylic dehydration, followed by esterification.

Photolysis of dichloroacetyl chloride in argon matrices with product analysis by IR revealed the formation of dichloroketene, $Cl_2C=C=O$ (**86**), with absorption at 2155 cm^{-1}, and chloroketene ClCH=C=O (**87**) at 2150 cm^{-1}, both as minor products, while the major pathways involved C–C bond cleavage.[73]

2-Fluorobenzoyl chloride upon photolysis in an Ar matrix underwent rotational isomerization and also formation of ketene **88** and dissociation leading to fluorobenzoyl radical, which upon decarbonylation forms *o*-chlorofluorobenzene, *m*-chlorofluorobenzene and CO (Scheme 41).[74]



Scheme 41. Ketene formation by photolysis of 2-fluorobenzoyl chloride.

Reduction of stearic acid on Ni/ZrO_2 is interpreted as involving formation of the ketene **89** (*n*-$C_{14}H_{29}CH=C=O$) (**89**), as detected by strong IR absorption at 2050–2150 cm^{-1},[75] and formed by an elimination process followed by further hydrogenation to the alcohol and then decarbonylation (Figure 9).[76]

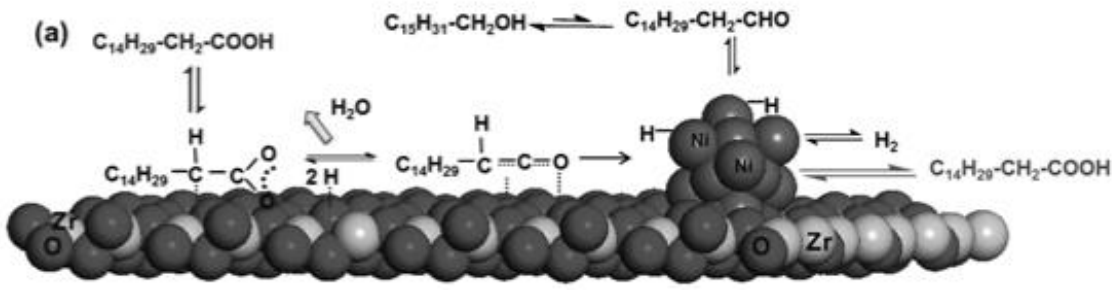


Figure 9. Ketene formation by carboxylic acid reduction (Reprinted with permission from the publisher [76]).

Studies of formation of gold ketenylidene species from carboxylic acids show that reactions of propionic and butyric acids on Au/TiO_2 proceed by dehydrogenation at the C2-C3 positions and oxidation to β-keto acids and decarboxylation with conversion into the gold ketenylidene intermediate $Au_2C=C=O$ (**90**), which also formed from acetic acid (Figure 10).[77]

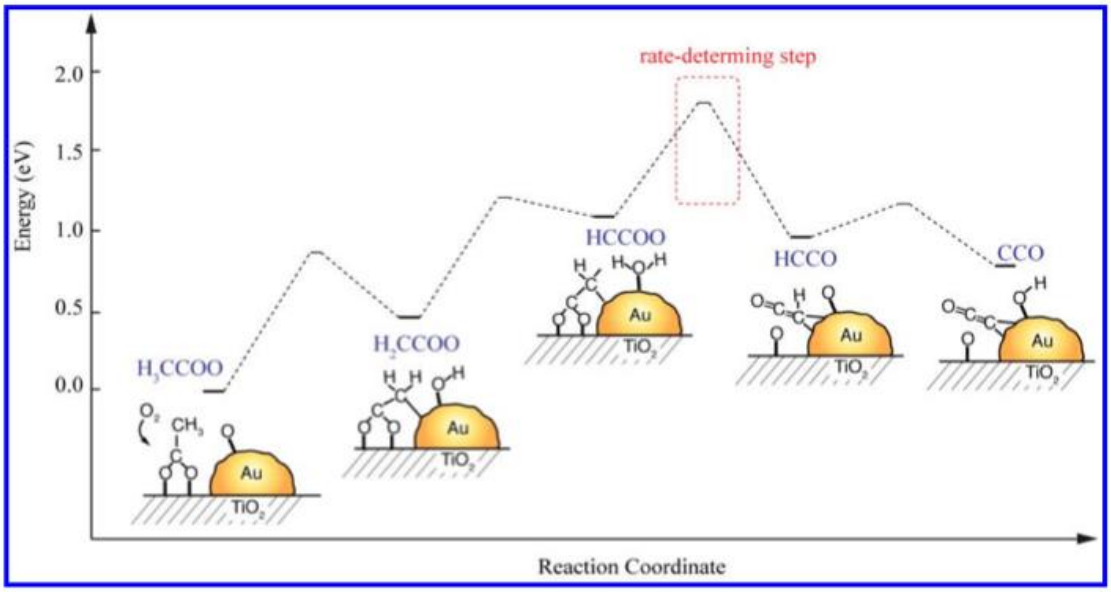
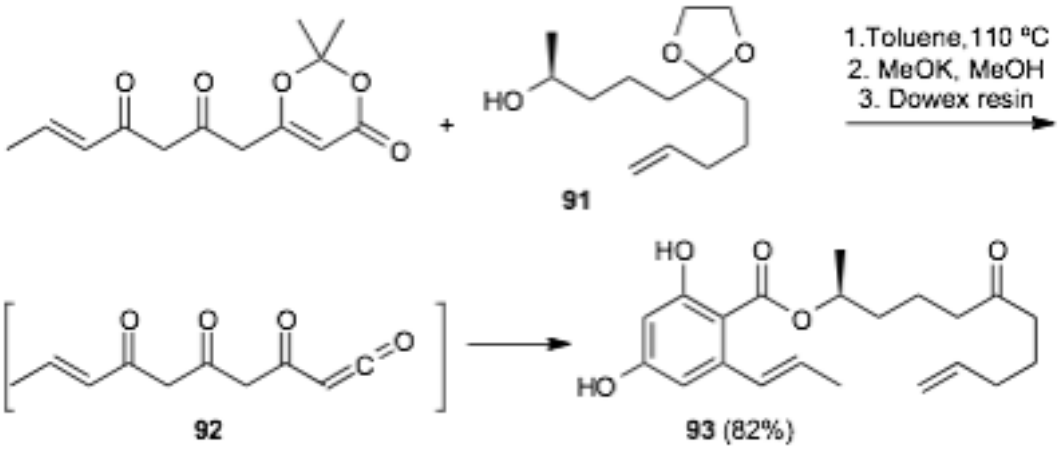


Figure 10. Gold ketenylidene formation for acetate oxidation on Au/TiO_2 (Reprinted with permission from the publisher [77]).

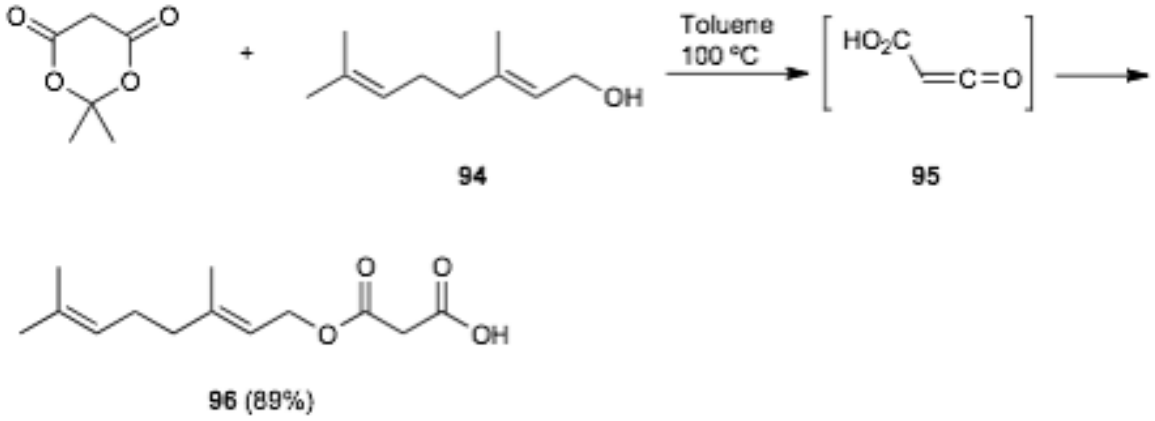
3.7. Ketenes from dioxinones and ethynyl ethers

Applications of ketenes generated by dioxinone thermolysis in synthesis have been reviewed;[78] in the example of the synthesis of zearalenone (**93**, Scheme 42)[79] the ketene intermediate **92** reacts with alcohol **91**, followed by cyclization of the side chain after the esterification step.



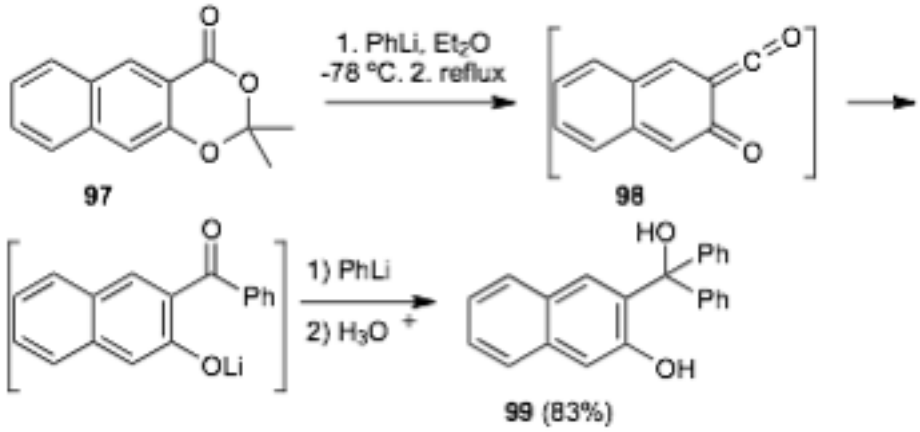
Scheme 42. Ketene generation with esterification and cyclization.

Dioxinone thermolysis also provides a useful route to carboxy-substituted ketenes, as in the generation of the simple carboxyketene from Meldrum's acid, probably via its enolic form. Ketene **95** was trapped by alcohol **94** to give the product ester **96** (Scheme 43).[80]



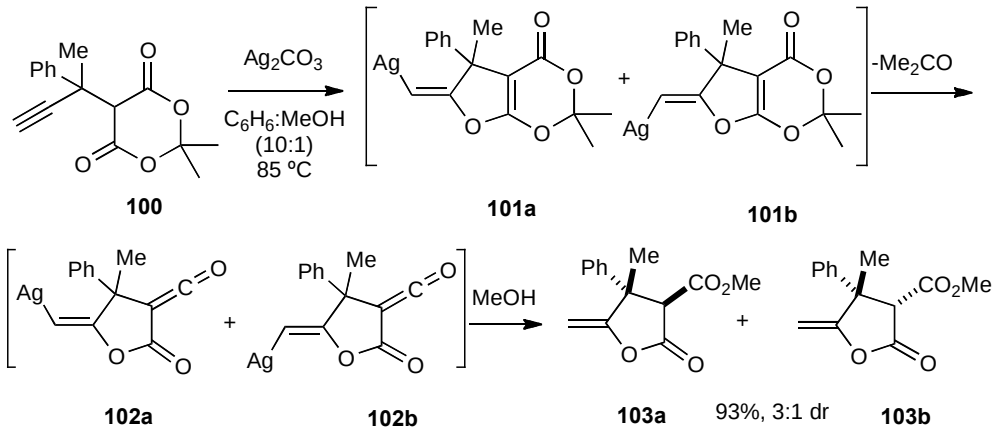
Scheme 43. Generation and capture of a carboxyketene.

The naphthodioxinone **97** upon reaction with three equivalents of phenyllithium in toluene at -78 ºC followed by reflux gave the triarylmethanol **99** in a reaction interpreted as proceeding through formation of the ketene **98** (Scheme 44).[81]



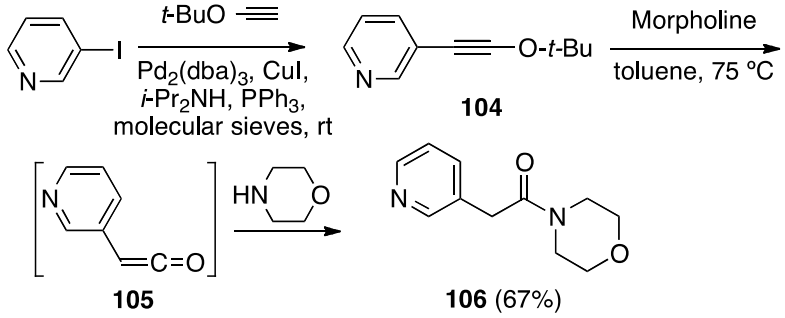
Scheme 44. Ketene generation with *in situ* capture by phenyllithium.

Meldrum's acid derivative **100** upon thermolysis with silver ion catalysis leads to γ-alkylidene butyrolactones **103** in reactions interpreted as involving formation of dioxinones **101** which form acylketene intermediates **102** (Scheme 45).[82] The possibility of stereoselective complexation of the silver ion affecting the product stereochemistry was also considered.



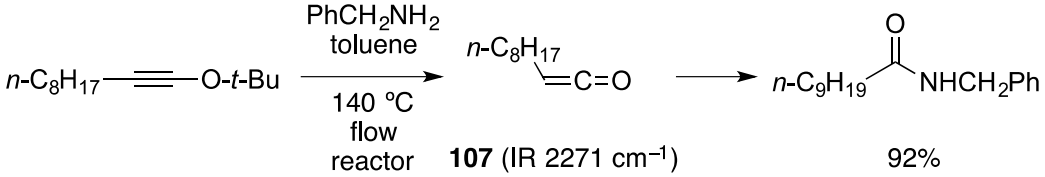
Scheme 45. Generation of acylketenes by thermolysis of Meldrum's acid derivatives with silver catalysis and esterification.

3-Pyridyl ketene **105** generated by thermolysis of intermediate *tert*-butyl arylethynyl ether **104**, prepared from 3-iodopyridine by palladium-catalyzed coupling with *tert*-butyl ethynyl ether, reacts with morpholine in toluene forming the morpholide **106** (Scheme 46).[83]



Scheme 46. Amide from ketene generated by thermolysis of pyridylethynyl *tert*-butoxy ethers.

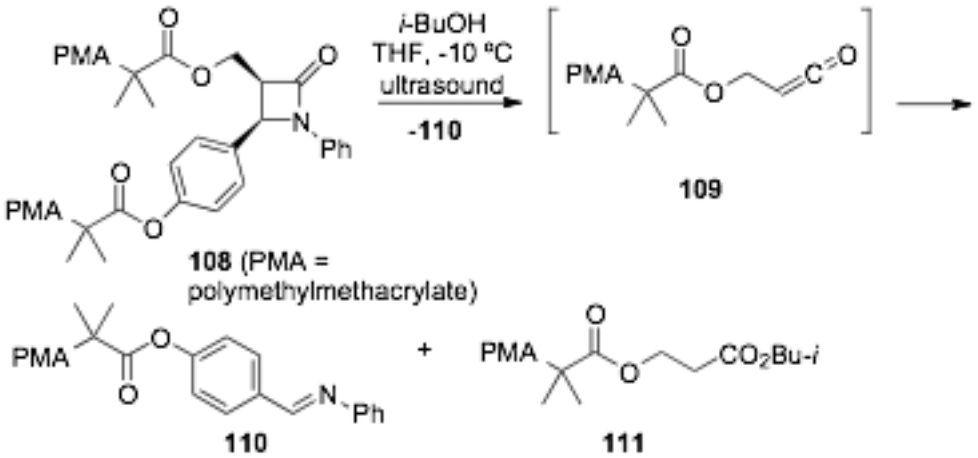
Ketene **107** generated by alkoxyalkyne thermolysis under flow conditions reacts with amines or alcohols forming amides (Scheme 47) or esters, respectively.[84]



Scheme 47. Ketene generation and amination in a flow reactor.

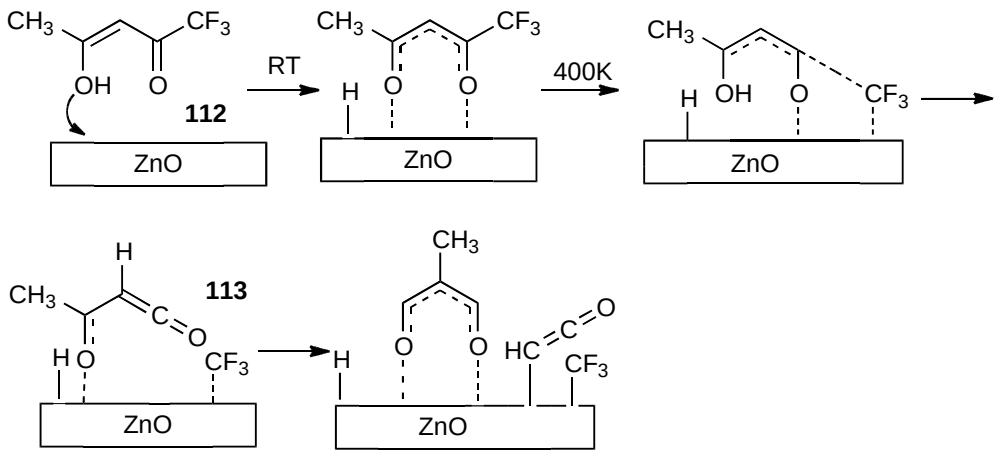
3.8. Ketenes by other methods

Cleavage of model β-lactams by mechanical activation using ultrasound was studied by both computational and experimental methods.[85] Ultrasonication of β-lactam **108** in THF in the presence of isobutanol as a trapping agent resulted the formation of imine **110**, as well as the ester **111** from trapping of ketene **109** (Scheme 48).[85] GPC analysis indicated that 68% of the chains were cleaved.



