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Ketene Chemistry after 100 Years: Ready for a New Century

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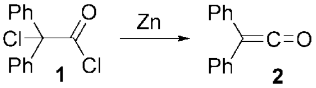
The existence of ketenes was established 100 years ago, and in recent years the pace of discovery in the study of these reactive intermediates has accelerated – extremely unstable ketenes such as difluoroketene have been directly observed for the first time, while a variety of bisketenes stabilized by silyl substituents have been isolated as long-lived compounds at room temperature. New methods for generating ketenes for applications in synthesis have been devised, and these have been applied in the preparation of many valuable targets. Asymmetric synthesis by nucleophilic additions and by [2+2] cycloadditions to ketenes to form β-lactams and β-lactones has been achieved with high yields and high stereoselectivities. The free-radical chemistry of ketenes is receiving increasing levels of attention, and new rearrangement reactions of ketenes have been developed. These advances create new opportunities to utilize the unique structures and high reactivity of ketenes for even greater progress in the future.

I. Introduction

The preparation of diphenylketene (**2**) in 1905 by Hermann Staudinger, by the dehalogenation of chlorodiphenylacetyl chloride (**1**) with zinc, marked the discovery of the first representative of one of the last of the major organic functional groups [Equation (1)].[1] Ketenes possess highly reactive carbonyl and alkenyl groups, and the many possible transformations of one or both of these make ketenes highly useful and versatile organic reactive intermediates.



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The historical development of the early years of ketene chemistry has recently been described,[2a] and there are extensive reviews of ketene chemistry.[2b–2e] However, the past 10 years have shown remarkable developments in this field, with important new discoveries from laboratories around the world. This report marks the Centennial year of ketenes by describing some of the most important of these recent advances.

II. Haloketenes

Haloketenes were latecomers to the ketene family, and were generated only as highly reactive species that were trapped as unobserved intermediates in 1965–1966, despite many earlier attempts at their preparation.[2a] It is somewhat paradoxical that ketenes are characterized by a high electron density at the substituted carbon (C^2), but ketenes substituted with the highly electronegative halogens (and oxygen) are not stabilized, but are very reactive. This was finally understood with the realization that ketenes are stabilized by electropositive substituents, which can donate

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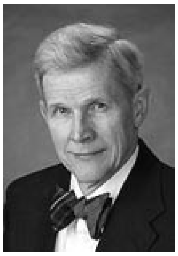
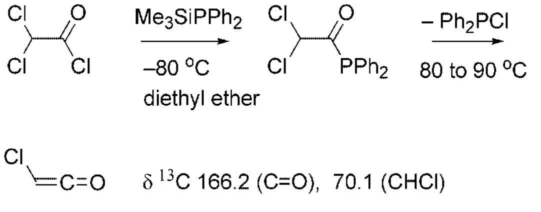


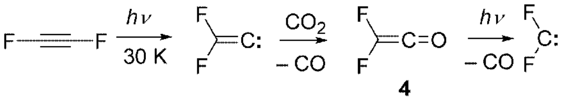
Thomas T. Tidwell received his BS degree from the Georgia Institute of Technology in 1960, and his PhD from Harvard University in 1964 for research with P. D. Bartlett. He was a postdoctoral fellow at the University of California, San Diego, with Teddy Traylor and the University of East Anglia (UK) with Alan Katritzky, and since 1972 has been at the University of Toronto, where he is Professor of Chemistry. He has research interests in steric crowding, carbocation chemistry, antiaromaticity, and ketene chemistry, and as diversions he enjoys tennis and chemical history.

electrons by σ-π conjugation in the ketene plane from the substituent-ketene bond to the ketenyl carbonyl group, and by π-acceptor substituents, such as acyl groups, which can accept electrons conjugatively from the ketenyl group perpendicular to the ketene plane.[2b] The halogens, oxygen, and nitrogen are electronegative, not electropositive, and are π-donors, and so lose on both counts, and lack the ability to stabilize ketenes. As a result, there is an inverse correlation of computed ketene stabilities with substituent group electronegativities, with positive deviations for π-acceptor groups. Chloroketene (**3**) is a highly reactive species and was first obtained as an observable species in solution in an experimental tour de force by the reaction of dichloroacetyl chloride with Me_3SiPPh_2 at low temperature, followed by heating and trapping of the ketene at –80 °C, permitting measurement of the ^{13}C NMR spectrum, with the distinctive high-field shift for C^2 that is characteristic of ketenes and indicative of the high electron density at that position [Equation (2)].[3a] The haloketenes HalCH=C=O (Hal = F, Cl, Br, I) have all been generated in the gas phase and identified by their IR spectra.[3b] Fluoroketenes are remarkably reactive, and CFH=C=O and CF_2=C=O (**4**) have not been observed directly in solution.



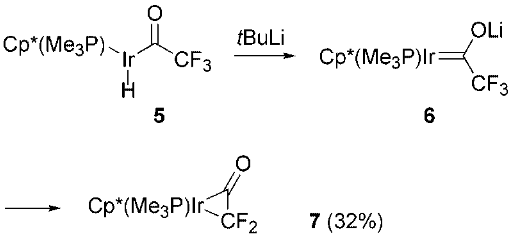
(2)

Difluoroketene (**4**) is unstable and has a strong tendency to decarbonylate,[3c] but was finally observed in a condensed phase when generated in an Ar matrix by photolysis of difluoroacetylene at 193 nm to form difluorovinylidene, which forms **4** upon oxygenation with CO_2 [Equation (3)].[3c] The ketene was identified by its IR band at 2162 cm^{-1}, and upon further photolysis underwent decarbonylation to CF_2 [Equation (3)].[3c] Difluoroketene (**4**) was also generated recently and observed in the gas phase by electron-impact mass spectrometry of perfluoromethyl vinyl ether and neutralization-reionization of the resulting ion.[3d] The most recent computational study indicates the dissociation into CF_2 and CO has a barrier of only 10 kcal mol^{-1}, and so the difficulty of observing this compound is understandable.[3e]



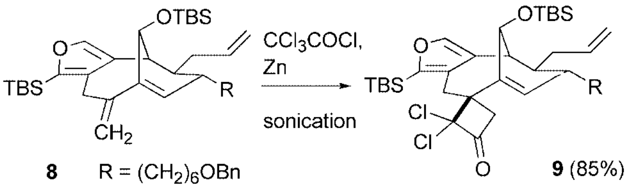
(3)

The iridium complex **7** of difluoroketene has recently been prepared by reaction of the iridium complex **5** with *tert*-butyllithium from –196 to –80 °C to give the complex **6**, observed by NMR spectroscopy, which, upon warming to 22 °C, formed the difluoroketene complex **7**, which has ^{13}C NMR signals at δ = 207.2 (CO) and 178.0 ppm (CF_2) and the ketenyl IR signal at ṽ 1725 cm^{-1} [Equation (4)].[3f] The structure of **7** was confirmed by an X-ray determination.[3f]



(4)

The high reactivity of haloketenes makes them very useful in synthesis, as in the preparation of the enzyme inhibitor CP compounds by [2+2] cycloaddition of dichloroketene, generated by zinc dehalogenation, with high selectivity for the hindered *exo*-methylene group of **8**, to give **9**, even in the presence of an unhindered allylic group [Equation (5)].[3g] Dechlorination with zinc and ring cleavage provide a key carboxylic acid intermediate.[3g] Chloroketenes also play a key role in ketene-Claisen rearrangements (vide infra).