Scheme 48. Ketene generation by β-lactam cleavage and capture by alcohols.

Trifluoroacetylacetone **112** on a ZnO surface, as studied by Fourier-transform infrared spectroscopy (FT-IR), X-ray photoelectron spectroscopy (XPS), and density functional theory (DFT) computations, is proposed to form complexes of acetylketene ($CH_3COCH=C=O$, **113**) intermediates by loss of the CF_3 group near 400 K, as observed by IR absorption in the region near 2084 and 1990 cm^{-1} (Scheme 49).[86]



Scheme 49. Ketene formation on a ZnO surface.

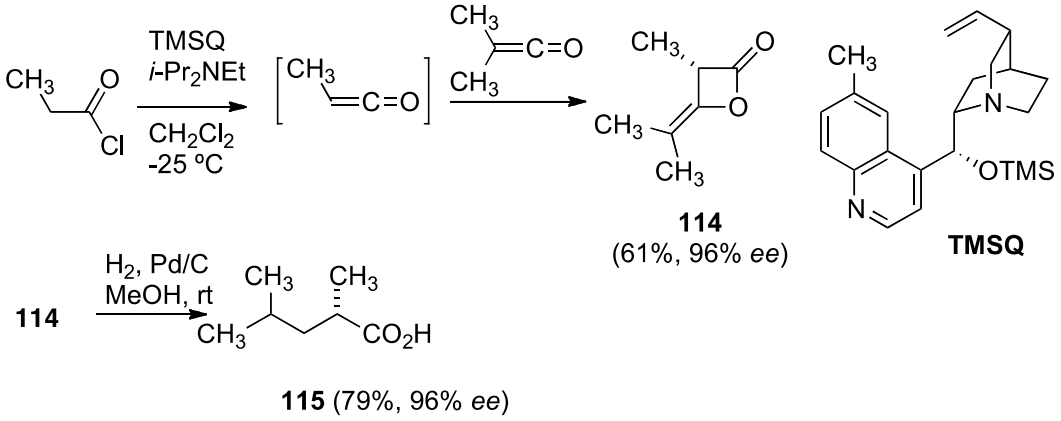
The gas-phase structure of ketene generated by pyrolysis of acetic anhydride has been determined, using a recently developed very high temperature inlet nozzle system.[87]

Analysis of available telescopic data for the solar-type protostar IRAS16293-2422 led to the identification of the parent ketene formed in space, together with other small organic molecules.[88]

4. Cycloaddition Reactions of Ketenes

4.1. Ketene dimers, preparations and applications

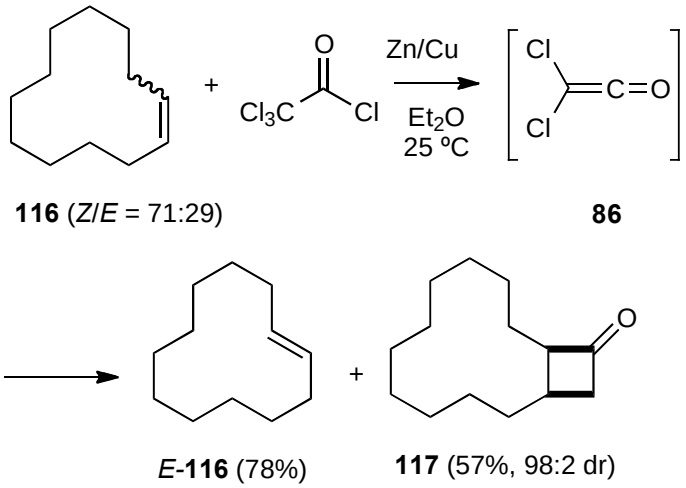
Asymmetric ketene dimers including **114** are prepared by a process where a more reactive ketene is generated in the presence of a less reactive ketene in the presence of a chiral catalyst (Scheme 50).[89] The catalyst adds to the more reactive ketene and the resulting reactive enolate reacts with the less reactive ketene to form the unsymmetrical dimer. By this process methylketene formed by dehydrochlorination in methylene chloride in the presence of the chiral catalyst TMS-quinine (TMSQ) reacts with dimethylketene forming the mixed dimer **114** (Scheme 50).[89] The dimer is converted by catalytic hydrogenolysis with regioselective ring opening to form **115** (Scheme 50).[90] See also Scheme 66



Scheme 50. Stereoselective formation of mixed ketene dimer and subsequent hydrogenolysis.

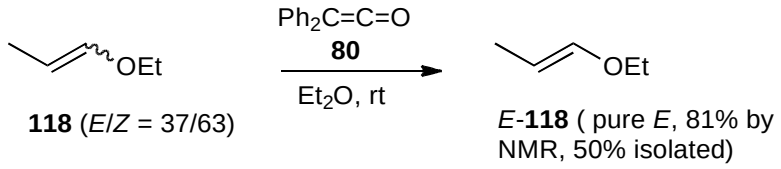
4.2 [2+2] Cycloaddition reactions with carbon-carbon double and triple bonds

Limited amounts of a ketene such as **86** can react with a mixture of *Z* and *E* olefins **116** resulting in kinetic resolution by [2+2] cycloaddition, with isolation of pure unreacted *E* alkenes, as well as isolation of pure *cis*-cyclobutanone **117** (Scheme 51; dechlorination by the zinc-copper couple occurs). This result is attributed to the much greater reactivity of the *Z*-alkenes, which permits more facile reaction from the unsubstituted side by the ketene.[91]



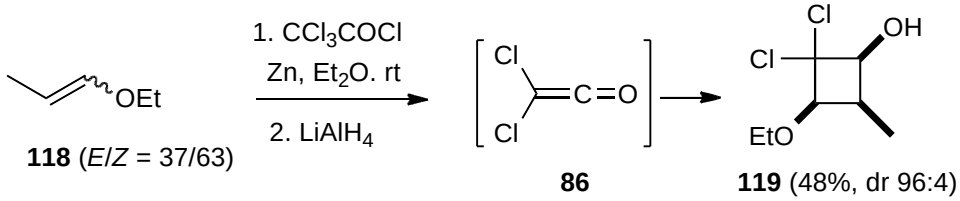
Scheme 51. Kinetic resolution of *E/Z* alkenes by ketene [2+2] cycloaddition.

In a further application of this methodology reaction of alkenes **118** as a *Z*/*E* mixture of isomers with diphenylketene gave the pure *E*-allylic ether (*E*)-**118**, isolated in 50% yield. (Scheme 52).[91]



Scheme 52. Kinetic resolution of *E*/*Z* alkenes by selective reaction of *Z*-isomers with ketenes.

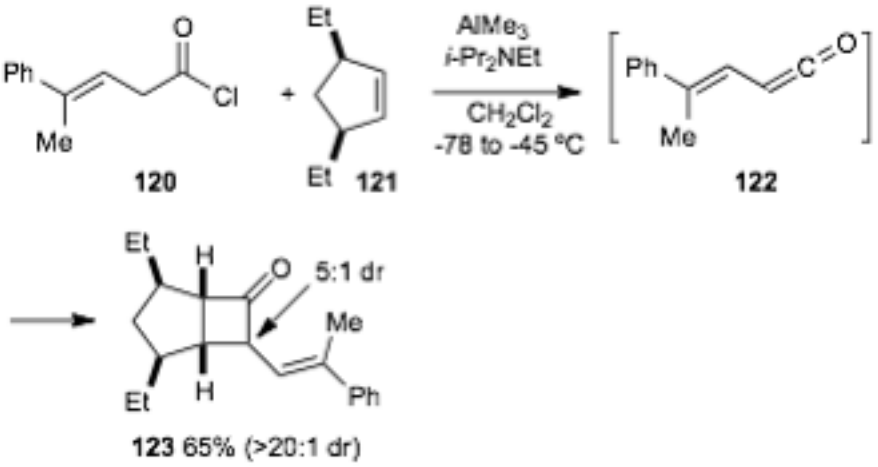
In another example, reaction of **118** with 0.15 equivalents of *in situ* generated dichloroketene (**86**) followed by reduction with lithium aluminum hydride gave the cyclobutanol **119** (Scheme 53).[91]



Scheme 53. Selective reaction of *E*-isomers with ketenes.

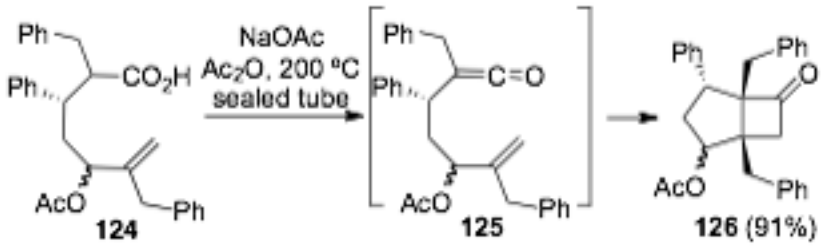
Vinylketene **122** generated by dehydrochlorination of **120** reacts in a [2+2] cycloaddition with alkene **121** with catalysis by trimethylaluminum forming the cyclobutenone **123** (Scheme 54), which was used in the synthesis of gracilioether F.[92] The stereoselectivity of the

cycloaddition was >20:1, and the stereochemistry of the substituent at C7 was not relevant in the remaining synthesis.



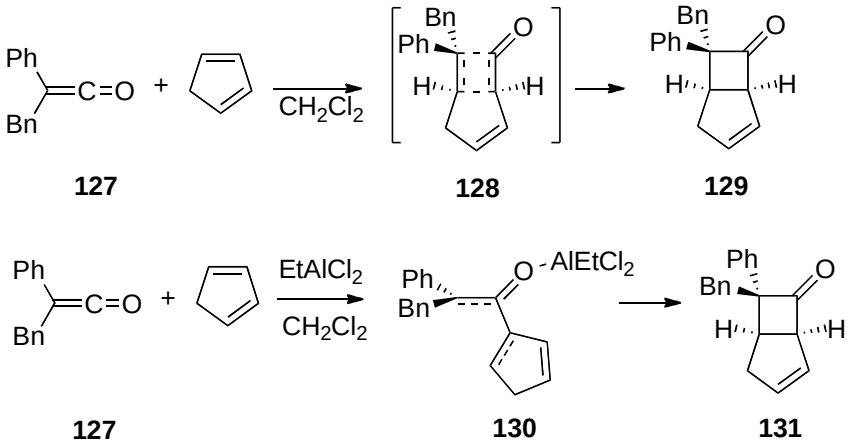
Scheme 54. Stereoselective [2+2] cycloaddition to alkenes.

Ketene **125**, generated by dehydration of carboxylic acid **124**, in an intramolecular [2+2] cycloaddition forms cyclobutanone **126** (Scheme 55), and this was used as a precursor of ophiodilactones.[93]



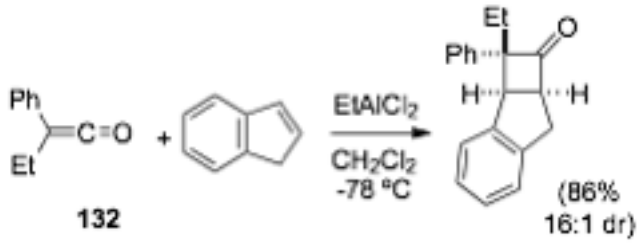
Scheme 55. Ketene generation and intramolecular [2+2] alkene cycloaddition.

A computational study of [2+2] cycloaddition of benzylphenylketene (**127**) with cyclopentadiene shows a preference for formation of **129** in an uncatalyzed concerted reaction through transition state **128** (Scheme 56).[94] The computations suggest that the reaction promoted by Lewis acid catalysis with ethylaluminum dichloride ($EtAlCl_2$) proceeds in two steps with formation of an intermediate **130** which closes to form the stereoisomeric product **131** (Scheme 56).[94]



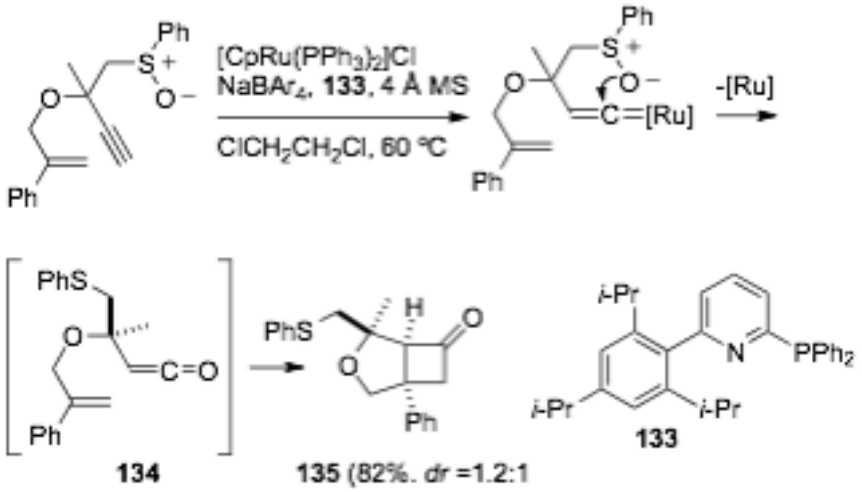
Scheme 56. Computed stereoselectivity in uncatalyzed and catalyzed ketene [2+2] cycloaddition with alkenes.

Computational analysis was also used to interpret the stereoselective Lewis acid catalyzed [2+2] cycloaddition of phenylethylketene (**132**) with arylalkenes (Scheme 57).[95]



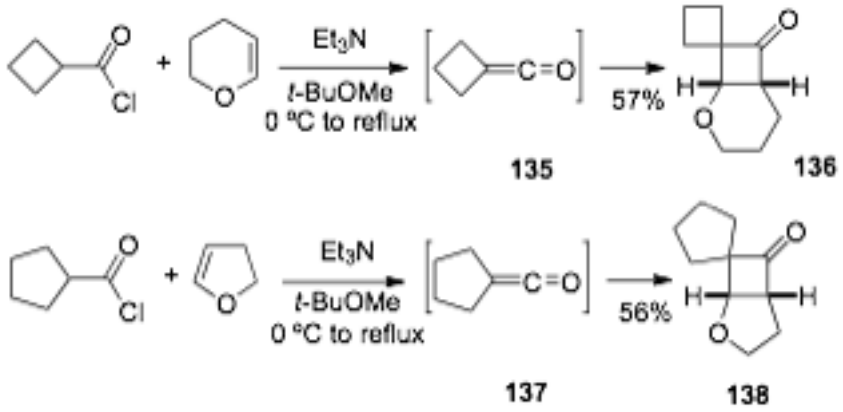
Scheme 57. Stereoselectivity in ketene/alkene [2+2] cycloaddition.

Ketene generation from terminal alkynes using ruthenium catalyzed oxidation with use of the phosphine **133** as a co-catalyst gives intramolecular cyclobutanone (**135**) formation (Scheme 58).[95] Similar ketene generation in the presence of imines leads to β-lactams.[96]



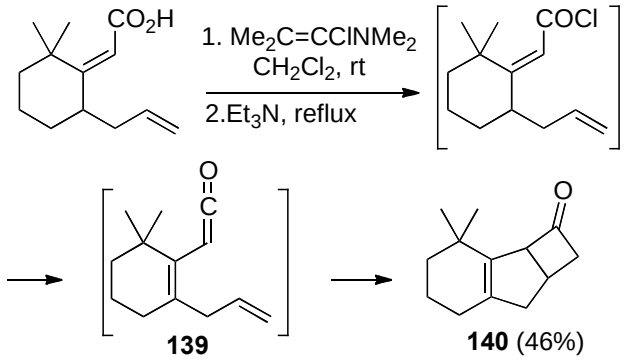
Scheme 58. Ruthenium-catalyzed ketene generation and stereoselective cycloaddition.

Trimethylene- and tetramethylene-ketenes (**135**, **137**) generated by acyl chloride dehydrohalogenations give [2+2] cycloaddition reactions with dihydrofuran and dihydropyran forming spirocyclic cyclobutanones **136**, **138** (Scheme 59).[97]



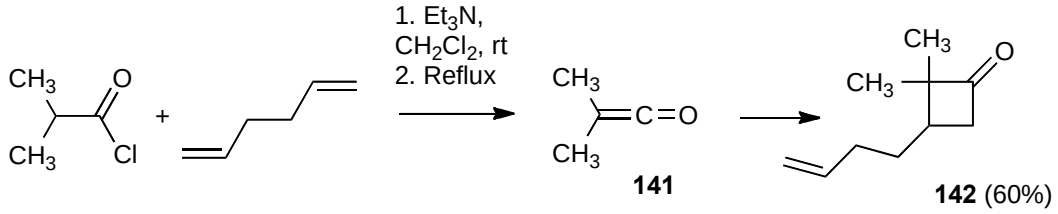
Scheme 59. Ketene [2+2] cycloaddition with cyclic vinyl ethers forming spirocyclic cyclobutanones.