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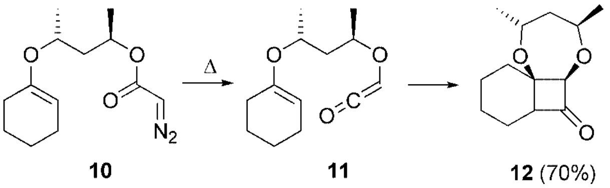
III. Wolff Rearrangements

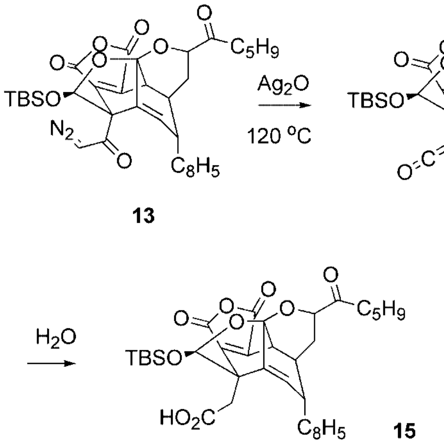
The Wolff rearrangement was discovered in 1902,[4a] and has been used since then for the generation and direct observation of many highly reactive ketenes,[4b] although it has not found application in the preparation of halo ketenes. This otherwise very versatile reaction has also been of limited utility for generation of oxygen-substituted ketenes because of the low migratory aptitude of oxygen in this reaction.[4c] However, under flash vacuum pyrolysis conditions diazoacetate ester **10** has been found to form the ketene **11**, leading to **12** in yields as high as 70 %, with high stereoselectivity [Equation (6)].[4c] This reaction is interpreted[4c] to be



(6)

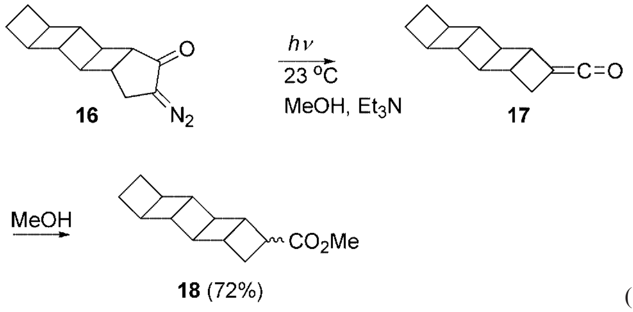
successful because the intermediate keto carbene undergoes greatly reduced intermolecular atom abstraction in the gas phase, and so the Wolff rearrangement eventually occurs.

The utility of the Wolff rearrangement has increased continually, and, for example, has found application in the synthesis of the CP molecules by silver-ion-catalyzed thermolysis of the extremely crowded diazo ketone **13** to give the unobserved ketene **14** and finally the acid **15** [Equation (7)].[4d,4e] This ketene reaction has been utilized for construction of the acetic acid side-chain at the highly hindered C^7 position, just as was the case of generation of **9** [Equation (5)].[4d,4e]



(7)

In another application using the Wolff rearrangement, ring contraction upon photolysis of the diazo ketone **16** forms the unobserved ketene **17**, which was trapped as a 3:1 mixture of *endo*- and *exo*-methyl esters **18** [Equation (8)].[4f] These were used in a synthesis of the unusual "ladderane" natural product C_{20}-fatty acid methyl ester of (±)-pentacycloanammoxic acid.[4f]



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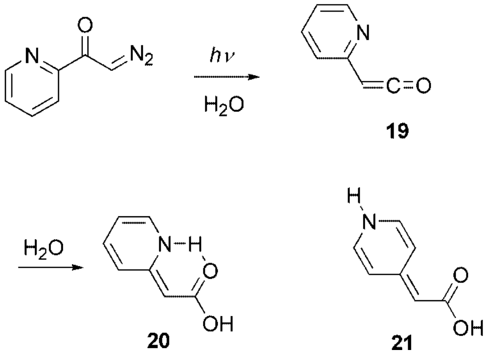
The photochemical version of the Wolff rearrangement is particularly valuable for the study of reactive intermediates, as highly reactive ketenes can be generated in various media from the reasonably stable diazo ketones. Addition of water to the ketenes gives acid enols as further observable reactive intermediates, which then form the carboxylic acids.[4g] 2-Pyridylketene (**19**) formed in this way has been found to hydrate to give a rather long-lived dihydropyridine intermediate **20**, which is stabilized by an intramolecular hydrogen bond [Equation (9)].[4h] Surprisingly, 4-pyridylketene formed by a Wolff rearrangement also undergoes hydration to form a rather long-lived dihydropyridine intermediate **21**, which lacks this stabilization due to an intramolecular hydrogen bond [Equation (9)].[4h] The dihydropyridine intermediates **20** and **21** are readily identified by their distinctive long-wavelength UV absorption, and their greater stability than the corresponding enols has been confirmed by DFT computations.



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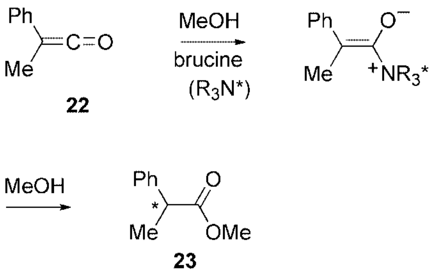
IV. Stereoselective Nucleophilic Attack on Ketenes

Additions of nucleophiles to unsymmetrical ketenes generate new chiral centers, and this has resulted in a long-lasting interest in stereoselective reactions of ketenes. Pioneering observations were made by Pracejus at the University of Rostock of stereoselectivity in the addition of methanol to phenyl(methyl)ketene (**22**), catalyzed by the chiral base brucine, to form the ester **23** [Equation (10)], a precursor of α-arylalkanoic acids, which are of major pharmaceutical importance.[5a] Further investigations at the Merck laboratories revealed excellent 99.5% diastereoselectivity for addition of the chiral alcohol (*R*)-pantolactone (**25**) to ketene **24** to form the 2-arylpropionate **26** [Equation (11)][5b] The origin of the stereoselectivity in this reaction has also been examined computationally.[5c]



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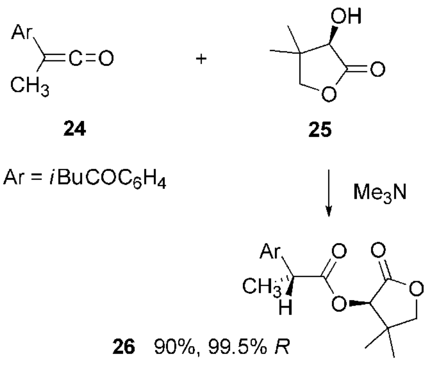
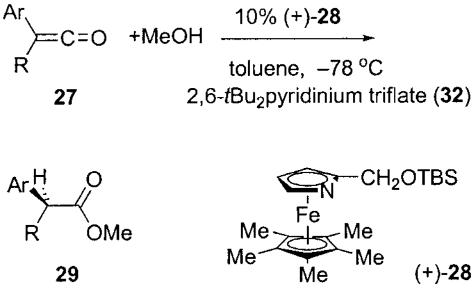
The catalytic asymmetric synthesis of esters from ketenes has been significantly extended by Fu and co-workers, who found that addition of methanol to aryl(alkyl)ketenes **27** catalyzed by azaferrocene **28** gave up to 80% *ee* in formation of ester **29** [Equation (12)].[6a,6b] They proposed that



(11)

this reaction takes place by a catalytic cycle with nucleophilic attack of the catalyst on the ketene to form the enolate **30**, which is protonated to form **31** stereoselectively, and then methanol displaces the catalyst to form the ester **29** [Equation (13)].[6a–6c] In further studies, the reaction of ketenes **27** with phenols **33** and catalyst **34** gave esters **35** with *ee*'s of 35–91 %, with the highest *ee* for the addition of 2-*tert*-butylphenol [Equation (14)].[6d] A variety of ketenes with this phenol gave *ee*'s of 79–94 % and yields of 66–97 %. The mechanism proposed for this process involves deprotonation of the phenol, phenoxide attack on the ketene to form enolate **36**, and proton transfer from the resulting ion pair to form **37** [Equation (15)].[6d]



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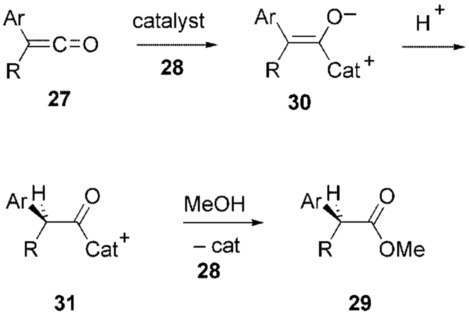

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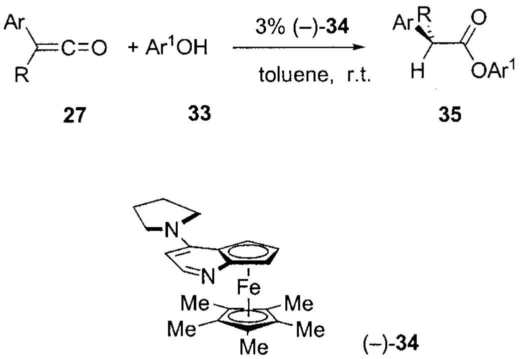

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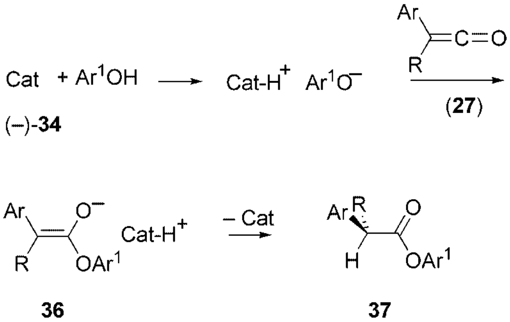
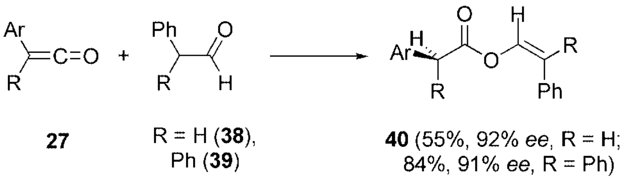


(15)

Aryl(alkyl)ketenes **27** react with readily enolizable aldehydes **38** and **39** with catalysis by (–)-**34** to give stereoselective formation of vinyl esters **40** [Equation (16)].[6e] The reactions of a number of ketenes **27** with **39** give good yields and stereoselectivity, and the esters can be converted into the carboxylic acids.[6e] Among possible mechanisms for this reaction is initial catalyst addition to the ketene to give **41**, which stereoselectively abstracts a proton from the aldehyde to give **42**, which then combines with the aldehyde enolate **43** [Equation (17)].[6e] Another possible mechanism is addition of **43** to the ketene to give **44**, which is converted into **40** by stereoselective proton transfer by the protonated catalyst [Equation (18)].[6e]



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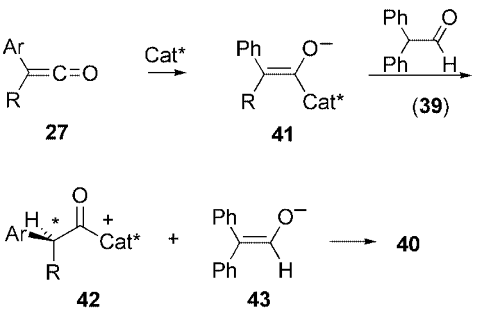

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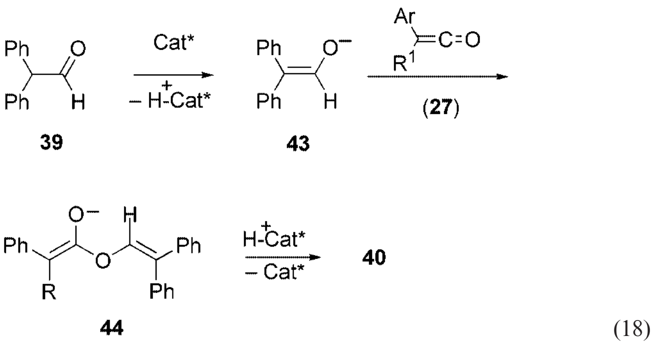
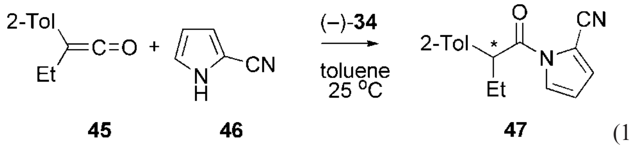
Stereoselective addition of chiral amines to aryl(alkyl)ketenes has also been studied by Pracejus,[7a] who found that for the addition of (*S*)-1-phenylethylamine to meth-



(18)

yl(phenyl)ketene in toluene at –105 °C there was 60% *ee* for formation of the *S*,*S*-amide. In an extension of this work,[6c,7b] chiral catalysis by (–)-**34** of the stereoselective addition of 2-cyanopyrrole (**46**) to 2-TolCEt=C=O (**45**) gave 95% yield and 98% *ee* in formation of **47** [Equation (19)].[7b] These stereoselective additions of nucleophiles catalyzed by chiral amines are believed to involve addition of the catalyst to the ketene, followed by proton transfer and displacement of the catalyst by the nucleophile.[6c,7b]



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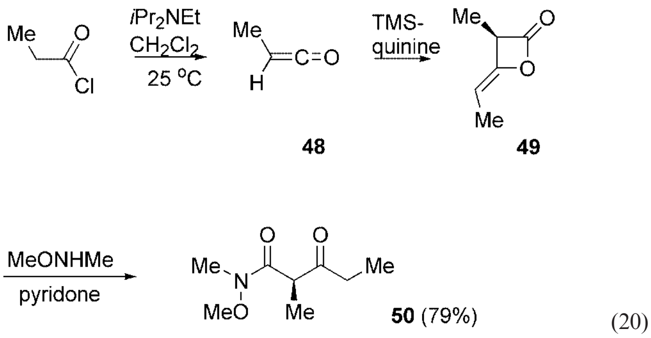
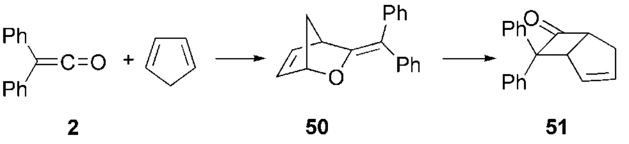
V. Ketene Dimerization and Alkene [2+2] Cycloadditions

Shortly after their discovery, many ketenes were found to have the unusual property of undergoing spontaneous dimerization, although it was some time before the β-lactone and 1,3-cyclobutanedione structures formed by [2+2] cyclodimerization of the parent ketene and monosubstituted ketenes were fully differentiated.[2a,2b] More recently, enantioselective dimerization of methylketene (**48**),[8] generated by in situ dehydrochlorination of propionyl chloride with *i*Pr$_2$NEt in CH$_2$Cl$_2$ at room temperature with 5 mol-% trimethylsilylquinine as catalyst, has been shown to give a 79% yield of the *R*-dimer **49** with 94% *ee*, which was isolated as the β-ketoamide **50** after reaction with methoxymethylamine [Equation (20)].[8a] The dimerization was proposed to occur with nucleophilic catalysis by amine addition to the carbonyl carbon of **48**, and kinetic studies showed that methylketene formation from propionyl chloride was rate determining. Methylketene generated thermolytically from propionic anhydride gave the same selectivity for dimer formation, thus indicating that dimerization involves two ketene molecules and not propionyl chloride. Dimers of other ketenes RCH=C=O (R = Et, *i*Pr, *t*Bu, TIPSOCH$_2$, MeO$_2$CCH$_2$, respectively) have been prepared similarly in 58–88% yields, and 91–96% *ee*.[8a]



(20)

Early in the study of ketene chemistry, diphenylketene (**2**) was found to undergo cycloaddition with cyclopentadiene to give the [2+2] cycloaddition product **52**, and this was the first example of this distinctive and useful process [Equation (21)].[9a] Surprisingly, it was shown by Machiguchi, et al., some 90 years later, that the initial reaction in this canonical process at low temperature is a [4+2] cycloaddition to the carbonyl oxygen to form **50**, which, upon warming, undergoes a Claisen rearrangement to **51** [Equation (21)].[9b] Similarly, **2** reacts with methyl isopropenyl ether by initial [2+2] cycloaddition to the carbonyl oxygen in CH$_2$Cl$_2$ at –25 °C to form the oxetane **52**, and this isomerizes at 25 °C to the enone **53** [Equation (22)].[9c] These developments are contrary to some previous interpretations of ketene cycloadditions and suggest a re-examination is needed to fully understand other earlier studied examples.