Generation of dienylketene **139** by dehydrochlorination of the acyl chloride prepared using the Ghosez reagent followed by intramolecular [2+2] ketene-alkene cycloaddition forms the ring-fused cyclobutanone **140**, used in the synthesis of strigolactones (Scheme 60).[98]



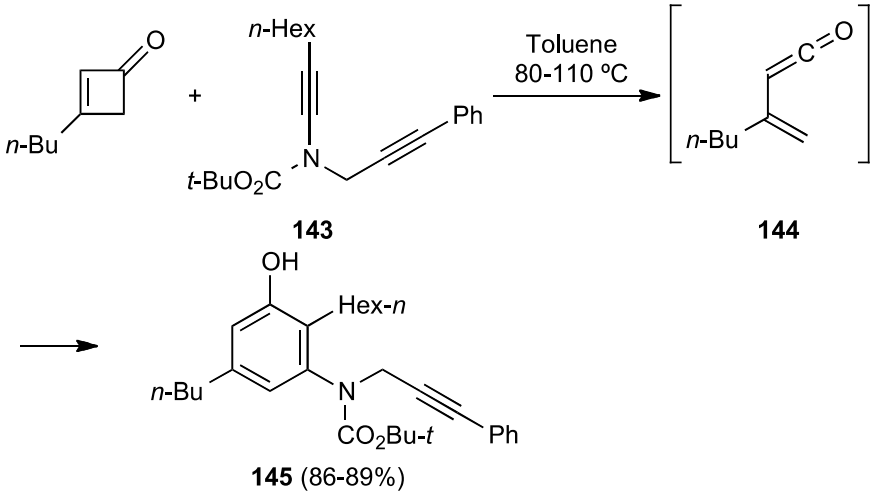
Scheme 60. Intramolecular dienylketene cyclization.

Dimethylketene (**141**) reacts with 1,5-hexadiene by [2+2] cycloaddition forming cyclobutanone **142**, used in the synthesis of junionone (Scheme 61).[99]



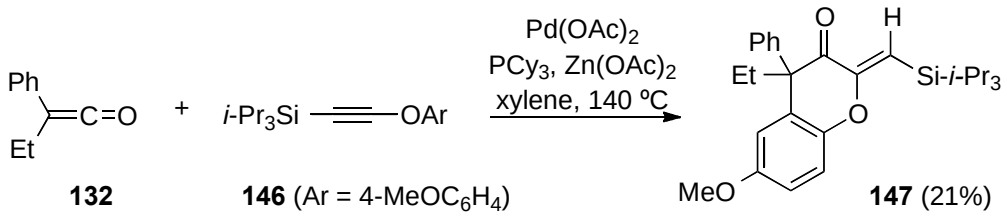
Scheme 61. Ketene alkene cyclization forming a junionone precursor.

Vinylketene **144** generated by cyclobutenone thermolysis undergoes [4+2] cycloaddition with ynamide **143** forming the phenol **145** (Scheme 62).[100] The reactions eventually led to a versatile synthesis of polysubstituted quinolines.



Scheme 62. Vinylketene/alkyne [4+2] cycloaddition for phenol synthesis.

Net [2+4] cycloadditions of phenylethylketene **132** with alkynyl ethers (*e.g.* Scheme 63) have been reviewed.[101]

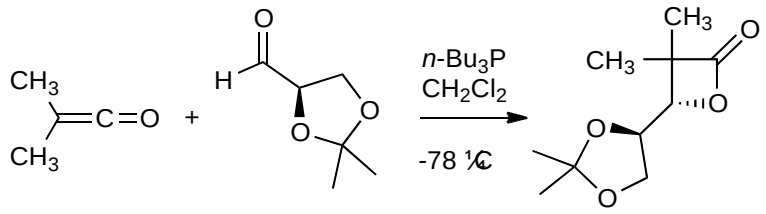


132 **146** (Ar = 4-$MeOC_6H_4$) **147** (21%)

Scheme 63. Net ketene alkynyl ether [4+2] cycloaddition.

4.3. [2+2] Cycloaddition reactions with carbon-oxygen bonds

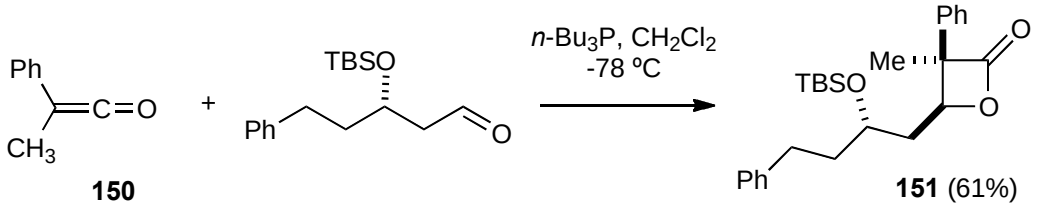
Dimethylketene (**141**) reacts with aldehyde **148** forming the β-lactone **149** (Scheme 64), which was used in a highly diastereoselective synthesis of (+)-peloruside A.[102]



141 **148** **149** (44%, dr 6:1)

Scheme 64. Ketene [2+2] cycloaddition with an aldehyde in diastereoselective synthesis.

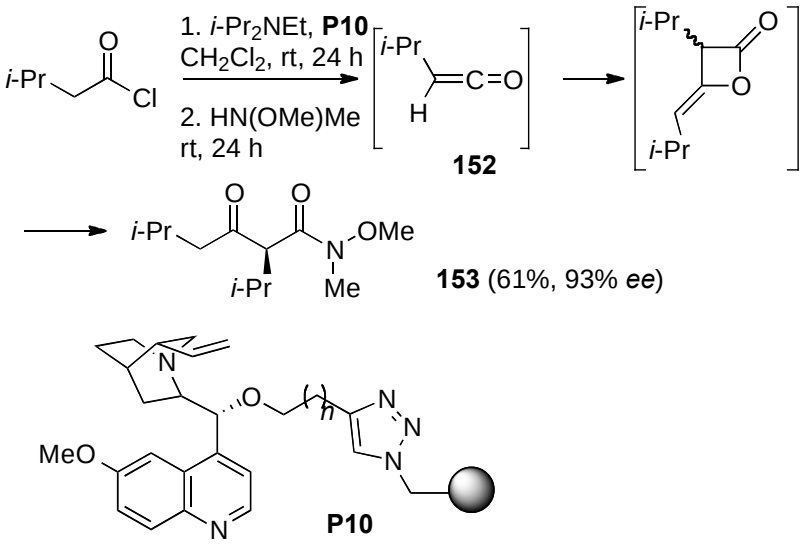
Stereoselective [2+2] cycloadditions of ketenes with chiral aldehydes catalyzed by tri-*n*-butylphosphine give β-lactones with diasteroselectivity up to 4:1 (Scheme 65).[103]



150 **151** (61%)

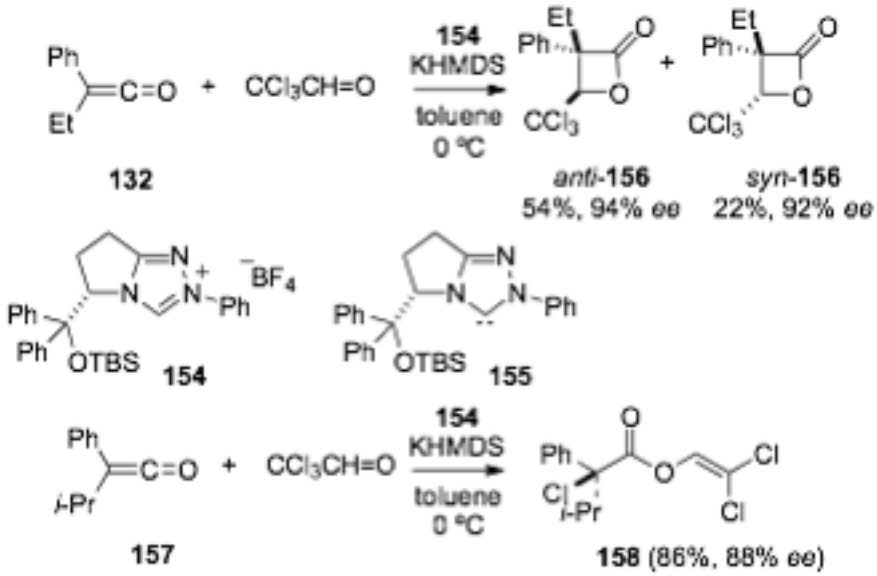
Scheme 65. Stereoselective ketene cycloaddition with an aldehyde.

Polymer supported cinchona alkaloid **P10** serves as a catalyst for dimerization of ketenes including **152**, with subsequent amination of the dimer forming **153** (Scheme 66).[104]



Scheme 66. Stereoselective ketene dimerization.

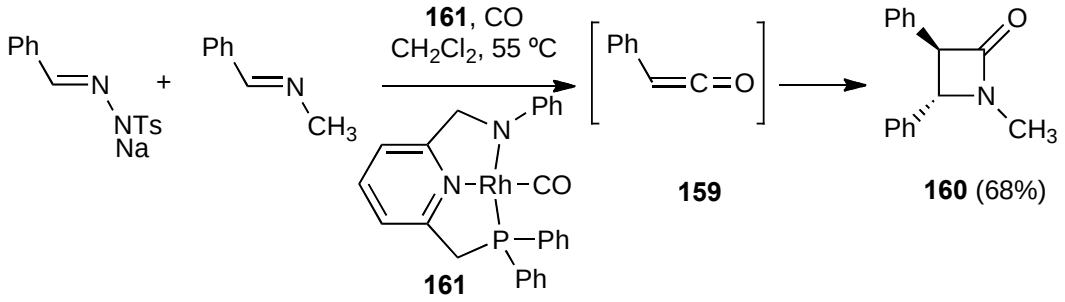
Phenylethylketene (**132**) reacts with trichloroacetaldehyde with catalysis by *N*-heterocyclic carbene **155** generated *in situ* from the salt **154** with selective formation of β-lactones **156)**, while **157** forms the α-chloro ester **158** (Scheme 67).[105] The chlorination pathway is favored by 2-substitution on the aryl group or branching in the alkyl substituent.



Scheme 67. Ketene substituent effects on reactivity with chloral using a chiral catalyst.

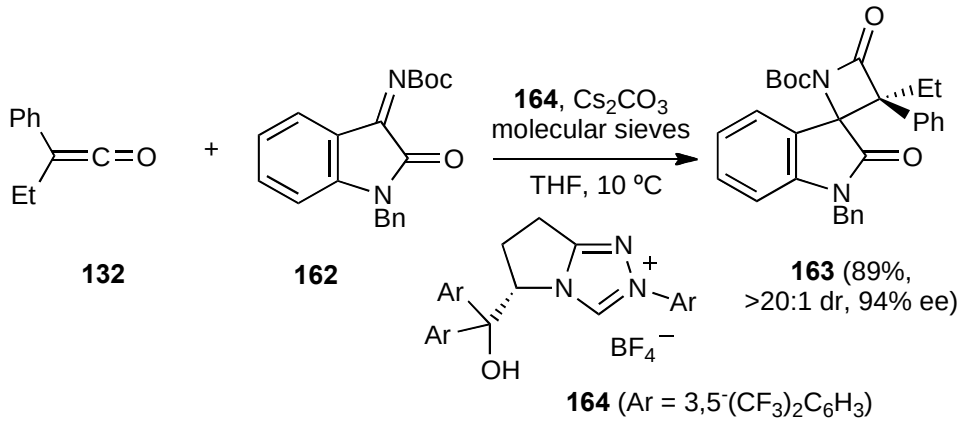
4.4. [2+2] Cycloaddition reactions with carbon-nitrogen bonds. β-Lactam formation by ketene / imine [2+2] cycloaddition is one of the most characteristic and widely-studied ketene reactions, and is the subject of recent reviews.[106,107]

Phenylketene (**159**) generated from benzaldehyde *N*-tosylhydrazone salt by carbonylation using the rhodium catalyst **161** reacted with imines to give stereoselective formation of the β-lactam **160** (Scheme 68).[108]



Scheme 68. Ketene generation by *N*-tosylhydrazone carbonylation with imine cycloaddition.

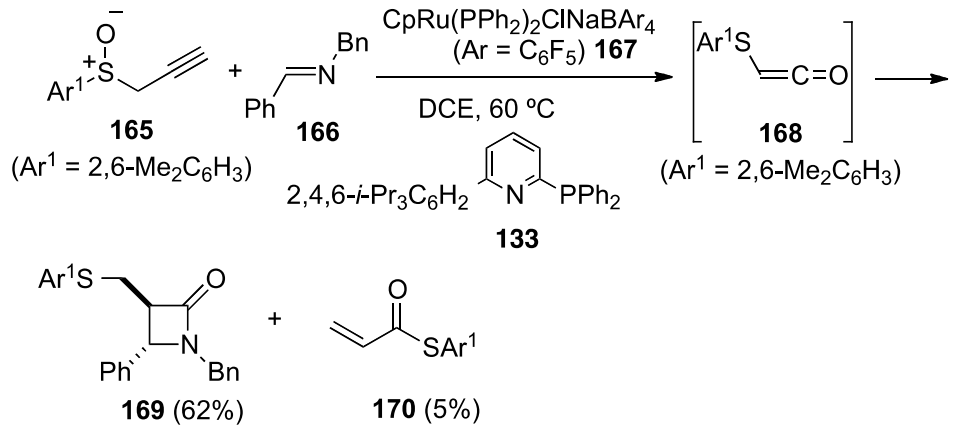
Phenylethylketene (**132**) undergoes stereoselective [2+2] cycloaddition with imine **162** forming β-lactam **163** with catalysis by the *N*-heterocyclic carbene generated from **164** (Scheme 69).[109\]



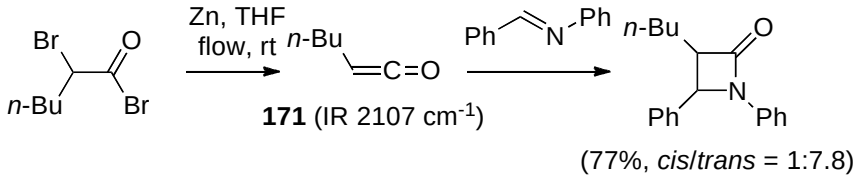
Scheme 69. Spiro β–lactam formation by ketene-imine [2+2] cycloaddition.

Thermolysis of propynyl sulfoxide **165** in the presence of imine **166** and a ruthenium catalyst **167** and ligand **133** is proposed to give ketene **168** which reacts with the imine by [2+2] cycloaddition forming β-lactam **169**, together with small amounts of thioester **170**, suggested to result from ketene rearrangement (Scheme 70).[110] In the absence of imines thioesters are the major products.

Ketenes including **171** generated by zinc debromination of α-bromoacyl bromide under flow conditions were observed by their characteristic IR absorption, and in the presence of imines they efficiently formed β-lactams (Scheme 71).[111]

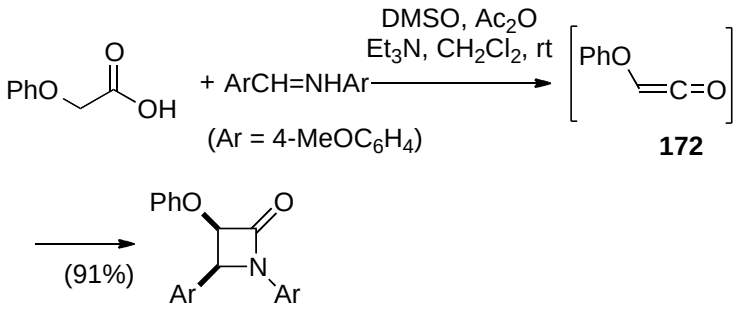


Scheme 70. Ketene generation by propynyl sulfoxide thermolysis and [2+2] imine cycloaddition with β–lactam formation.



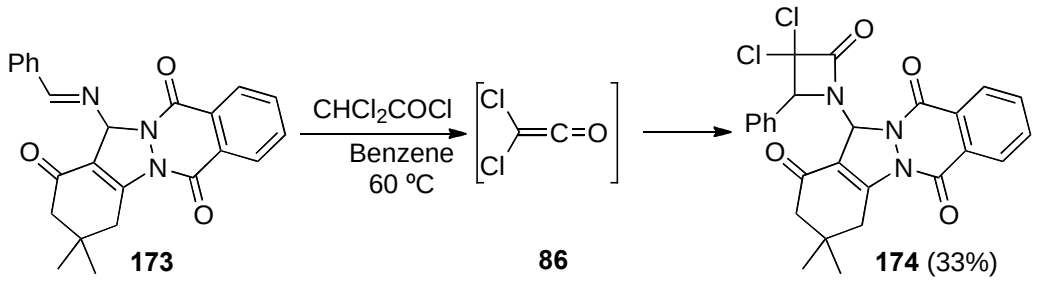
Scheme 71. Ketene-imine [2+2] cycloaddition with β–lactam formation in a flow system.

Ketenes generated from carboxylic acids using dimethyl sulfoxide and acetic anhydride give β-lactams by [2+2] cycloaddition with imines (Scheme 72).[112]



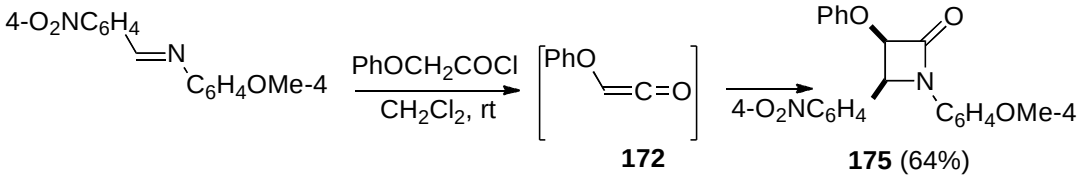
Scheme 72. Ketene generation by carboxylic dehydration, and cycloaddition with imines.

Dichloroketene (**86**) generated by thermal dehydrochlorination reacts with the 2*H*-indazolo[2,1-*b*]phthalazinetrione **173** forming the corresponding phthalazine substituted β-lactam **174** (Scheme 73), evaluated for its inhibitory effect on the activity of purified human carbonic anhydrase.[113]



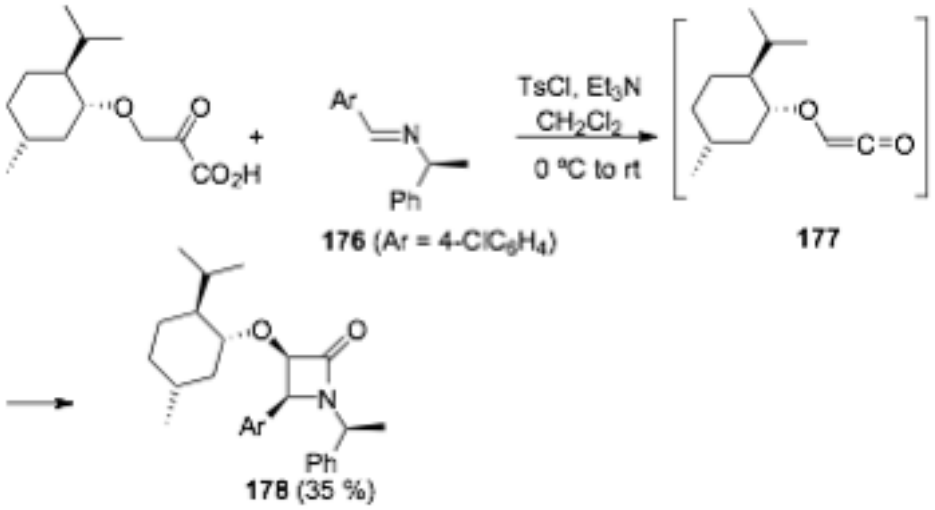
Scheme 73. Dichloroketene [2+2] indazolo-phthalazine cycloaddition.

Aryloxyketenes including **172**, generated by dehydrochlorination, give [2+2] cycloaddition with 4-nitroaryl substituted imines forming β-lactams **175** (Scheme 74), and then the aryl nitro groups are converted into $NHCOCH=CH_2$ groups and the resulting vinyl monomers are copolymerized giving nanopolymers containing β–lactam groups.[114]



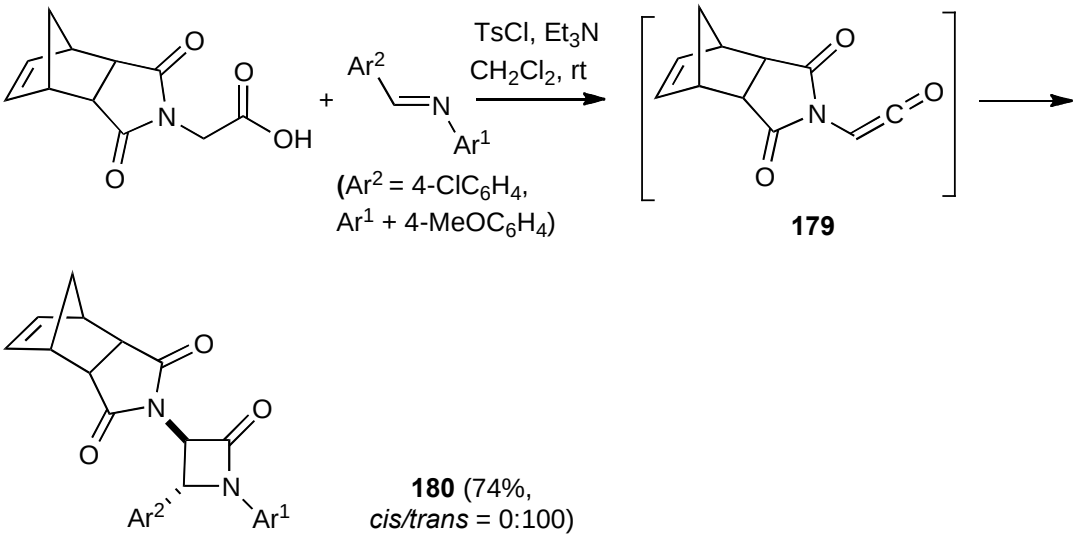
Scheme 74. Phenoxyketene [2+2] imine cycloaddition.

cis-3,4-Disubstituted β-lactams **178** were prepared by [2+2] cycloaddition of chiral imines **176** with chiral ketene **177**, and were evaluated for their antimalarial activity (Scheme 75).[115]



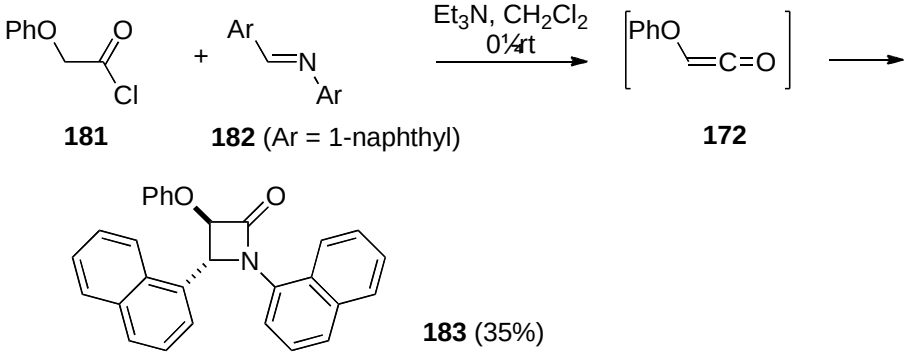
Scheme 75. Chiral ketene/chiral imine [2+2] cycloaddition.

Ketene **179** generated by net dehydration of a carboxylic acid by reaction with tosyl chloride and triethylamine gives [2+2] cycloaddition with imines, forming β-lactams (Scheme 76).[116]



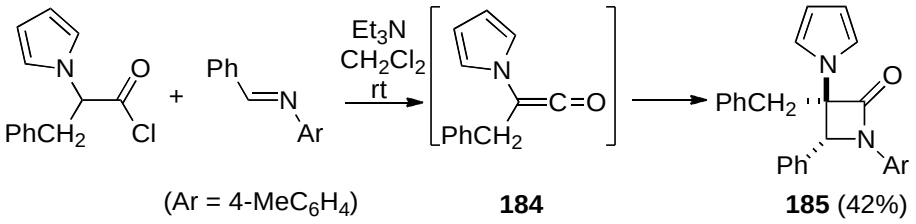
Scheme 76. Selective [2+2] ketene cycloaddition with diaryl imines.

Phenoxyketene (**172**) generated by dehydrochlorination of phenoxyacetyl chloride (**181**) reacts with imines such as **182** substituted by polycyclic aryl groups forming the corresponding β-lactams (Scheme 77).[117]



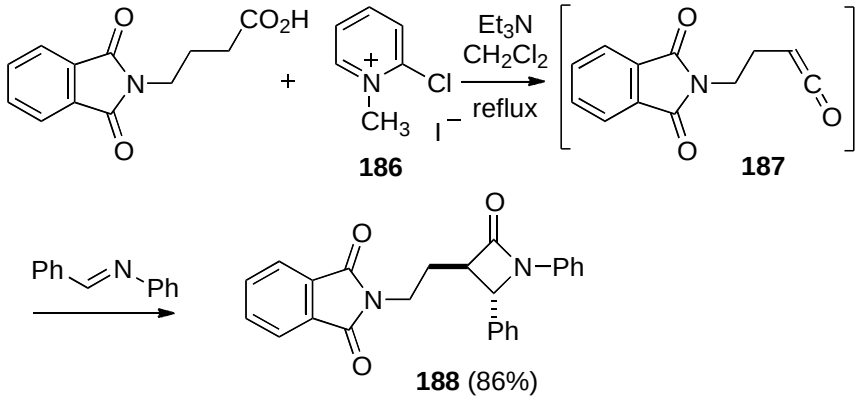
Scheme 77. Selective [2+2] ketene cycloaddition with di(polycycloaryl) imines.

Ketene **184**, generated by acyl chloride dehydrochlorination, reacts by [2+2] cycloaddition with imines with selective formation of β-lactams such as **185**, as single stereoisomers (Scheme 78).[118]



Scheme 78. Cycloaddition of an *N*-pyrrolylketene with imines.

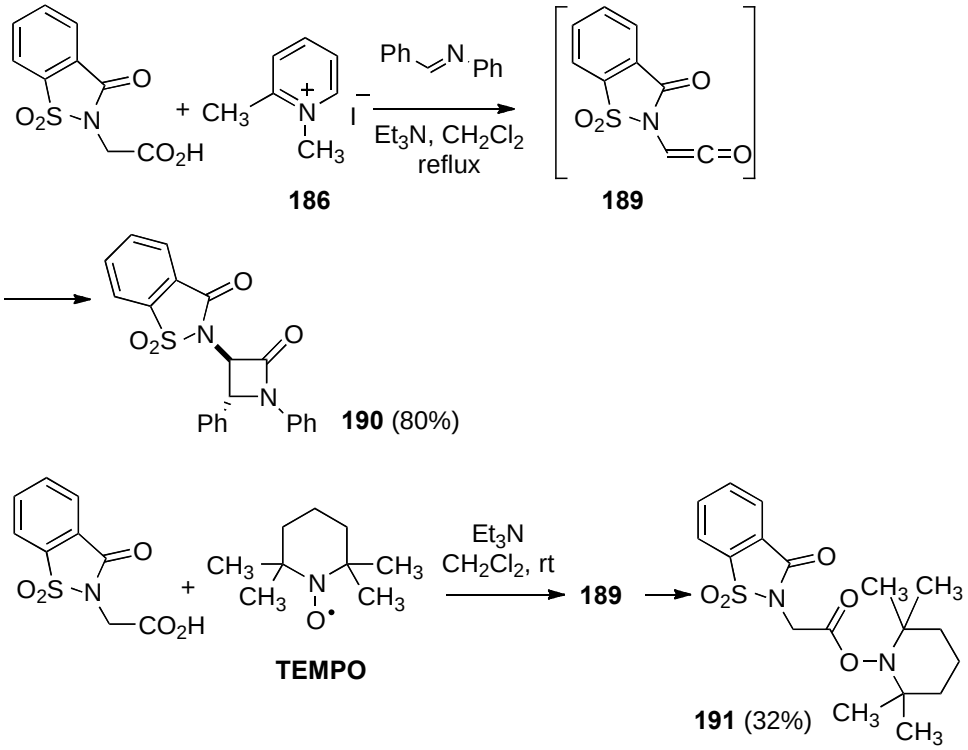
Carboxylic acid activation with Mukaiyama's reagent **186** followed by imine addition gave the β-lactam **188**, evidently through the intermediacy of ketene **187** (Scheme 79).[119] (See also Scheme 37 and ref. 69).



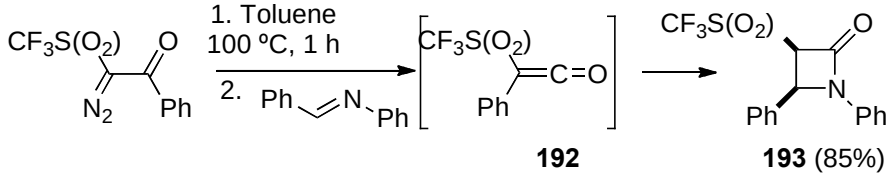
Scheme 79. Ketene generation with Mukaiyama's reagent and cycloaddition with imines.

Saccharin-substituted ketene **189**, generated by carboxylic acid dehydration with Mukaiyama's reagent **186**, reacted with imines to produce saccharin-substituted β-lactams, including **190** (Scheme 80), which was tested for biological activity.[120] Mukaiyama's reagent also was used to generate other ketenes for β-lactam formation. Ketene **189** generated similarly also reacted with the stable free radical TEMPO forming **191**, confirming the identity of the free ketene (Scheme 80).[120]

The new triflyl-substituted ketene **192**, generated by thermal diazoketone Wolff rearrangement, gives [2+2] cycloaddition with imines forming the corresponding substituted β-lactams (Scheme 81).[121]

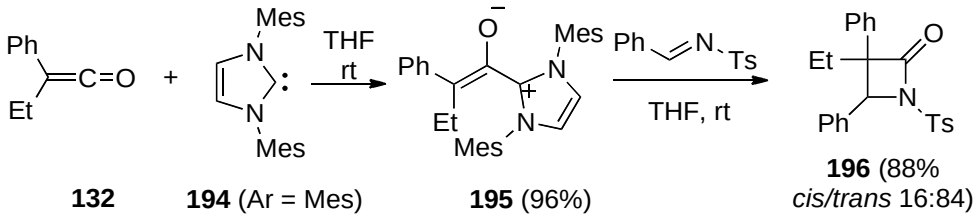


Scheme 80. Generation and reactivity of a saccharin substituted ketene.



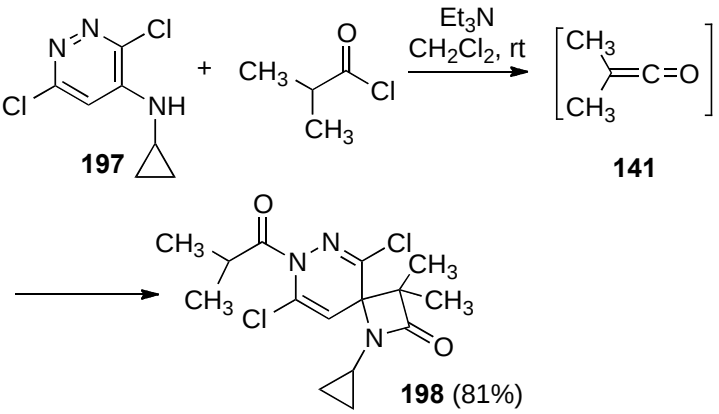
Scheme 81. Cycloaddition of a triflyl-substituted ketene.

Reaction of ketenes including **132** with catalysis by *N*-heterocyclic carbene **194** forms azolylium enolate **195**, which was isolated, and the X-ray structure of **195** was determined. Reaction of **195** with imines formed β-lactams such as **196** (Scheme 82).[122]



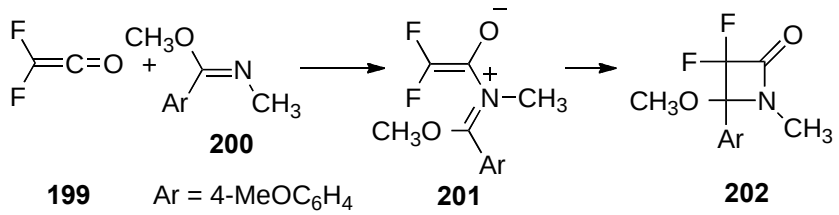
Scheme 82. Azolylium enolates from ketenes and conversion into β-lactams.

Reactions of pyridazines such as **197** with dimethylketene (**141**) generated *in situ* from isobutyryl chloride give the spiro-β-lactam **198** by ketene-imine [2+2] cycloaddition (Scheme 83). This and similar products are used in the synthesis of pyrrolo[2,3-*c*]pyridazin-6-ones.[123]



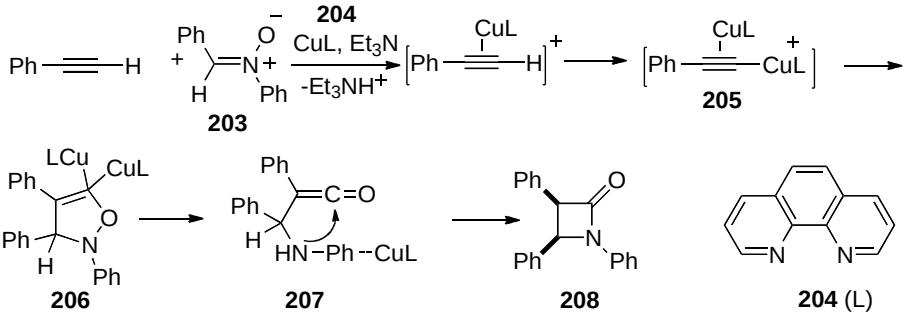
Scheme 83. Spiro-β-lactam from ketene cycloaddition with pyridazines.

The reactions of difluoroketene (**199**) with imines including **200** forming **202** were interpreted by computational studies as involving a [2+2] cycloaddition by a stepwise process through intermediate **201** (Scheme 84).[124]



Scheme 84. Difluoroketene cycloaddition with imines.

A computational study of the Kinugasa reaction of phenylacetylene with nitrone **203** catalyzed by the copper-phenanthroline ligand L (**204**) favors a pathway with formation of complex **205** leading to intermediate **206** which ring opens to the ketene intermediate **207** which undergoes a cycloaddition forming the product β-lactam **208** (Scheme 85).[125] The calculated structure of **207** is shown in Figure 11.



Scheme 85. Kinugasa reaction of phenylacetylene with a nitrone.