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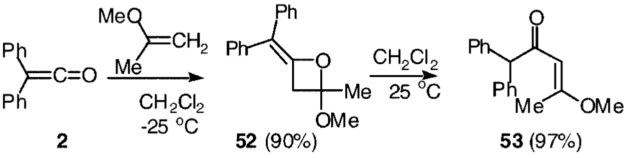

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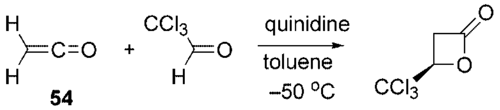
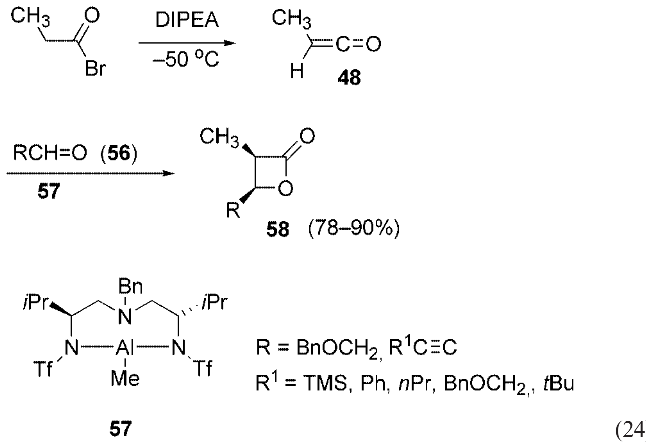
VI. β-Lactones by Ketene Aldehyde [2+2] Cycloaddition

The [2+2] cycloaddition of ketenes to carbonyl compounds to form β-lactones was another of the first ketene reactions to be discovered.[9a] Just as for ketene dimerization [Equation (20)], new chiral centers are formed in many of these ketene cycloaddition reactions, and the search for stereoselectivity in these and other ketene reactions has gained increasing urgency.[10a] A prominent early example is the addition of trichloroacetaldehyde to ketene (**54**) catalyzed by the chiral tertiary amine quinidine, which gives β-lactone **55** with high stereoselectivity [Equation (23)].[10b,10c]



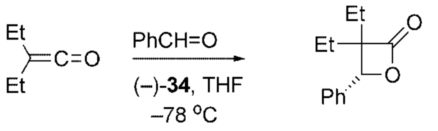
55 (89%, 98% *ee*) (23)

The further development of catalytic, enantioselective methods has increased the utility of β-lactone formation by ketene cycloaddition to carbonyl groups. Dehydrochlorination of propionyl bromide by diisopropylethylamine (DIPEA) forms methylketene (**48**), which, in reactions induced by catalyst **57**, undergoes [2+2] cycloadditions with aldehydes **56** to form β-lactones **58** with high *cis*/*trans* product ratios and 90–94% *ee*. [Equation (24)].[11a,11b] This reaction was improved with a second-generation catalyst and by using benzotrifluoride as solvent, which resulted in precipitation of the ammonium salt.[11c,11d]



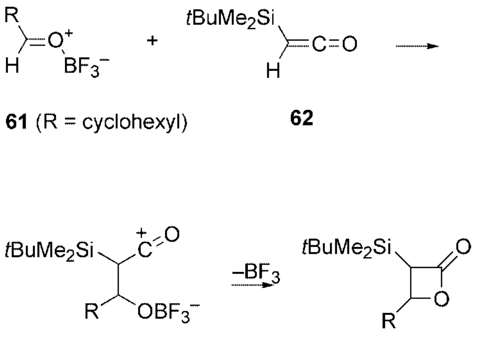
(24)

In an extension of this procedure to disubstituted ketenes, asymmetric synthesis was achieved using the catalyst (–)-**34** and diethylketene (**59**) to form β-lactone **60** with a quaternary carbon in 92% yield and 91% *ee* [Equation (25)].[11e] The unsymmetrical dialkylketene *i*PrCMe=C=O reacts similarly, with 48% yield, 91% *ee*, and 4.5:1 selectivity for the *cis*-lactone.[11e]



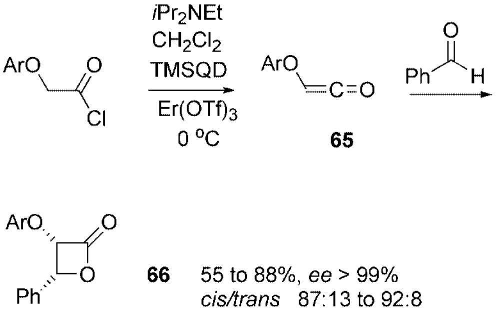
59 **60** (92%, 91% *ee*) (25)

The stereoselectivity of the BF_3-catalyzed cycloaddition of cyclohexanecarboxaldehyde (**61**) to ketene **62** [Equation (26)] has been studied both computationally and by measurement of the ^{13}C kinetic isotope effects.[12a] The reaction gives greater than 90% yields of **64** as a *cis*/*trans* mixture with a diastereoselectivity that varies from 2.7–3.1:1 at 23 °C to 1.3:1 at –21 °C.[12a] Distinctly different ^{13}C kinetic isotope effects were observed for formation of the two diastereomeric products, and these were interpreted as forming from a stepwise process [Equation (26)].[12a] The first step – the formation of **63** – was proposed to be rate-limiting for formation of the *trans* product, whereas the second step – the formation of **64** from **63** – was found to be rate-limiting for formation of the *cis* product.



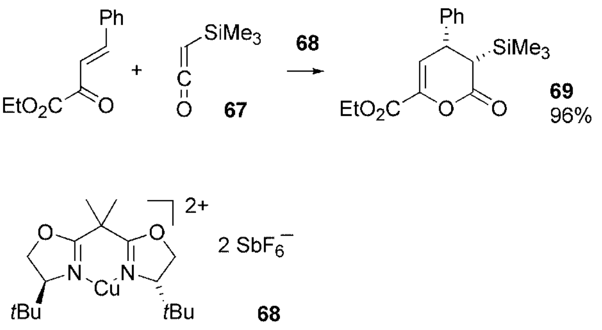
63 **64** (26)

Aryloxy- and alkylketenes have been found to undergo stereoselective [2+2] cycloaddition with aryl aldehydes when the reactions are promoted by a Lewis acid together with trimethylsilylquinidine (TMSQD).[12b–12g] Thus, β-lactone formation from benzaldehydes with methyl- and ethylketenes with catalysis by $Sc(OTF)_3$ and TMSQD gave product *trans*/*cis* ratios of 91:9 to 95:5, yields of 75–82%, and 92–99% *ee*.[12g] Aryloxyketenes **65** with $Er(OTf)_3$ gave a preference for formation of *cis* β-lactone **66**: *cis*/*trans* 87:13 to 92:8, 55–88% yields, and *ee* > 99% [Equation (27)]. Without the Lewis acid catalyst the reactions were not successful.