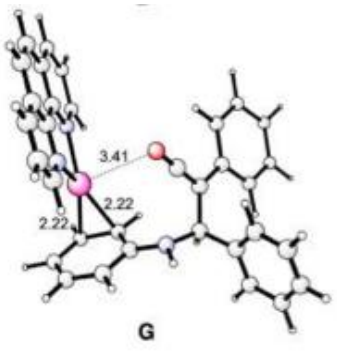
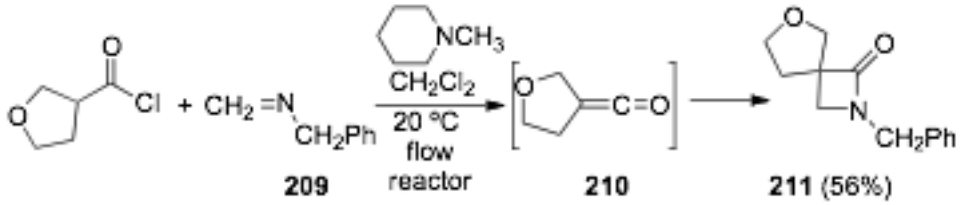


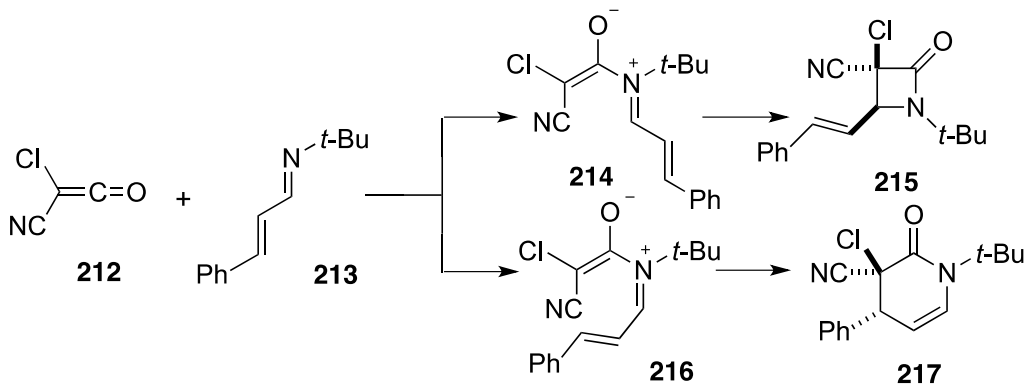
Figure 11. Calculated structure of Kinigusa intermediate for β-lactam formation (Reproduced with permission from the publisher [125]).

Acyl chloride dehydrochlorination with *N*-methylpiperidine in dichloromethane in a flow reactor with in-line monitoring by IR of the reactant and final product proceeded through the unobserved ketene **210**, which reacts *in situ* with the imine **209** forming the β-lactam **211** (Scheme 86).[126]



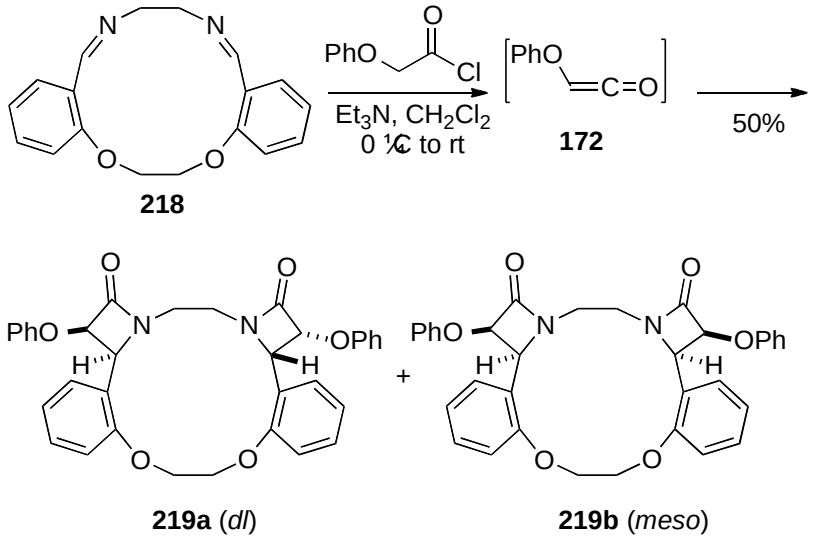
Scheme 86. Ketene-imine reaction in a flow reactor.

The selectivity in the reaction of chlorocyanoketene (**212**) with vinylimines by [2+2] and [4+2] cycloadditions forming β- and δ-lactams, respectively (Scheme 87), has been studied by computational methods. Topological analysis indicates that the reactions do not occur by one-step electrocyclizations.[127]



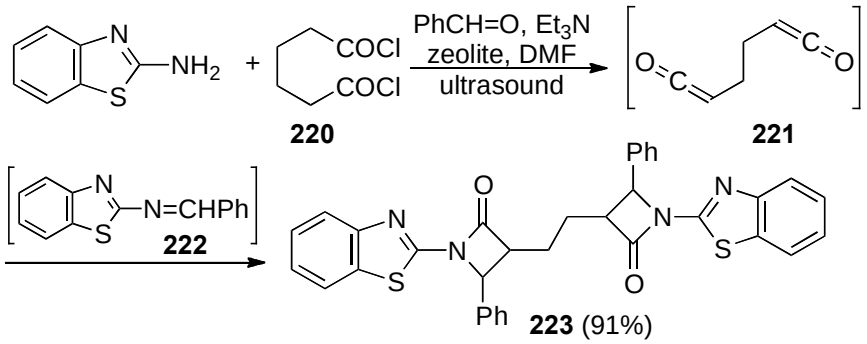
Scheme 87. Competitive [2+2] and [4+2] ketene-vinylimine cycloaddition.

Phenoxyketene (**172**) reacts with the bis(imine) **218** by double *trans*-[2+2] cycloaddition giving the diastereomeric bis-β-lactams **219** in a 50% overall yield (Scheme 88). The bis-β-lactams were evaluated for antimicrobial activity.[128]



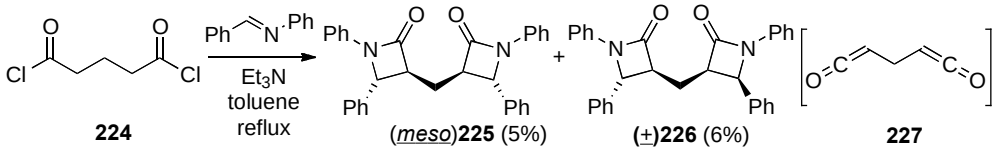
Scheme 88. Phenoxyketene cycloaddition with a *bis*-imine.

Adipoyl chloride (**220**) reaction with triethylamine promoted by ultrasound irradiation in the presence of 2-aminothiazole and zeolite gives formal generation of bisketene **221**, which reacts by a double [2+2] cycloaddition with the *in situ* generated imine **222** forming the bis-(β-lactam) **223** (Scheme 89).[129]

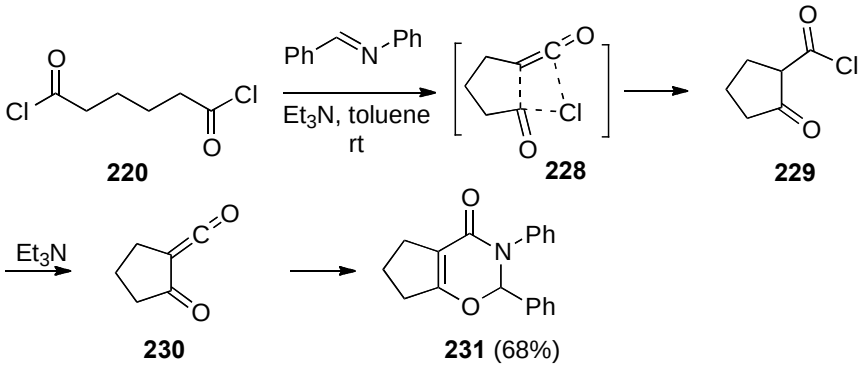


Scheme 89. Bis-(β-lactam) formation from a bis(acyl chloride).

Dehydrochlorination of bis(acyl chlorides) in the presence of imines forming ketenes which react with formation of bis-β-lactams was examined in a further study by computational and experimental methods.[130] With pentanedioyl dichloride (**224**) bis-β-lactams **225** and **226** were formed at reflux as *cis*/*trans* mixtures (Scheme 90), but the conceivable formation of the bisketene **227** under these conditions was considered to be unlikely. Adipoyl chloride (**220**) at room temperature formed **231**, proposed to result from initial dehydrochlorination with chlorine migration via **228** to **229** (Figure 12), followed by dehydrochlorination to the acyl ketene **230**, which reacts further by [4+2] cycloaddition forming **231** (Scheme 91).[130]



Scheme 90. Bis-β–lactam formation through a formal 1,1-bisketene.



Scheme 91. Chlorine migration in reaction of a bis(acyl chloride).

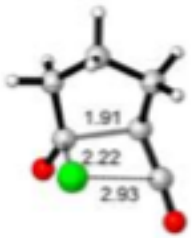
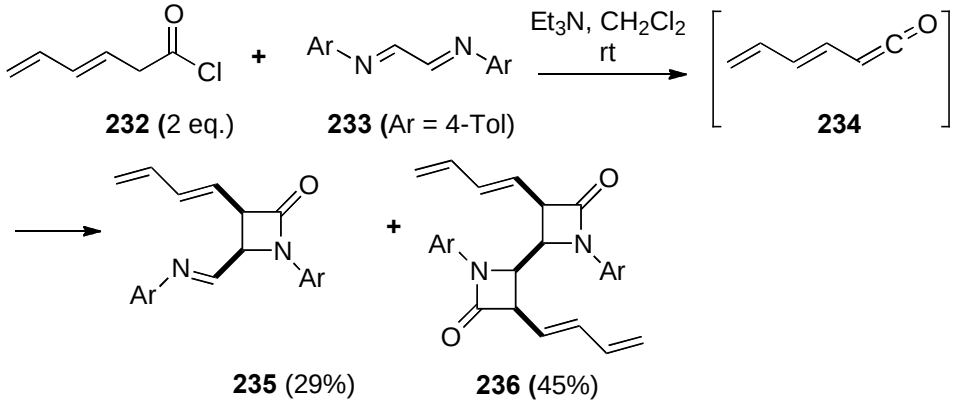


Figure 12. Calculated transition state for chlorine migration during ketene formation (Reprinted with permission from the Publisher [130]).

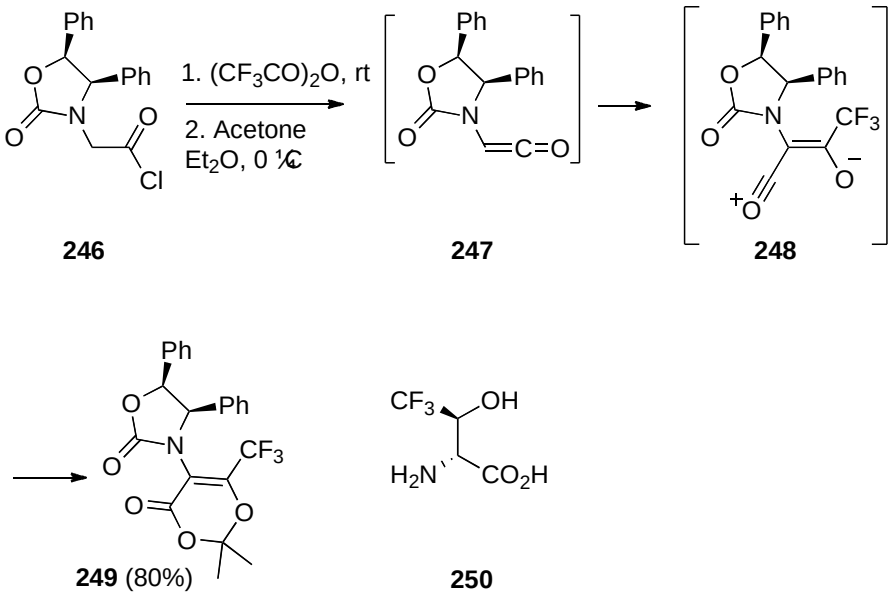
Butadienylketene (**234**) generated by dehydrochlorination of **232** reacts with the 1,4-diaza-buta-1,3-diene **233** forming the mono(*cis*-β-lactam) **235** and bis(*cis*-β-lactam) **236** (Scheme 92).[131]



Scheme 92. Dienyl β-lactams from a glyoxal bis-imine.

4.5. [2+2+2] Cycloadditions

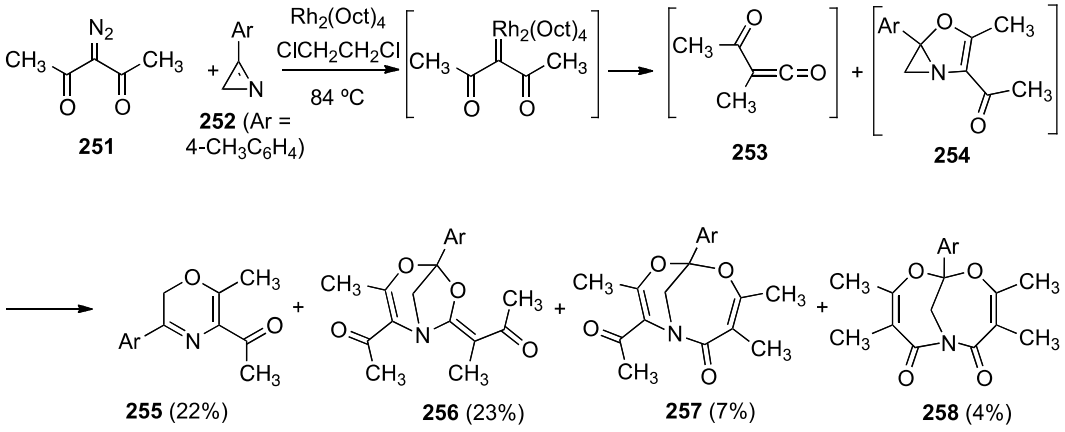
The reaction of acyl chloride **246** with a chiral oxazolidinone substituent and trifluoroacetic anhydride and acetone forming **249** was suggested to proceed by formation the ketene **247**,[132] which undergoes trifluoroacetylation by a process proposed earlier,[133] leading to **248** by trifluoroacetylation of the ketene, and then **249**, incorporating the ketene, acetone, and a trifluoroacetyl group in a net [2+2+2] cycloaddition (Scheme 93).[132] Note that the final step forming the dioxinone **249** is the reverse of the ketene-generating reactions described in Section 3.7. The product was used in the stereoselective preparation of (2*R*,3*S*)-4,4,4-trifluoro-*allo*-threonine (**250**).



Scheme 93. Ketene trifluoroacetylation and capture with acetone.

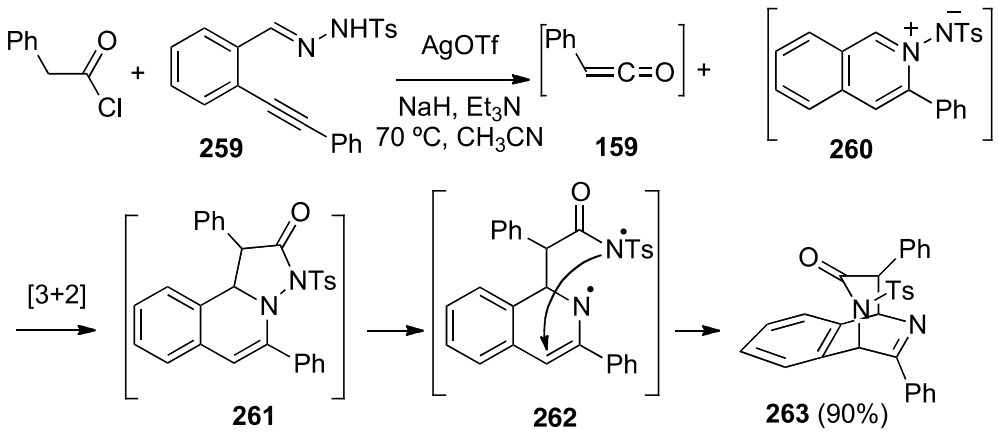
4.6. [3+2] Cycloadditions involving ketenes

Ketene, having a linear skeleton, is not the right shape to provide three atoms in a [3+2] cycloaddition. The precursor of a ketene in the Wolff rearrangement, an acylcarbene (or carbenoid), can so react, as was recently reported by Russian workers.[134] The diazodiketone **251** in the presence of dirhodium tetraacetate or tetraoctanoate is suggested to generate a rhodium carbenoid which reacts with the 2*H*-azirine **252** in a [3+2] cycloaddition forming the intermediate **254**, which rearranges to **255**, and reacts further with acetyl methyl ketene **253**, also formed by rearrangement of the carbenoid, by 1,2- and 1,4-cycloadditions, forming **256**-**258**. (Scheme 94) A number of analogous reactions were studied.[134]



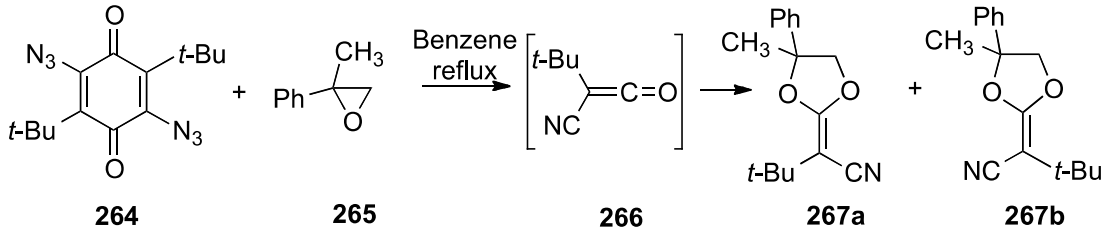
Scheme 94. Ketene-imine cycloaddition with rearrangement and further reactions.

N'-(2-Alkynylbenzylidene)hydrazides (**259**) react with ketenes such as **159** with catalysis by silver triflate forming fused 2,6-diazabicyclo[3.2.2]non-6-en-3-ones (**263**) in a process interpreted as involving an initial [3+2] cycloaddition with **260** formed *in situ* leading to **261**which ring-opens to **262** which then cyclizes to **263** (Scheme 95).[135,136]



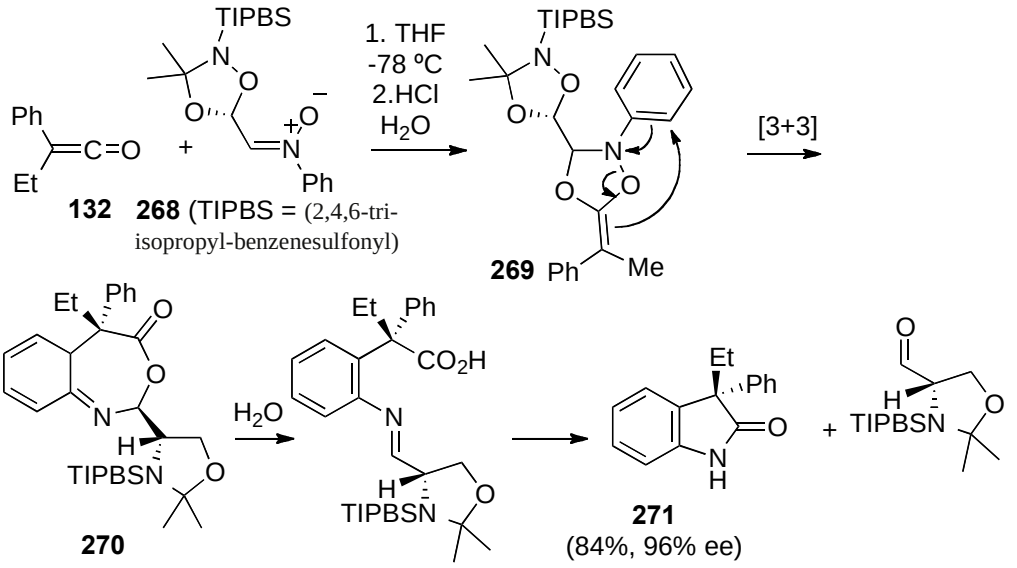
Scheme 95. Ketene [3+2] cycloaddition with *N´*-(2-alkynylbenzylidene)hydrazides.

tert-Butylcyanoketene (**266**), generated *in situ* by thermolysis of quinone **264** by the method of Moore *et al.*,[137] reacts with the epoxide **265** forming **267** by a net [3+2] cycloaddition (Scheme 96).[138]



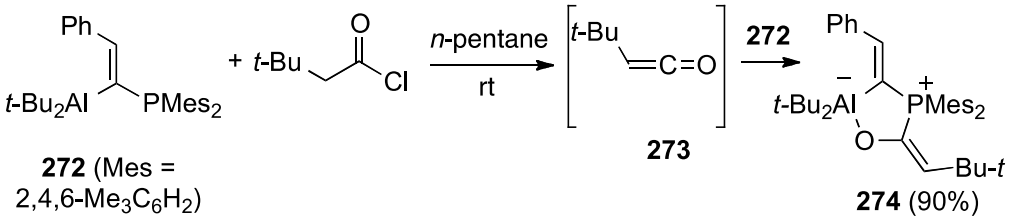
Scheme 96. Generation of *tert*-butylcyanoketene and reaction with 2-methyl-2-phenyloxirane.

Arylalkylketenes react with *L*-serine-derived *N*-arylnitrones **268** with enantioselective formation of 3-alkyl-3-aryloxindoles **271** in a process interpreted as involving an initial [3+2] cycloaddition on the ketene carbonyl forming **269** followed by a [3+3] electrocyclization forming **270**. Hydrolysis yields the oxindole **271** (Scheme 97).[139]



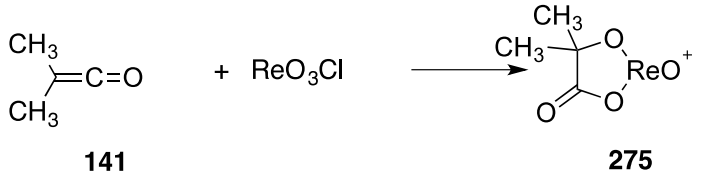
Scheme 97. Enantioselective formation of 3-alkyl-3-aryloxindoles by [3+2] ketene carbonyl cycloaddition followed by [3+3] electrocyclization and hydrolysis.

The frustrated Lewis ion pair **272** is suggested to react with ketene **273** generated by acyl chloride dehydrohalogenation, and the ketene reacts with a second molecule of **272** by formal [3+2] cycloaddition to form **274** (Scheme 98).[140]



Scheme 98. Ketene reaction with a frustrated ion pair.

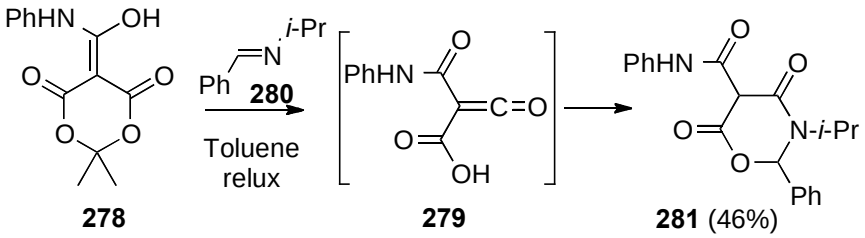
Computational studies of cycloaddition reactions of ketenes $CH_3CR=C=O$ with ReO_3Cl forming products such as **275** (Scheme 99) and with manganese oxo complexes MnO_3L (L = Cl, O-, OCH_3, CH_3) (Scheme 99), forming **276** and **277,** have been reported.[141,142]



Scheme 99. Computations of dimethylketene reaction with metal oxides.

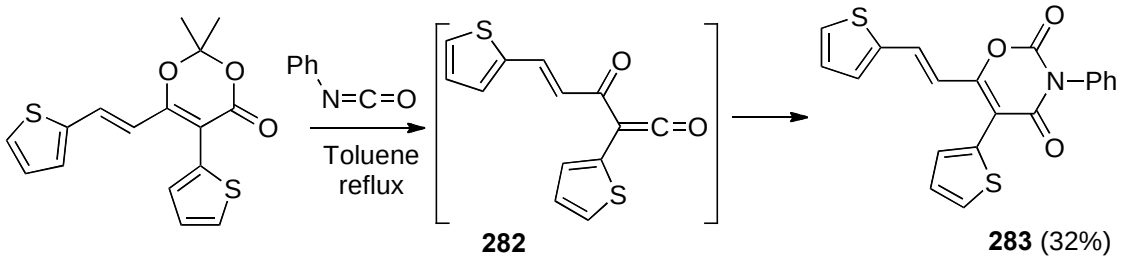
4.7. Ketene [4+2] cycloadditions and cyclizations

Thermolysis of carbamoyl Meldrum's acid **278** forms ketene **279** that undergoes net [4+2] cycloaddition with imine **280** forming the 5-carbamoyl-1,3-oxazine-4,6-dione **281** (Scheme 100).[143]



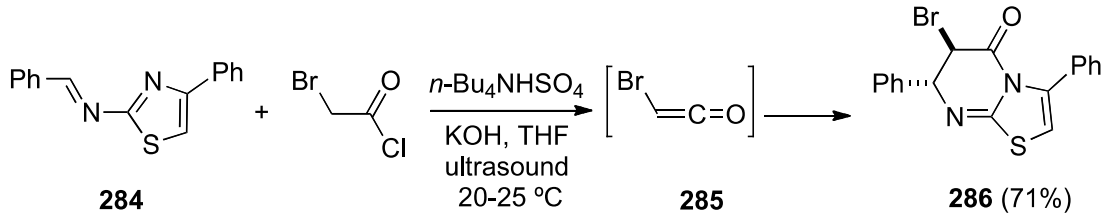
Scheme 100. Carboxyketene-imine [4+2] cycloaddition.

Diversely substituted acylketenes including **282** generated from dioxinones give [4+2] cycloadditions with isocyanates (forming **283**) and isothiocyanates (Scheme 101).[144]



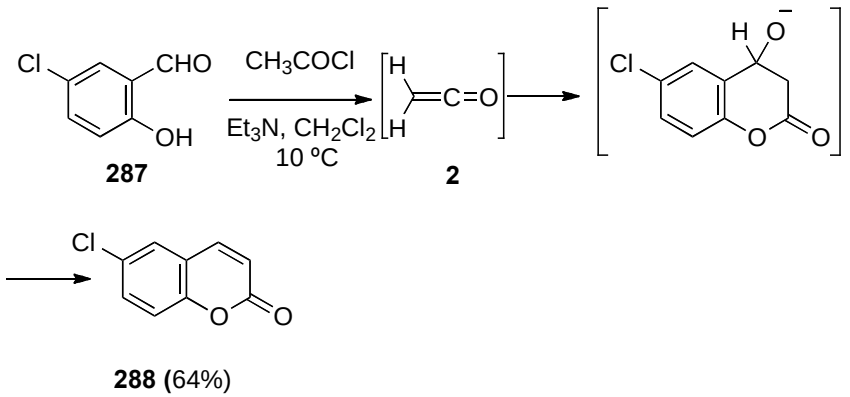
Scheme 101. Acylketene/isocyanate [4+2] cycloaddition.

Bromoketene (**285**), generated by dehydrochlorination of bromoacetyl chloride, reacts by a aza-Diels-Alder reaction with 2-arylideneamino-4-arylthiazoles including **284** forming the product thiazolo[3,2-*a*]pyrimidin-5-ones (**286**) (Scheme 102).[145]



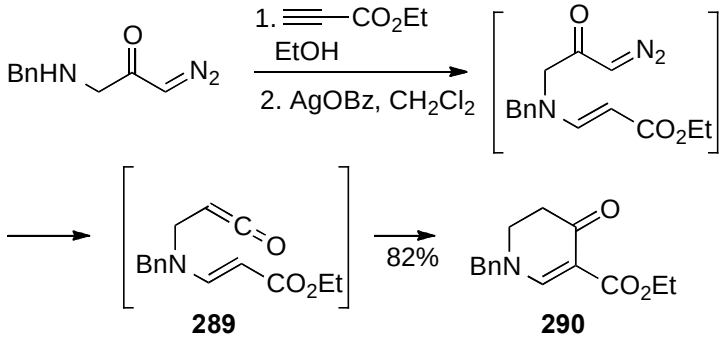
Scheme 102. Aza-Diels-Alder reaction with bromoketene.

Ketene generated *in situ* by dehydrochlorination reacts with substituted salicylaldehydes including **287** by a net [4+2] cycloaddition leading to coumarin products **288** (Scheme 103).[146]



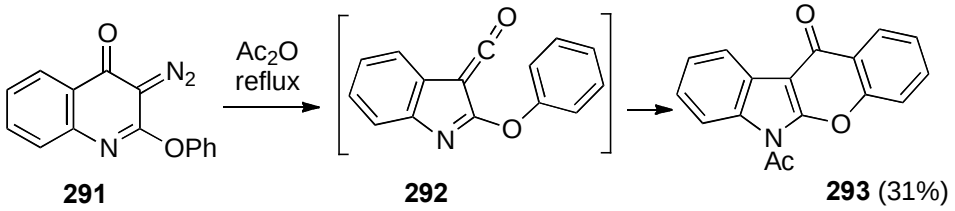
Scheme 103. Ketene [4+2] cycloaddition with salicylaldehydes.

Amino-substituted diazoketones react with alkynes forming diazo-keto esters which are directly treated with silver salts giving, by Wolff rearrangement, the corresponding ketenes, including **289**, which cyclize by intramolecular nucleophilic addition to enaminones (**290**; Scheme 104), which are used in alkaloid synthesis.[147-149]



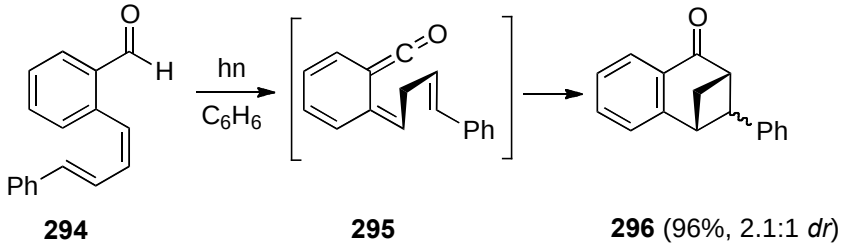
Scheme 104. Ketene formation by Wolff rearrangement and intramolecular nucleophilic substitution.

Ketene **292**, generated by thermal Wolff rearrangement of 3-diazoquinolin-4-one **291** in refluxing acetic anhydride, gave **293** by an intramolecular Friedel-Crafts [4+2] cyclization (Scheme 105).[150]



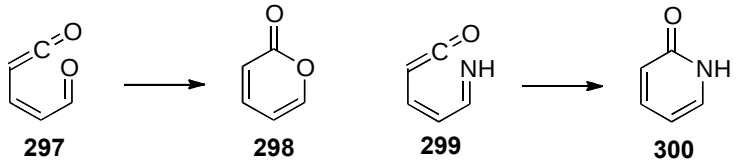
Scheme 105. Intramolecular ketene Friedel-Crafts [4+2] electrophilic cyclization.

Extended vinylketenes including **295** are formed by [1,5]-hydrogen transfer upon photolysis of 1,3-butadienyl-2-benzaldehydes **294**, and are converted into benzobicycloheptanones **296** by intramolecular Diels-Alder reaction (Scheme 106). Ketene formation under these conditions was demonstrated by capture of the ketene with piperidine. Computational studies of the transition state for the proposed [1,5]-H shift are consistent with the observed chemoselectivity.[151]



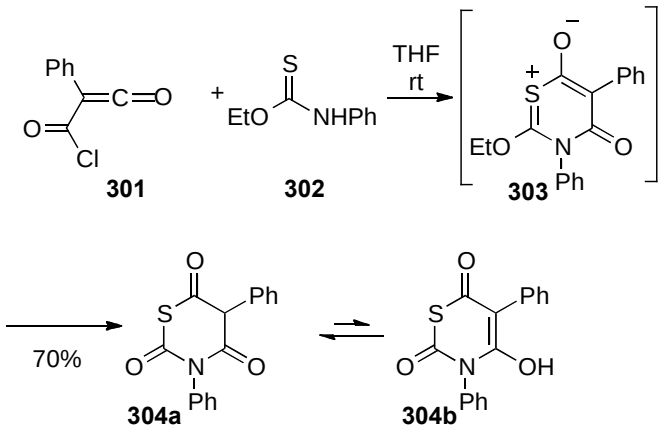
Scheme 106. Intramolecular ketene Diels-Alder reaction.

The question of whether the ring closure of ketene **297** to **298**, and of **299** to **300** (Scheme 107), occurs by a pericyclic or a pseudopericyclic mechanism has been studied by computational methods, and it was confirmed in both cases that it occurs by a pseudopericyclic reaction mechanism.[152]



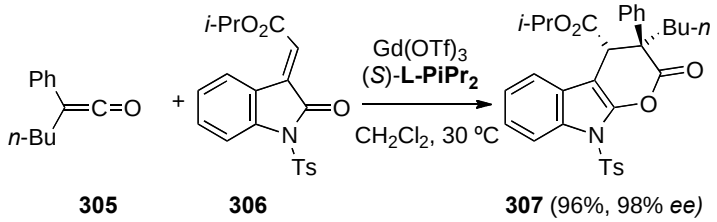
Scheme 107. Pseudopericyclic cyclization of vinylketenes.

Chlorocarbonylketenes such as **301** take part in [3+3] cycloaddition and elimination with *N*-phenylthiocarbamates **302** giving unstable mesoionic 1,3-thiazinium-4-olates **303**, which undergo alkene elimination forming 3,5-diaryl-1,3-thiazine-2,4,6-triones **304** (Scheme 108).[153]



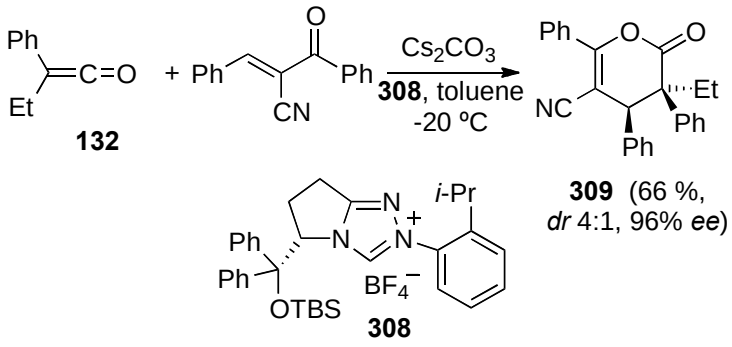
Scheme 108. Chlorocarbonylketene cycloaddition and elimination.

In an asymmetric inverse electron-demand Diels-Alder cycloaddition catalysed by the chiral *N*,*N'*-dioxide gadolinium complex (*S*)-L-PiPr$_2$ derived from (*S*)-pipecolic acid, the ketene **305** and 3-alkenyloxindole **306** form the indolo-fused dihydropyranone **307** (Scheme 109).[154]



Scheme 109. Ketene asymmetric inverse electron demand Diels-Alder reaction.