66 55 to 88%, *ee* > 99%
cis/trans 87:13 to 92:8 (27)

The bis(oxazoline)-Cu^{II} complex **68** catalyzes not only [2+2] cycloadditions of trimethylsilyketene (**67**) to form β-lactones, but also stereoselective [4+2] cycloaddition of a keto ester to form **69** in 96% yield, *endo*/*exo* >95:5, and 97% *ee* [Equation (28)][12b] Carboxylic acid dehydration with Mukaiyama's reagent **70** gave intramolecular cyclization with catalysis by nucleophilic addition of 9-*O*-acetylquinine to form **72** in 54% yield and 92% *ee* in a reaction that may involve ketene **71**, although the ketene was not directly observed and may not be an intermediate in the reaction [Equation (29)].[12c–12e]



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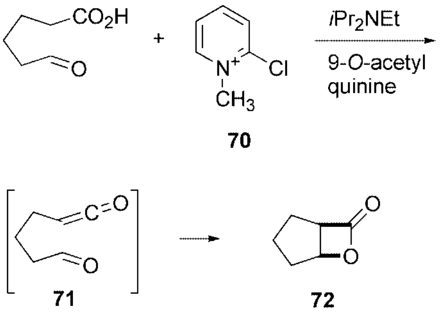


(29)

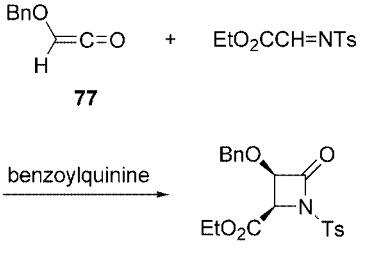
VII. Ketene-Imine [2+2] Cycloadditions to Form β-Lactams

The [2+2] cycloaddition of ketenes with imines has long been known,[9a] and is one of the best routes for forming β-lactams. Because of their importance in medicinal chemistry, the search for stereoselectivity in the ketene [2+2] cycloaddition with imines to form β-lactams has been vigorously pursued, and considerable success has been achieved using chirally substituted ketenes and imines, and chiral catalysts.[13]

Together with this quest for improved stereoselectivity in β-lactam formation, a new methodology has been created for the generation of ketene solutions by dehydrochlorination. This was achieved by using a combination of the reaction of the acyl chloride with a stoichiometric amount of base, which reacts irreversibly with the HCl generated, and a trialkylamine as a catalyst, which serves as a shuttle base.[14a–14g] The trialkylamine rapidly effects the dehydrochlorination and then transfers the proton to the stronger base, with regeneration of the catalytic base (Scheme 1).

The stoichiometric base NaH with 15-crown-5 (**73**) was used for the preparation of phenylketene (**74**) by dehydrohalogenation of the acyl chloride in toluene (Scheme 1).[14a,14c] The initial $Et_3NH^+Cl^-$ salt transfers the proton to NaH, which reacts irreversibly and regenerates the Et_3N. The polymer-bound triaminophosphoramide imine base BEMP (**75**) used in column synthesis also irreversibly generates ketenes,[14a] and 1,8-bis(dimethylamino)naphthalene (**76**) has also been used as a stoichiometric base, but may give reversible deprotonation to form phenylketene, so the ketene may not be involved in the product forming step.[14b]

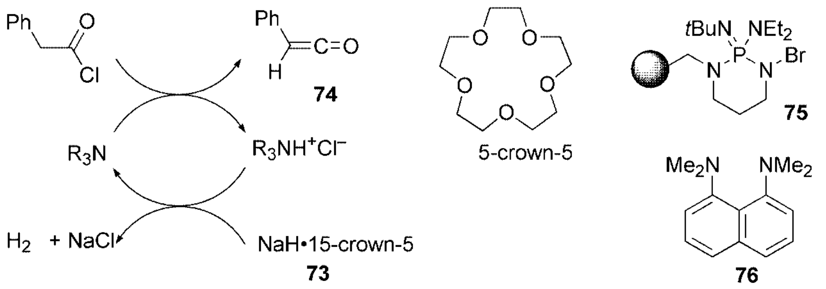
With the chiral base benzoylquinine as a kinetic shuttle base at –78 °C the amine also acts as a catalyst for stereoselective addition to the ketene, and benzyloxylketene (**77**), generated as in Scheme 1, undergoes [2+2] imine cycloaddition to form the β-lactam **78** in 65% yield, 99% *ee*, and 25:1 *dr* [Equation (30)].[14c,14e] The use of $In(OTf)_3$ as a cocatalyst increases the yield to 98%.[14f] Mechanistic analysis led to the conclusion that benzoylquinine (R_3N) forms the zwitterionic enolate **79**, which reacts with the imine, and the use of $In(OTf)_3$ was found to catalyze the reaction by increasing the rate of reaction of the imine with **79** [Equation (31)].[14f] A bifunctional salicylquinine catalyst has also been devised. This complexes the In^{III} and combines the nucleophilic and electrophilic catalytic functions in one molecule.[14f] An achiral anionic nucleophilic catalyst has also been found, which preferentially gives *trans*-β-lactams from this imine and ketenes ArCH=C=O and PhSCH=C=O with *trans*/*cis* ratios of 5:1 to >50:1, and yields of 35–70%.[14g]



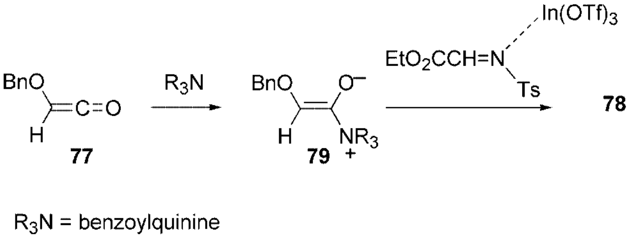
78 (65%, 99% *ee*)

(30)

Stereoselective formation of β-lactams has also been achieved with catalyst (–)-**34** and phenyl(alkyl)ketenes **27** (alkyl = Me, Et, *i*Bu) with imines to give an 8:1–15:1 *cis*/



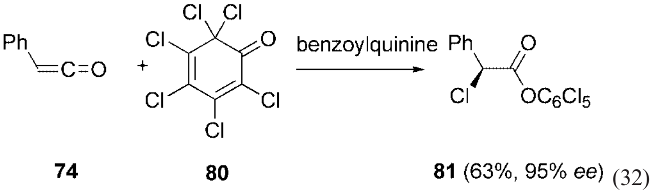
Scheme 1. Generation of phenylketene (**74**) by dehydrochlorination with a shuttle base and NaH·15-crown-5 (**73**).



(31)

trans preference, 89–98% *ee*, and 88–97% yields with ArCH=NTs,[14h] and 84:14–98:2 *trans*/*cis* preference, 63–99% *ee*, and 60–89% yields with ArCH=NTf.[14l]

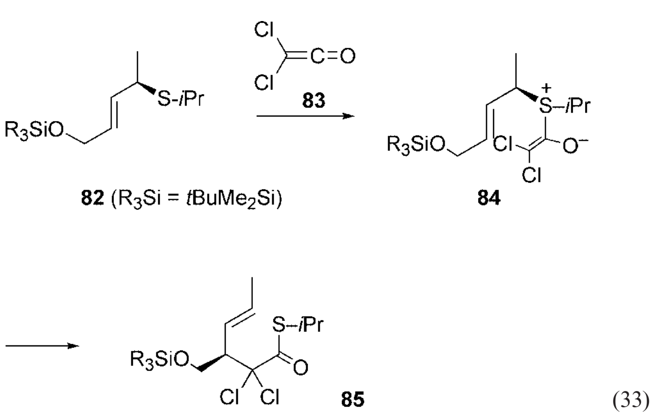
Reaction of **74** and benzoylquinine with hexachlorocyclohexadienone (**80**) as a mild chlorinating agent gives stereoselective formation of the α-chloro ester **81** [Equation (32)].[14a]



(32)

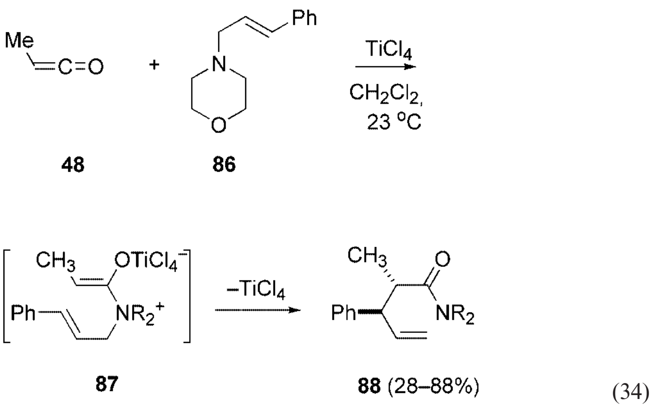
VIII. Ketene-Claisen and Ketene-Cope Reactions