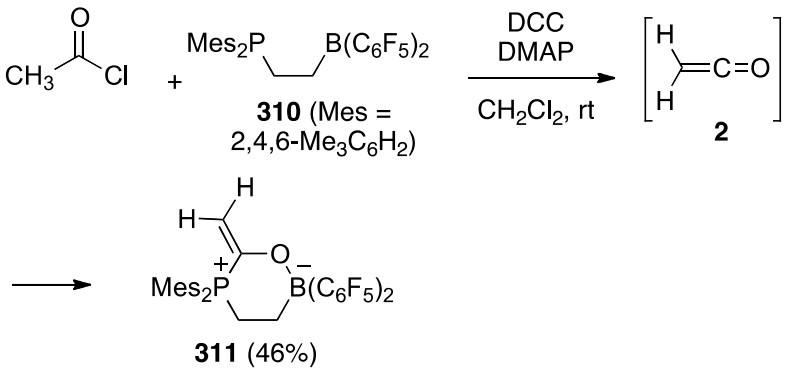
Arylalkylketenes including **132** react with α-cyanochalcones by [4+2] cycloaddition in the presence of the chiral *N*-heterocyclic carbene catalyst generated from **308** forming dihydropyranones **309** (Scheme 110).[155]



Scheme 110. Arylalkylketene [4+2] cycloaddition with α-cyanochalcones.

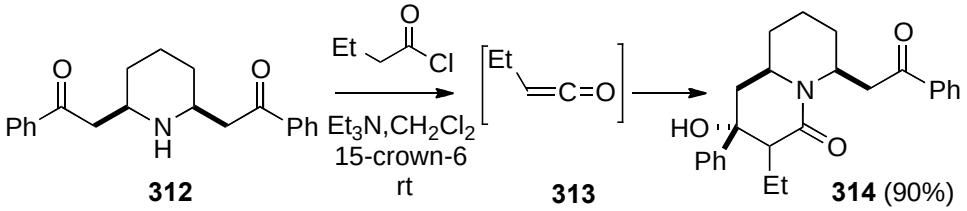
Other examples of [4+2] cycloadditions after this model (the ketene providing the 2-atom element in the cyclization) have been referred to earlier (Schemes 63, 102). Scheme 62 features [4+2] cycloaddition of a vinylketene to an ynamine.

Acetyl chloride reacts with the frustrated phosphane/borane Lewis pair **310** in a reaction interpreted as proceeding through the ketene (**2**) generated *in situ* and then formation of the P/B adduct **311** (Scheme 111).[156]



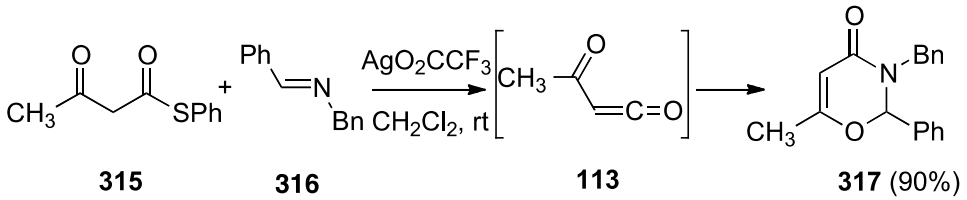
Scheme 111. Ketene [4+2] cycloaddition with a frustrated phosphane/borane Lewis pair.

Reaction of norlobelanine (**312**) with ethylketene (**313**), generated from butyryl chloride with sodium hydride, triethylamine, and 15-crown-6, formed quinolizidinone **314** in a two-component domino ketene amination/intramolecular aldol reaction (Scheme 112).[157]



Scheme 112. Ketene [4+2] cycloaddition with norlobelanine.

Acetylketene (**113**) generated from thioester **315** in the presence of silver trifluoroacetate reacts with the imine **316** by [4+2] cycloaddition forming 2,3-dihydro-1,3-oxazin-4-ones **317** (Scheme 113).[158]



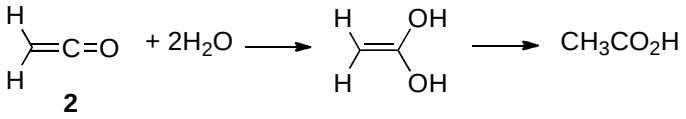
Scheme 113. Acetylketene [4+2] cycloaddition with imines.

The 1,4-addition of a cinnamylideneimine to chlorocyanoketene, forming a dihydro-pyridone, was noted in Scheme 87

5. Nucleophilic Additions to Ketenes

5.1. Hydration and addition of other oxygen nucleophiles

The mechanism of ketene hydration has long been the subject of experimental and computational studies, and a recent computational study of this process with two water molecules concludes that the reaction occurs by formation of the ene-diol $H_2C=C(OH)_2$, which then isomerizes to acetic acid (Scheme 114),[159] in agreement with earlier interpretations.[8,11] In the presence of formic acid as a catalyst this is suggested to participate in the addition, forming acetic acid directly (Figure 12).[160]

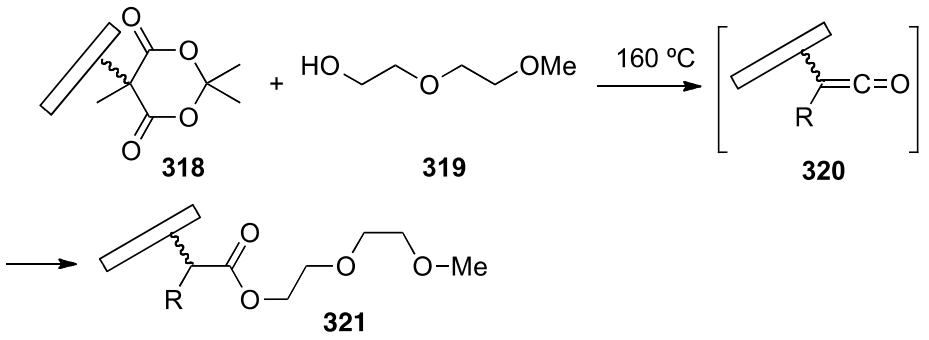


Scheme 114. Computational study of ketene hydration.

Figure 12. Ketene hydration with formic acid catalysis (Reprinted with permission from the American Chemical Society [160]).

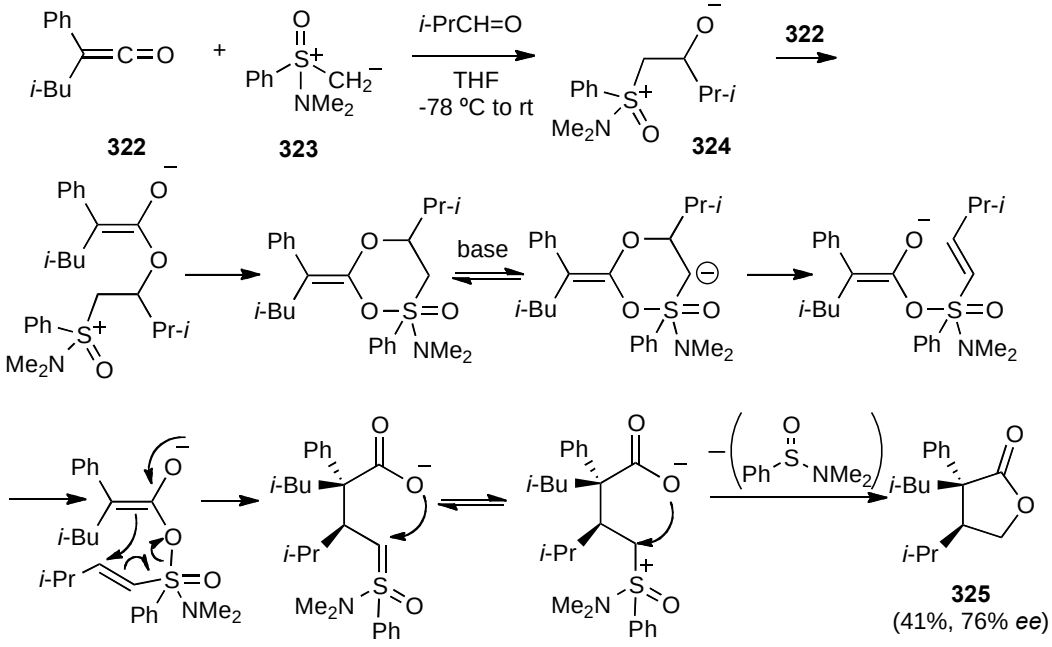
An experimental study with infrared spectroscopic detection of gas-phase ketene generated by thermal cracking of acetone at 750 ºC in the presence of water showed the formation of acetic acid, which reacts with further ketene to form acetic anhydride.[161]

Dioxinones attached to glass plates (**318**) upon thermolysis in the presence of neat hydroxypolyethers **319** form ketenes **320** on the surface as detected by X-ray photoelectron spectroscopy, and these ketenes add the alcoholic groups forming coated plates **321** (Scheme 115); the use of perfluorinated glycols formed potentially oil-repellent surfaces.[162]



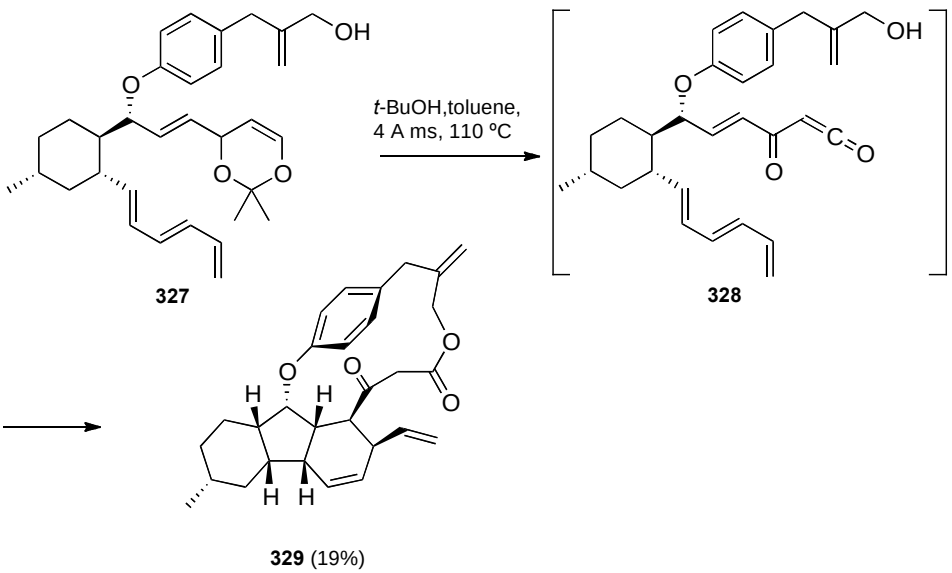
Scheme 115. Ketene generation and capture on a glass plate.

Ketene reactions with enantioenriched sulfoxonium ylides and aldehydes provide a synthesis of γ-lactones, as in the preparation of **325**, proposed to occur by a complex process with initial nucleophilic attack on the ketene **322** by **324**, formed from the sulfur ylide **323** and the aldehyde (Scheme 116).[163]



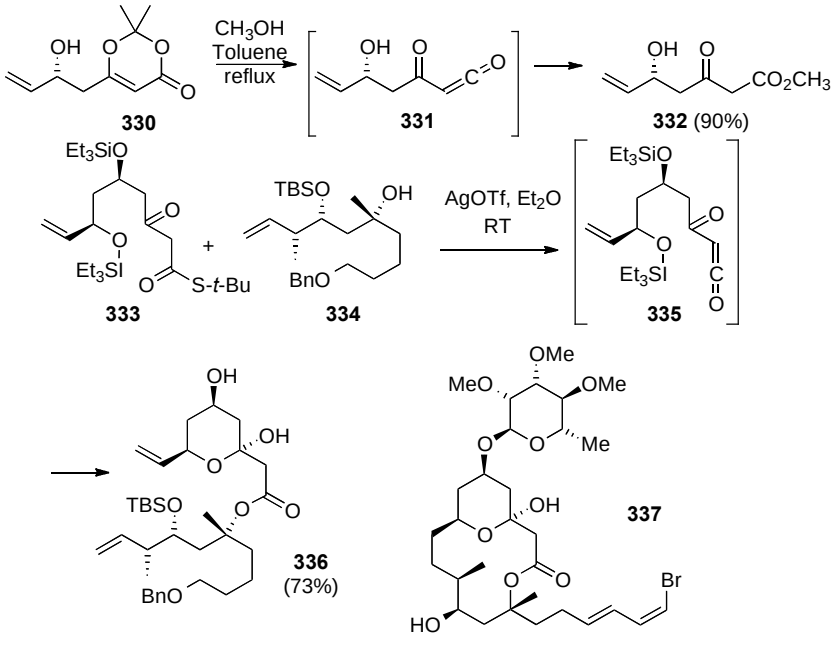
Scheme 116. γ-Lactones from ketene reaction with sulfoxonium ylides and aldehydes.

Acylketene **328** generated by pyrolysis of dioxinone **327** was used in the preparation of hirsutellone B (**329**) proceeding by a tandem nucleophilic addition to the ketene followed by an intramolecular Diels-Alder reaction (Scheme 117).[164]



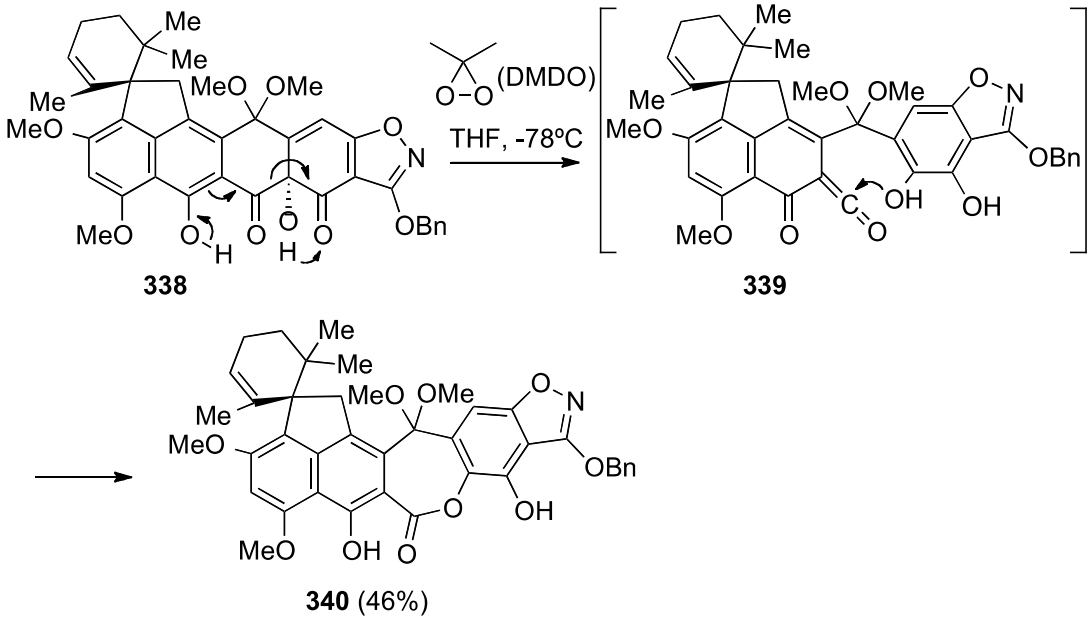
Scheme 117. Tandem ketene nucleophilic addition with subsequent intramolecular Diels-Alder reaction

Two ketene coupling reactions are used in a synthesis of lyngbyaloside C (**337**) from **330**, beginning with generation of acyl ketene **331** by dioxinone thermolysis to form **332**, a precursor of **333**. This is converted to ketene **335** by silver triflate in the presence of **334** to form **336** (Scheme 118).[165]

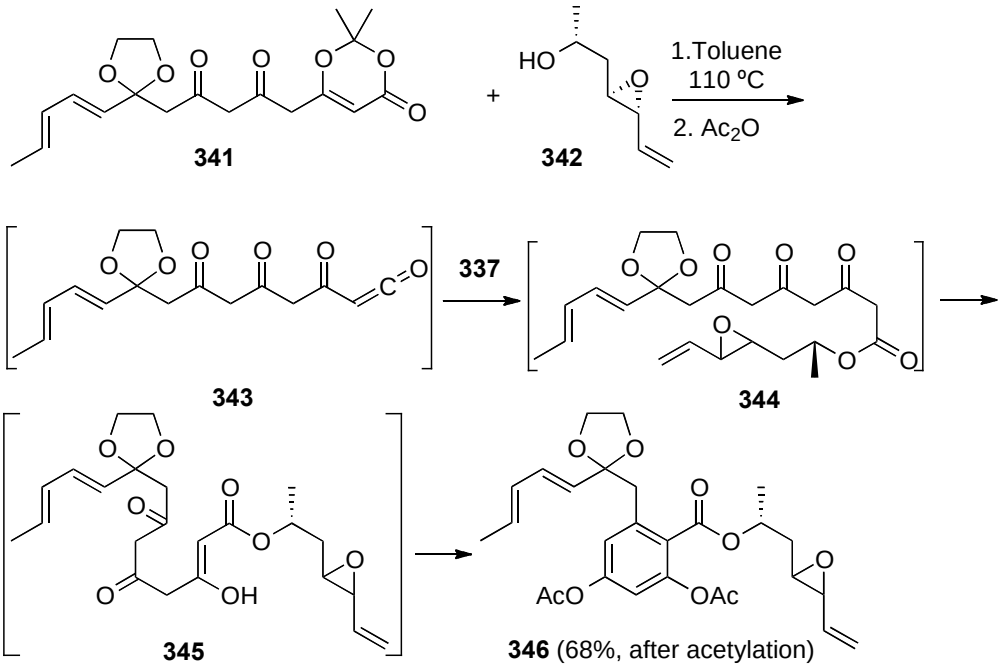


Scheme 118. Ketene coupling reactions in the synthesis of lyngbyaloside C.

In a study of the total synthesis of viridicatumtoxin B, treatment of **338** with dimethyldioxirane (DMDO) at -78 ºC gave **340**, in a process that may involve capture of acylketene **339**, although this species was not observed directly (Scheme 119).[166]



Scheme 119. Intramolecular ketene esterification in the synthesis of viridicatumtoxin B intermediates.

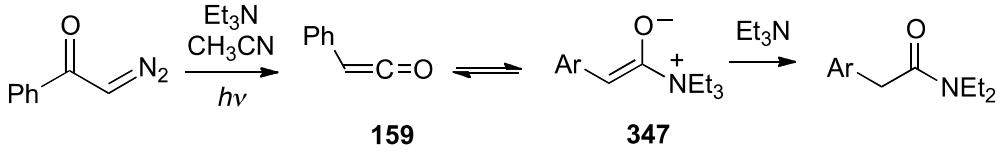


Scheme 120. Ketene esterification with product aromatization.

Ketene **343** generated by thermolysis of the dioxinone **341** reacted with alcohol **342** to form the ester **344**, used as a precursor in a total synthesis of radicicol, in a process suggested as proceeding through **344**, which is converted through the intermediate enol **345** into the final product **346** by spontaneous aromatization followed by acetylation (Scheme 120).[167]

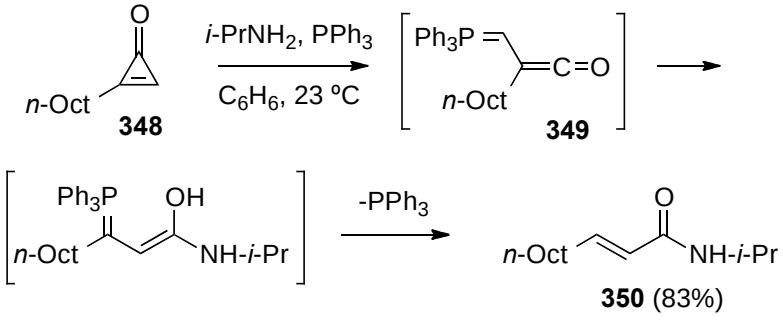
5.2 Addition of nitrogen nucleophiles

Phenylketene (**159**) reacts with tertiary amines, *e.g*. triethylamine, forming the observable zwitterionic intermediate **347**, which decays by reaction with a second amine in a reaction attributed to either competitive displacement of an alkyl group by the second amine, or an amine-catalyzed elimination (Scheme 121).[168]



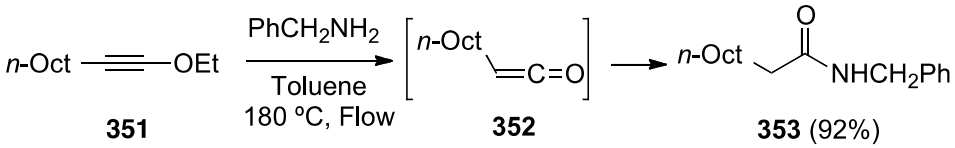
Scheme 121. Ketene reaction with tertiary amine with net dealkylation.

Cyclopropenone **348** reacts with amines in the presence of a phosphine catalysts forming unsaturated amide **350** in a reaction interpreted as proceeding through ketene intermediate **349** (Scheme 122).[169] Lysozyme-substituted cyclopropenones were used similarly for ligation in biological systems.[169]



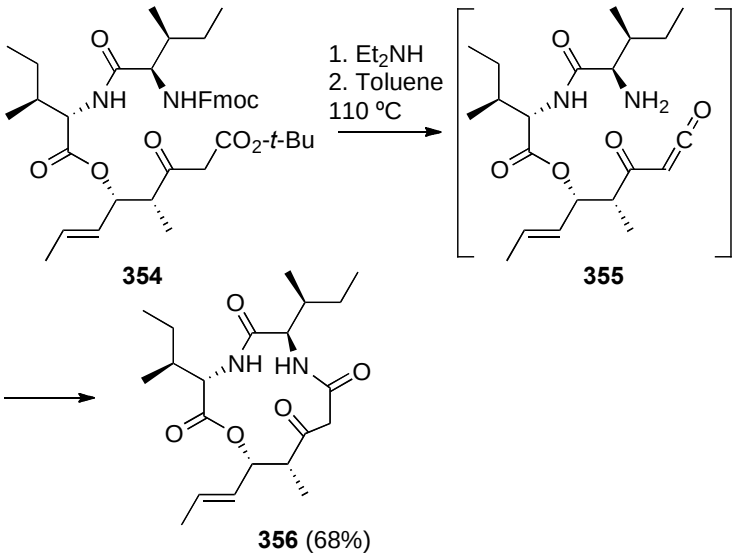
Scheme 122. Ketene generation by cyclopropenone ring opening.

n-Octylketene (**352**), generated by alkynyl ether (**351**) thermolysis in a flow reactor, was trapped by benzylamine giving amide **353** (Scheme 123).[170]



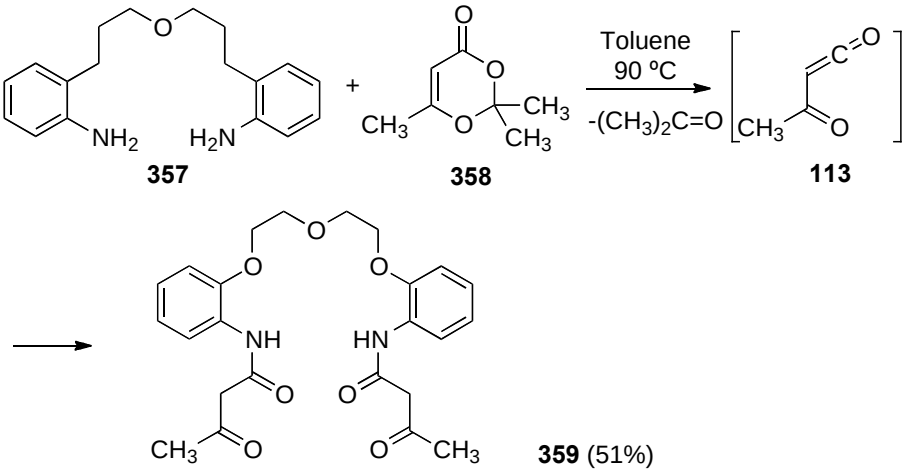
Scheme 123. Ketene formation from alkynyl ether thermolysis.

Acyl ketene **355** generated by thermolysis of the acyl ester **354** underwent cyclization by intramolecular ketene amination to give the lactam **356**, establishing the stereochemistry of the taumycin natural product (Scheme 124).[171]



Scheme 124. Ketene generation by ester elimination with subsequent cyclization.

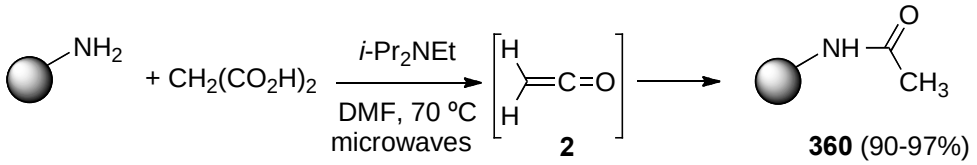
Acetylketene **113** generated by thermolysis of the dioxinone **358** reacts with the aminoaryl podand **357** to form acetoacetanilide podand **359** (Scheme 125).[172] Such acetoacetanilide-containing podands were then used in the Biginelli reaction as CH-active components.



Scheme 125. Ketene formation by dioxinone thermolysis and double acylation.

Ketene generation from malonic acid is applied to the *N*-acylation of a variety of peptides, as well as in the formation of the resin-bound amide **360** (Scheme 126).[173] The ketene

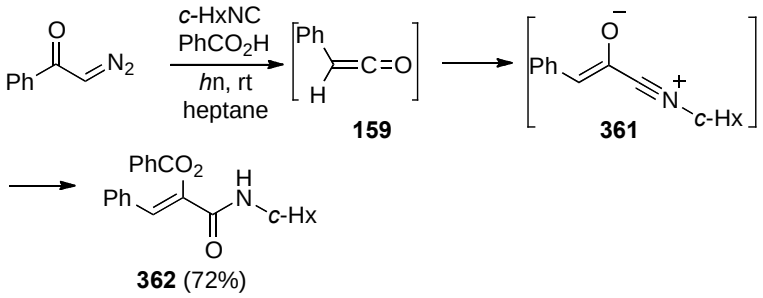
intermediate was detected *in situ* by the ^{1}H NMR absorption at 2.6 ppm during the reaction of the peptide of 2-Boc-ethylamine (*t*-$BuO_2CCH_2CH_2NH_2$), and DFT studies support the proposed mechanism.



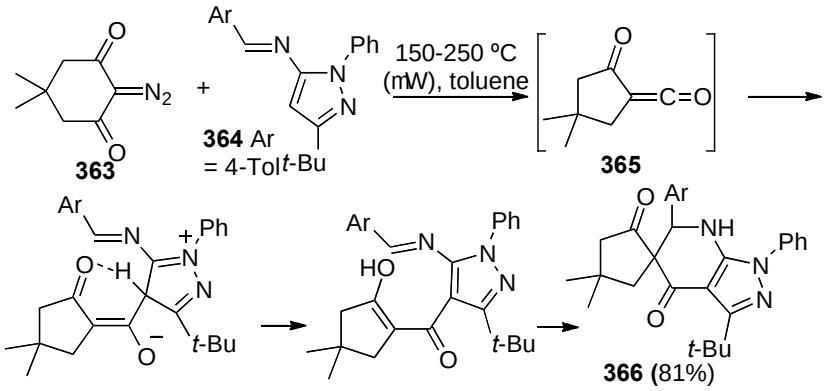
Scheme 126. Ketene generation from malonic acid and peptide acylation.

5.3 Addition of carbon nucleophiles

Ketenes including **159** generated by Wolff rearrangement in the presence of an isocyanide and a carboxylic acid undergo stereoselective formation of (*Z*)-acyloxyacrylamides **362** by initial attack of the isocyanide giving a zwitterionic intermediate **361** which is acylated forming the product (Scheme 127).[174] Photoisomerization of the product alkenes was also observed, and this procedure was also successful with disubstituted ketenes.[174]



Scheme 127. Isocyanide addition to ketenes.



Scheme 128. Acylketene reaction with a carbon nucleophile and spiro-dihydropyridin-4-one formation.

Ketene **365** from thermolysis of diazo ketone **363** reacts with the iminopyrazole **364** by spiro-cyclization proposed to involve Friedel-Crafts type addition followed by hydrogen transfer and intramolecular cyclization leading to **366** (Scheme 128), as supported by computational studies.[175] The calculated transition state for the hydrogen transfer is shown in Figure 13.[175]

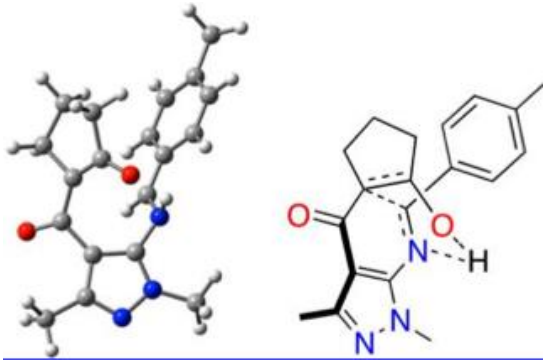
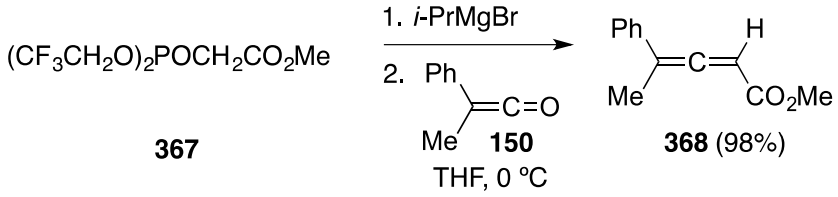


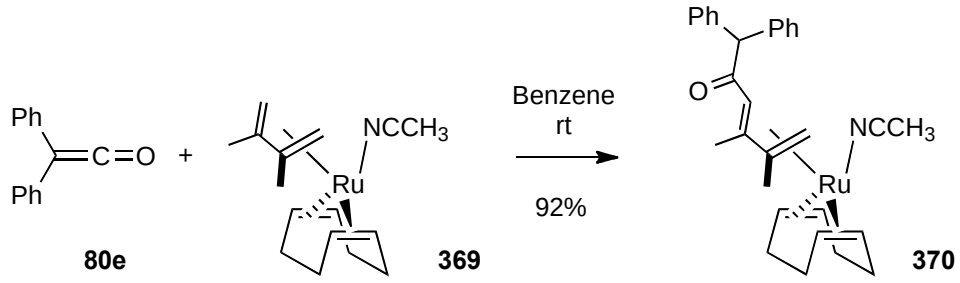
Figure 13. Calculated transition state for hydrogen transfer. (Reprinted with permission from the American Chemical Society [175]).

Phosphonate **367** reacts with ketenes by the Horner-Wadsworth-Emmons reaction forming trisubstituted allenes **368** in high yield (Scheme 129).[176]



Scheme 129. Horner-Wadsworth-Emmons ketene to allene transformation.

Diphenylketene reacts with the ruthenium(0) complex **314** by addition to the dienyl grouping to form **315** (Scheme 130).[177]



Scheme 130. Diphenylketene reaction with a dienyl ruthenium complex.

Intramolecular *C*-acylation of enamine carbon by a ketene component (Scheme 104), and similar intramolecular acylation of a phenoxy substituent (Scheme 105), have been noted earlier. (Section 4.7)

6. Electrophilic Additions to Ketenes

Carbon-protonated ketene, the acetyl cation, is formed from methyl acetate or acetone in a pulsed discharge as the most stable product, while oxygen protonated ketene, formed only from acetone as a minor component, is formed as the next most stable ion.[178] The energies of six isomeric structures of protonated ketene are reported there (Figure 14).

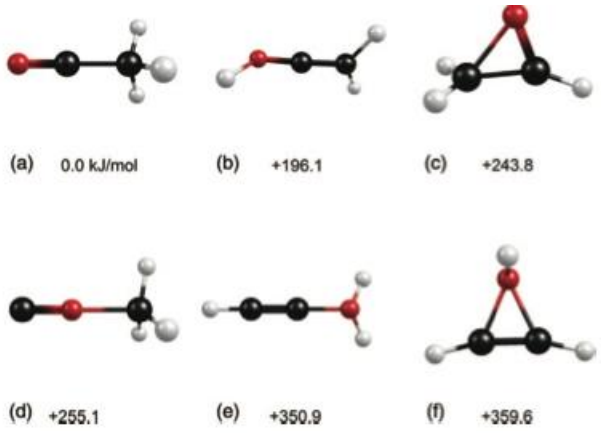
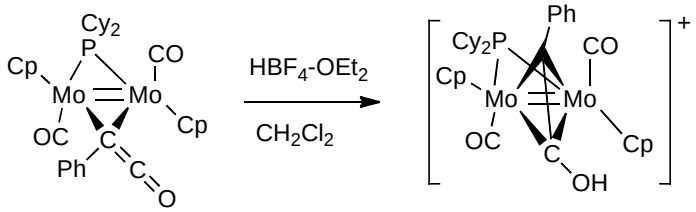


Figure 14. Relative calculated energies (kJ/mol) of 6 isomers of protonated ketene (Reproduced from reference 179 with permission of the publisher)

Protonation of the ketene complex **371 (**[Mo_2Cp_2\{μ-C(Ph)CO)\}(μ-PCy_2)$(CO)_2$]) gave the metal complex **372** in 88% yield as a red solid, and was interpreted as involving protonation on oxygen (Scheme 131).[179,180] The structure of **372** was confirmed by an X-ray determination.[180]

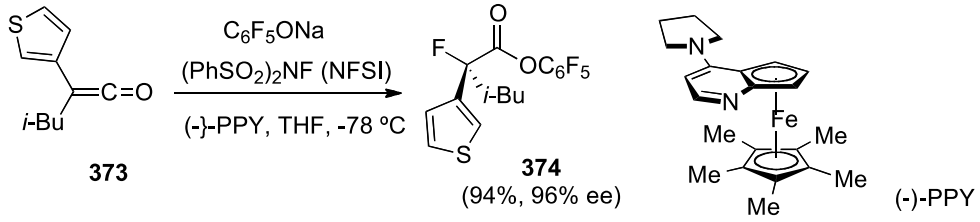


371 (IR 1993 cm^{-1})
Cp = C_5H_5, Cy = cyclohexyl

372 (88%)

Scheme 131. Protonation of a molybdenum ketene complex.

Catalytic asymmetric fluorination of ketene **373** occurs with the catalyst (-) –PPY and *N*-fluorodibenzenesulfonimide (NFSI) as the fluorine source (Scheme 132). The reaction is proposed to occur by complexation with the catalyst and then fluorine transfer.[181]



Scheme 132. Catalytic asymmetric fluorination.

7. Conclusions

The distinctive bonding in ketenes and the great utility of these materials have attracted the attention of talented investigators for more than a century. Remarkable achievements have been reported in the formation of ketenes by oxidation processes, reactions of ketene radical cations, unusual new ketenes, and organometallic ketenes The outstanding creativity shown by investigators, and the continued success that has been reported, indicates that there will be continued progress in the future.

8. Acknowledgements

Professor Melvin Newman provided the inspiration for our studies of ketenes, as described above. Facilities provided by the University of Toronto made the preparation of this review possible.

9. References

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