The ketene-Claisen reaction was discovered by Bellus and Malherbre, and involves the reactive dichloroketene **83**, formed in situ by zinc dechlorination, which reacts with allyl thioethers such as **82** to form the zwitterionic species **84**, which then undergoes a [3,3] sigmatropic rearrangement to give the ester **85**, with 83% *ee* [Equation (33)].[15a]



(33)

Methylketene **48**, generated by dehydrochlorination with $i\mathrm{Pr_2NEt}$, reacts with allyl morpholines such as **86** through a ketene aza-Claisen complex **87** to form amides **88** with high selectivity [Equation (34)].[15b] Allylic diamines give cascade reactions with two molecules of **48**,[15c] and use of the chiral catalyst **89** with benzyloxyketene (**77**) and *N*-allylmorpholine gives the product **90** in 80% yield and 91% *ee*.[15d]



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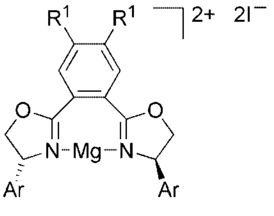
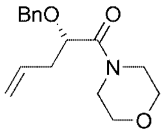
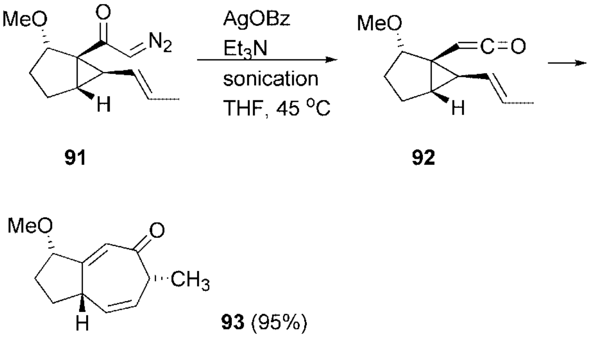


89
[Mg•Arbox](I)$_2$



90

The ketene **92**, formed by sonochemically assisted silver benzoate catalyzed Wolff rearrangement of diazo ketone **91**, gives the cycloheptadienone **93** by a ketene-Cope rearrangement [Equation (35)].[16a] Modeling of the reaction by DFT calculations has allowed the prediction of the effects of substituents in order to design substrates that favor particular products.[16b]



(35)

IX. Bisketenes

Bisketenes have two ketene groupings in the same molecule, and the simplest known example is carbon suboxide (**94**), first prepared in 1906 by Diels and Wolf;[17a] the carbon monoxide dimer **95** is still unknown experimentally.[17b] The bisketene "anthraquinoketene" **96** was first obtained in

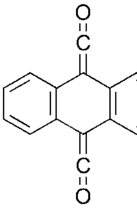
1957 as a reactive but isolable solid,[17c] and attracted interest for possible use in polymerization reactions. The first observable 1,2-bisketene was **97**, which was made in an argon matrix at 10 K in 1982 by Wolff rearrangement and identified by its IR absorption at 2125 cm^{-1}.[17d]

$O{=}C{=}C{=}C{=}O$

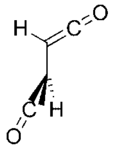
94

$O{=}C{=}C{=}O$

95

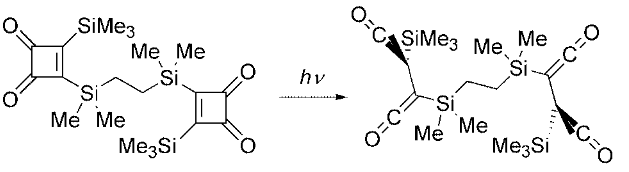


96



97 (IR 2125 cm^{-1})

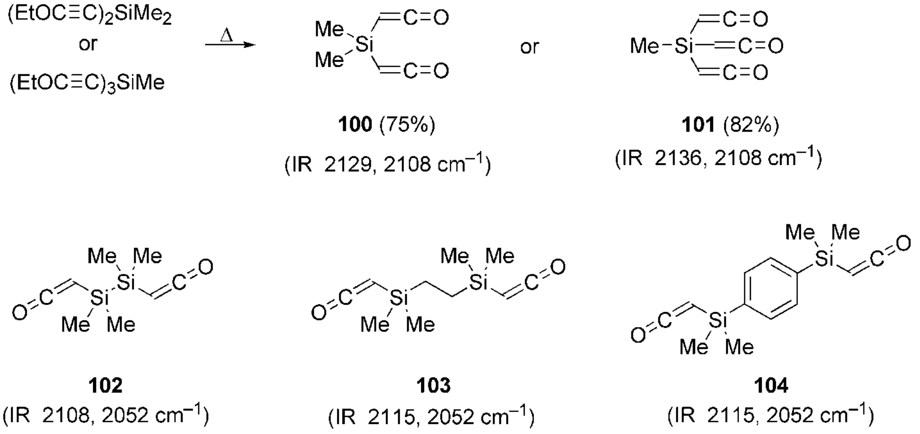
Such 1,2-bisketenes stabilized by trimethylsilyl groups have been prepared subsequently and found to be long-lived species.[18a] 1,2-Bisketenes, including **97**, have unexpectedly been shown by computational studies to have twisted, almost perpendicular, conformations instead of the typical coplanar structures of 1,3-butadienes,[18a] and this finding was confirmed by the X-ray structure of tetraketene **99**, which was formed as a stable product by photochemical ring opening of the bis(cyclobutenedione) **98** [Equation (36)].[18b] The nonplanarity of 1,2-bisketenes is not due to steric crowding, but is an electronic effect that may be attributed to electron–electron repulsion between the two adjacent central carbons in **97**, each with a high π-electron density.[2b,18a]



98 **99**

(36)

Advantage has been taken of the strong stabilizing effect of silyl groups on ketenes for the formation of the 1,3-bisketene **100** and trisketene **101**, by thermolysis of the bis- and tris(ethoxyethynyl)silanes, respectively [Equation (37)].[18c] Both **100** and **101** were isolated as long-lived species, and ab initio molecular orbital calculations indicated that the ketenyl groups in these molecules are each stabilized as much by the silicon as in $Me_3SiCH{=}C{=}O$.[18c] Analogous ethoxyalkyne decompositions gave the 1,4-bisketene **102**, the 1,6-bisketene **103**, and the 1,8-bisketene **104**.[18d,18e]



100 (75%)
(IR 2129, 2108 cm^{-1})

101 (82%)
(IR 2136, 2108 cm^{-1})

102
(IR 2108, 2052 cm^{-1})

103
(IR 2115, 2052 cm^{-1})

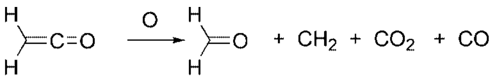
104
(IR 2115, 2052 cm^{-1})

(37)

The stabilization by the trimethylsilyl group in **100**–**104** is due to the β-silicon effect, and is a reflection of the general tendency of ketenes to be stabilized by electropositive groups by electron donation from ketenyl C–M σ bonds to the in-plane carbonyl π orbital.[19a,19b]

X. Free Radicals in Ketene Chemistry

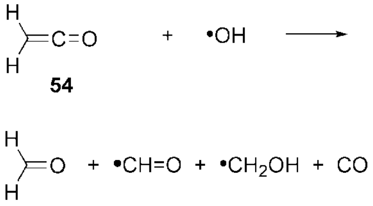
The sensitivity of ketenes to atmospheric oxygen was noticed in the first publication on these species,[1a] and indicates that ketenes are reactive towards free radicals. Because of the high reactivity of both ketenes and free radicals this aspect of ketene chemistry has received rather little attention until recently. However, free-radical reactions of ketenes are of importance because these are significant processes in the combustion of acetylene and other small, unsaturated hydrocarbons, and have been studied for their influence on air pollution. Some of the reactions included in computer simulations of the reaction of $CH_2{=}C{=}O$ (**54**) with oxygen atoms and hydroxyl radicals include highly exothermic radical additions followed by fragmentations, and atom abstractions [Equations (38) and (39)].[20]



54

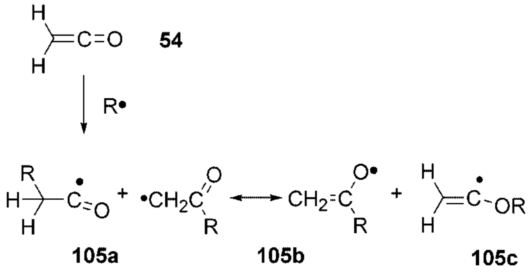
(38)

A computational study of the addition reactions of the radicals H, CH_3, OH, F, SiH_3, and Cl to $CH_2{=}C{=}O$ (**54**) has shown that these reactions are highly exothermic and form the products **105a**–**c** by addition to C^2, C^1, and the



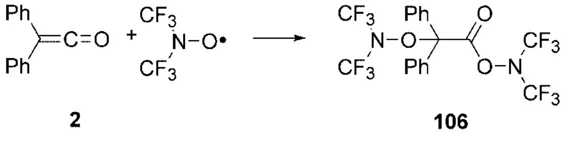
(39)

oxygen of the ketene, respectively. They give good agreement with available data on the relative stabilities of the products and of the barriers for attack [Equation (40)],[21a] as confirmed by later studies.[21b–21e] The results for H$^{\cdot}$ and $CH_3^{\cdot}$ were similar, with little selectivity for attack at C^1 and C^2, and there was little difference between the relative energies of the isomeric products [Equation (40)].[21] For HO$^{\cdot}$, F$^{\cdot}$, and Cl$^{\cdot}$, however, the product enolic radicals from attack at C^1 are significantly more stable than the products of attack at C^2. Small barriers for attack at C^1 were calculated while none were found for attack at C^2, and so selectivity for attack at C^2 was predicted, in agreement with the experiment. For $SiH_3^{\cdot}$, a preference for attack at C^2 was predicted, and this radical was also predicted to be the most stable.



(40)

Nitroxyl radicals have a greatly attenuated reactivity compared to hydroxyl or alkoxyl radicals, and the addition of the nitroxyl radical $(CF_3)_2NO^{\cdot}$ to Ph$_2$C=C=O (**2**) forms the 1,2-diaddition product **106** [Equation (41)].[22a] The less reactive nitroxyl radical 2,2,6,6-tetramethylpiperidinyloxy (TEMPO, TO$^{\cdot}$) also reacts with diphenylketene (**2**), but does not add a second TEMPO [Equation (42)].[22b] On standing in air, reaction with oxygen forms the peroxide **109**, whose structure has been confirmed by an X-ray determination.[22b] This result indicates that the nitroxyl radical adds initially at C^1 of the ketene to form the intermediate radical **107**, which is presumably in equilibrium with the unsymmetrical dimer, and upon exposure to O_2 forms the peroxide [Equation (42)].[22b]



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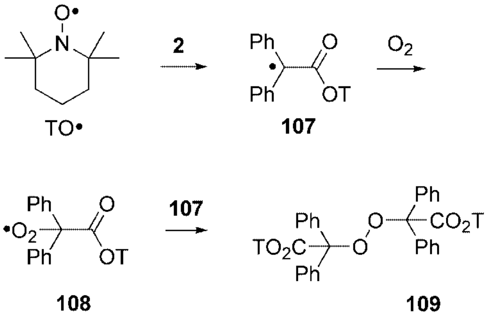
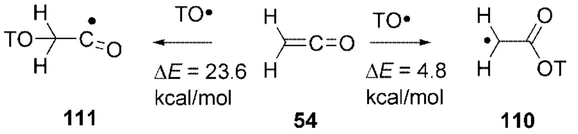


(42)

Computations at the B3LYP/6-31G* level have indicated that addition of TEMPO to ketene **54** is endothermic, but with a strong preference for addition at C^1 compared to C^2, with ΔE values of 4.8 and 23.6 kcal mol^{-1} for formation of **110** and **111**, respectively [Equation (43)].[22c] Thus, addition at C^1 was predicted to be favored, in agreement with the experimental results for addition to **2**.[22b] The reactions of a number of other ketenes with TEMPO have been studied, and typically occur with 1,2-addition [Equation (44)], or with allylic rearrangement for alkenyl-, alkynyl-, or allenyl-substituted ketenes.[23] A linear correlation (Figure 1) between log k_2(TO$^{\cdot}$) and the measured rate constants for hydration [log k(H$_2$O)] at 25 °C over eight orders of magnitude in reactivity with near unit slope was found [Equa-



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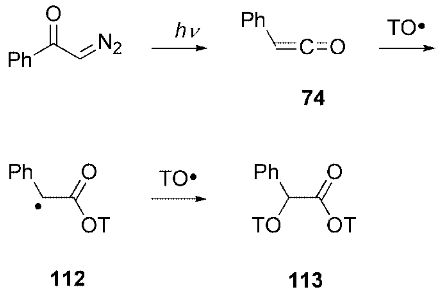

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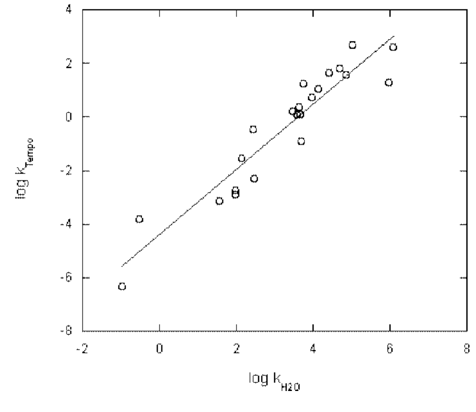
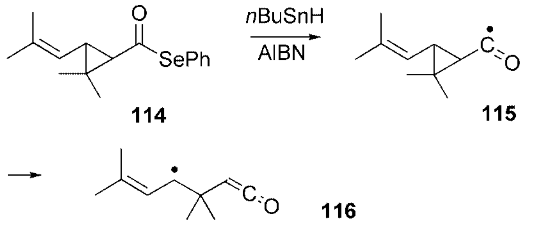


Figure 1. A plot of log k_2(TEMPO) vs. log k(H$_2$O) for ketenes.

tion (45)],[23] and this suggests nucleophilic character for the oxygen of the nitroxyl radical in attack on the carbonyl carbon of ketenes.

$$\log k_2(\text{TEMPO}) = 1.22 \log k(\text{H}_2\text{O}) - 4.93 \ (r = 0.94) \tag{45}$$

Ketenyl intermediates with radical character have been exploited in synthetic applications, as in the reaction of the selenyl ester **114** with $n\text{Bu}_3\text{SnH}$ to give the cyclopropylacyl radical **115** in hot benzene, which was proposed to open to the ketenyl radical **116**, which then forms the aldehyde **117** by ketene reduction, together with the dimer **118a**, while in MeOH the ester **118b** was the only observed product [Equations (46) and (47)].[24a] In a further experiment, the selenyl ester **119** gave the ketone **123** by a pathway proposed to involve the radical intermediates **120**–**122** [Equations (48) and (49)].[24b] An analogous reaction of an allenyl derivative gave a cyclooctadienone.[24c]



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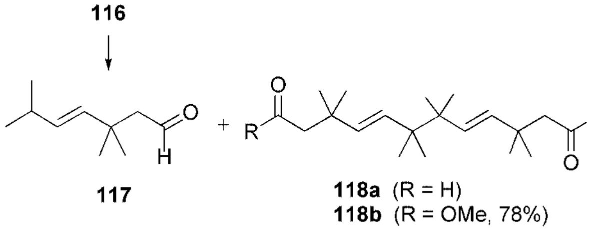
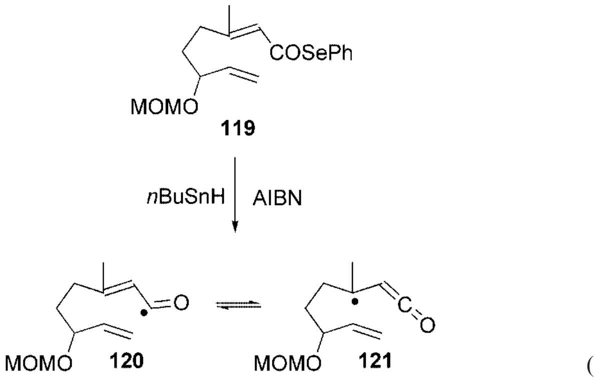


(47)

Reaction of the thioester **124** was proposed to give the ketenyl radical **125**, which reacts by an intramolecular 5-*exo-trig* cyclization to form the ketenyl radical **126**, which then undergoes a further intramolecular 5-*exo-trig* cyclization to give **127** and **128** [Equations (50) and (51)].[24c] An analogous sequence has been used in a formal synthesis of (±)-modhephene (**129**).[24c]



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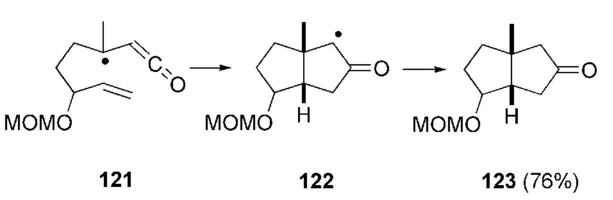

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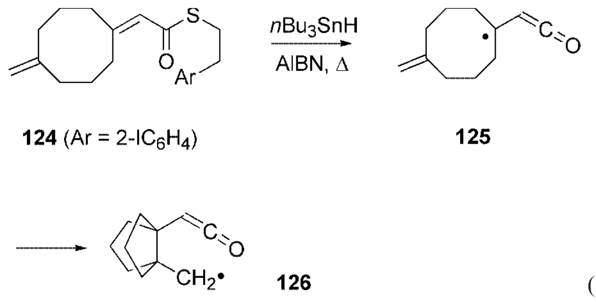

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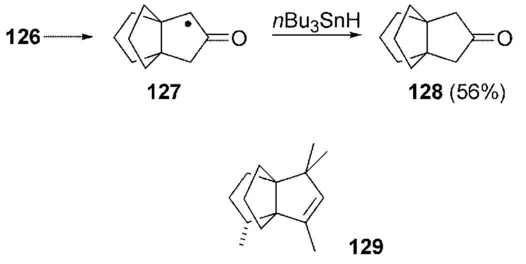

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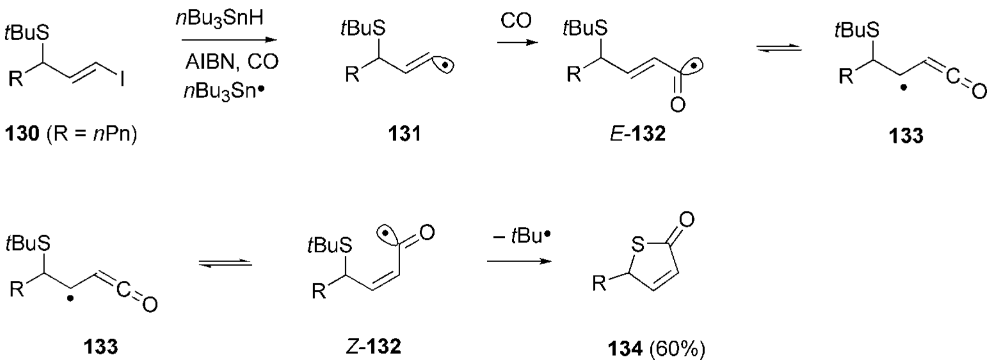
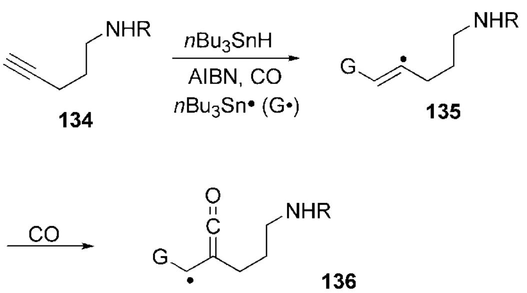


Scheme 2.

The addition of CO to vinyl radicals gives acyl radicals, and reaction of vinyl iodide **130** with n-Bu$_3$Sn$^{\cdot}$ under a pressure of CO gives vinyl radical **131**, which undergoes carbonylation to give ketenyl radical **132**, which then cyclizes to thiolactone **134** (Scheme 2).[25a]

Radicals such as **132** may be represented as existing as mixtures of equilibrating acyl radicals **132** and ketenyl radicals **133**. Studies of a number of such α,β-unsaturated radicals by ESR spectroscopy have found that only the acyl radicals are detectable by this method.[25b] However, computational studies indicate that the radicals may be close in energy in certain cases, so that there are viable reaction channels involving ketenyl radicals.[25c] In the example of Scheme 2, the radical (*E*)-**132** is formed with a geometry incapable of cyclization; isomerization through the ketenyl radical provides a simple mechanism to achieve the required geometry change.[25a]

An unusual amine cyclization occurs with the ketenyl radicals **135**, generated from ω-amino terminal alkynes **134** by free-radical carbonylation [Equation (52)].[26a] The reaction proceeds by addition of the radical n-Bu$_3$Sn$^{\cdot}$ (G$^{\cdot}$) to the alkyne to form **135**, which combines with CO to form **136**, and this cyclizes to **137**, which then undergoes partial destannylation, possibly with transfer of the amine hydrogen from oxygen and then to carbon through an intermediate lactam enol [Equation (53)].[26a]



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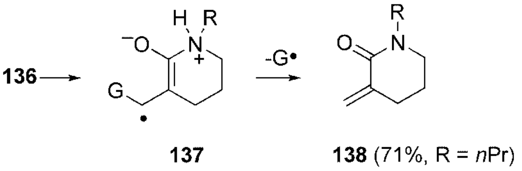
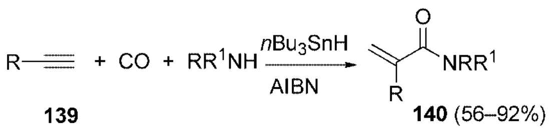


(53)

Carbonylation of alkynes **139** in the presence of amines proceeds via ketenyl radicals to form acrylamides **140** [Equation (54)].[26b] This reaction has been proposed to occur by addition of CO to the vinyl radical **141** to form the ketenyl radical **142**, which adds to the amine to form **143**, followed by intramolecular transfer of the amine hydrogen to oxygen and then to carbon, and finally expulsion of the tin radical to form **140** [Equations (55) and (56)].[26b] This 1,4-hydrogen shift is consistent with the results of DFT computations.[26b]



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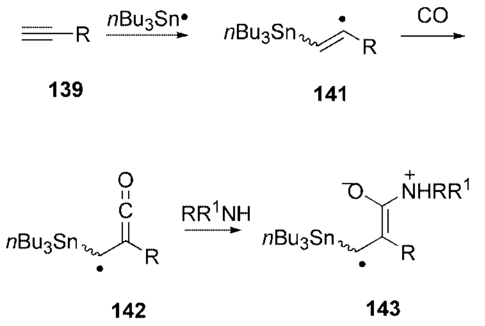

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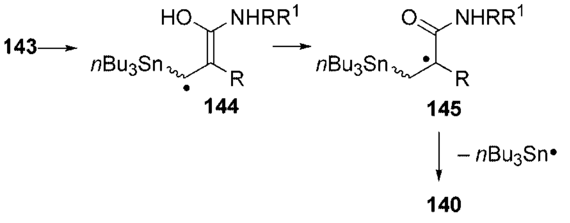

(56)

XI. Outlook

Ketene chemistry has already experienced many new discoveries in the 21st century, as described here, and in other developments, including polymer-assisted chemistry,[27] photolithography,[28a–28c] and drug discovery.[28d] With these vigorous beginnings the next 100 years of ketene chemistry can be expected to show many more new and useful developments that exploit the unique structure and reactivity of this family. With the continued improvement in experimental and spectroscopic techniques the direct observation and utilization of many hitherto elusive ketenes may be expected to become commonplace in the next century of ketene chemistry – the best is yet to come.

Acknowledgments

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